ARO-APOC3

STUDY NO. AROAPOC3-3001

A PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ARO-APOC3 IN ADULTS WITH FAMILIAL CHYLOMICRONEMIA SYNDROME

Amendment 8:	**08-November-2024**
Amendment 7:	**13-September-2024**
Region-Specific Amendment 6.2	**22-July-2024**
Region-Specific Amendment 6.1	**22-April-2024**
Amendment 6:	**31-August-2023**
Amendment 5:	**22-May-2023**
Amendment 4:	**12-April-2023**
South Korea-Specific Amendment 3.1	**20-March-2023**
Amendment 3:	**22-November-2022**
South Korea-Specific Amendment 1.4:	**29-December-2022**
Amendment 2:	**23-June-2022**
France-Specific Amendment 1.3:	**30-March-2022**
UK-Specific Amendment 1.2:	**22-March-2022**
Japan-Specific Amendment 1.1:	**22-April-2022**
Amendment 1:	**02-September-2021**
Original Protocol:	**04-May-2021**

Product Number: ARO-APOC3

Indication: Familial Chylomicronemia Syndrome (FCS)

IND Number: 144947

EU CT Number: 2024-514336-24

Study Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA

INVESTIGATOR'S AGREEMENT

Protocol Title: A Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Familial Chylomicronemia Syndrome

Protocol Number: AROAPOC3-3001

Version: Protocol Amendment 8.0

By my signature below, I attest to the following:

- I have received and read the Investigator's Brochure for ARO-APOC3.
- I have carefully read this study protocol.
- I agree to conduct the trial according to the protocol (subject to any amendments) and in accordance with the principles of International Council for Harmonisation (ICH) E6 Good Clinical Practice guidelines and all applicable regulations or requirements.
- I understand that any changes to the protocol must be approved by the Sponsor, Arrowhead Pharmaceuticals, Inc., the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and in certain cases, the US Food and Drug Administration (FDA) or other applicable regulatory agencies, before they may be implemented.
- I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Medical Monitor Contact

Medpace Medical Monitor Contact
[redacted] Telephone: [redacted]
[redacted] Telephone: [redacted]
[redacted] Telephone: [redacted]
Arrowhead Medical Monitor Contact
[redacted] Telephone: [redacted]
Arrowhead Global Safety Officer
[redacted] Telephone: [redacted]

1. SYNOPSIS

Name of Sponsor/Company: Arrowhead Pharmaceuticals, Inc.		
Name of Investigational Product: AROAPOC-3 Injection (also referred to as ARO-APOC3)		
Name of Active Ingredient: ARO-APOC3		
Protocol Number: AROAPOC3-3001, Amendment 8	**Phase:** 3	**Country:** Multiple
Title of Study: Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Familial Chylomicronemia Syndrome		
Study Center(s): Multiple sites globally		
Background: Familial chylomicronemia syndrome (FCS) is a severe and ultrarare genetic disease, with a prevalence of approximately 1 in 1,000,000, often caused by various monogenic mutations. FCS leads to extremely high fasting triglyceride (TG) levels, typically over 900 mg/dL. Such severe elevations lead to various serious signs and symptoms including acute pancreatitis (which can be fatal), chronic daily abdominal pain, type 2 diabetes mellitus, hepatic steatosis, and cognitive issues (aka "brain fog"). Currently, the therapeutic options that can adequately treat FCS are very limited with only one antisense oligonucleotide inhibitor of apolipoprotein C3 (APOC3, APOC-III), approved in Europe and Brazil. APOC3 is an 8.8 kilodalton (kDa) protein component of triglyceride-rich lipoproteins (TRLs) such as very-low-density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL-C), chylomicrons, high-density lipoprotein cholesterol (HDL-C), and remnant particle lipoproteins. APOC3 is synthesized predominantly in hepatocytes. It inhibits the hydrolysis of TG on TRLs at the muscle and adipose tissue capillary level through inhibition of lipoprotein lipase (LPL), and delays clearance of lipoprotein remnants by the liver by inhibiting hepatocyte receptor-mediated uptake. APOC3 functions as a key regulator of fasting and postprandial plasma TG levels. ARO-APOC3 is a synthetic, double-stranded, hepatocyte-targeted RNA interference (RNAi) trigger (also referred to as a small interfering RNA [siRNA]) designed to specifically silence messenger RNA (mRNA) transcripts from the *APOC3* gene using an RNAi mechanism. Given the important role of APOC3 in serum TG level modulation and its primary source of synthesis in hepatocytes, reduction of APOC3 through a hepatocyte-targeted RNAi strategy is likely to reduce circulating TG, benefiting several patient populations, including patients with FCS.		
Objectives: The objectives of the study are to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS. **Endpoints**: Primary and secondary endpoints are for the randomized period only, except as noted. <u>Primary Endpoint:</u> • Percent change from baseline at Month 10 in fasting TG		

Key Secondary Endpoints:

- Percent change from baseline at Months 10 and 12 (averaged) in fasting TG
- Percent change from baseline at Month 10 in fasting APOC3
- Percent change from baseline at Month 12 in fasting APOC3

Secondary Endpoints:

- Percent change from baseline at Month 10 in non-high-density lipoprotein cholesterol (non-HDL-C) and HDL-C
- Percent change from baseline at Month 12 in fasting TG, non-HDL-C, and HDL-C
- Proportion of participants achieving TG of <500 mg/dL at Month 10
- Proportion of participants achieving TG of <500 mg/dL at Month 12
- Change and percent change from baseline at each scheduled assessment in fasting TG up to Month 12
- Participant incidence of treatment-emergent adverse events (TEAEs) (either period)
- Incidence of positively adjudicated events of acute pancreatitis (either period)

  Note: All adverse events (AEs) and serious AEs (SAEs) reported by the Investigator during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the 2013 Atlanta definition meeting 2 of the following 3 criteria:

  1. Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
  2. Serum lipase activity (or amylase activity) ≥3 times the upper limit of normal (×ULN)
  3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography

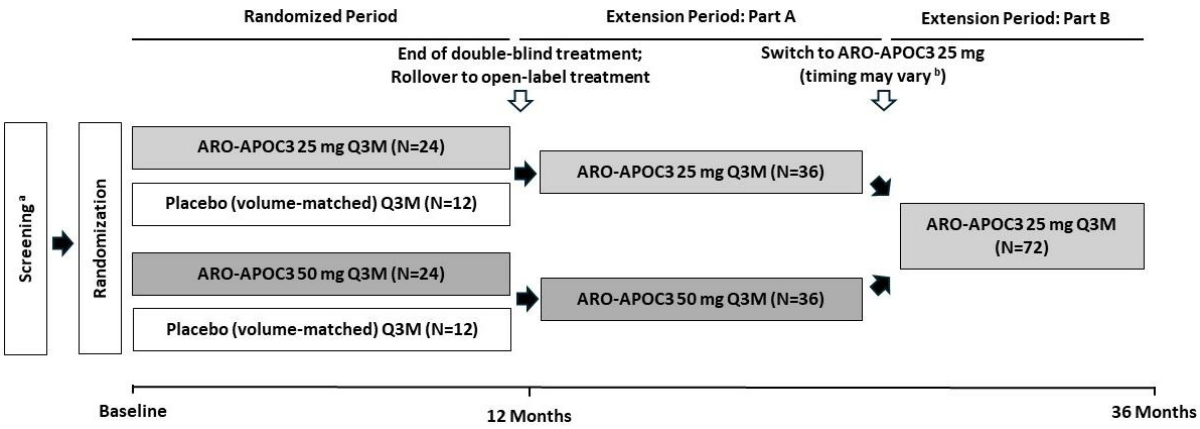
Exploratory Endpoints:

Exploratory endpoints are for both the randomized period and the extension period, except as noted.

- Change and percent change from baseline at each scheduled assessment in fasting lipid parameters (total cholesterol, low-density lipoprotein cholesterol [LDL-C], HDL-C, non-HDL-C, VLDL-C, total apolipoprotein B [APOB], APOB-48, lipoprotein(a) [LP(a)], APOB-100, APOC2, APOC3, apolipoprotein A-I [APOA1], and apolipoprotein A-V [APOA5]), with all values drawn after at least a 10-hour fast; LDL-C will be measured using ultracentrifugation methodology, preferentially, as well as Martin-Hopkins methodology.
- Changes from baseline at each scheduled assessment in fasting serum blood glucose, glycated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide
- Change and percent change from baseline at each scheduled assessment in TG, APOC3, non-HDL-C, and HDL-C (extension period only)
- Proportion of participants reaching TG of <500 mg/dL at each scheduled assessment
- Incidence of hospitalizations for abdominal pain
- Participant incidence of emergent apheresis
- Population pharmacokinetics (PK) of ARO-APOC3, with assessment of the covariates of Country (Japan) and Race (Asian) for any significant effect on ARO-APOC3 PK (randomized period only)

- Incidence of anti-drug antibodies to ARO-APOC3
- Change from baseline at each scheduled assessment in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 score
- Change from baseline at each scheduled assessment in EORTC QLQ-PAN26 score
- Change from baseline at each scheduled assessment in EuroQol 5-dimension instrument (EQ-5D-5L) score

Study Design:



Q3M=every 3 months.
[a] Screening: review and stabilization of diet, medications, and laboratory values
[b] The duration of Parts A and B depend on when the participant entered Part A and when the dose was selected for Part B.

Methodology:

This study will be conducted in adult participants with FCS. Participants with diagnosis of FCS will initiate a treatment stabilization period for at least 4 weeks, during which diet, lifestyle, and medication regimen will be stabilized. Enrolled participants will be counseled to remain on a diet comprising ≤20 g of fat per day and stable treatment regimen throughout the study, as per the Principal Investigator's (PI's) discretion and in accordance with local standard of care.

In the randomized period, approximately 72 participants who have met all protocol eligibility criteria during screening will be randomized in a double-blinded fashion to receive 4 total doses of ARO-APOC3, or matching placebo, administered subcutaneously (SC) once every 3 months (Q3M). Blinding will be preserved to the extent possible; however, treatment unblinding may occur, at the PI's or medical monitor's discretion, when deemed necessary for treatment of an AE or for a safety-related decision or a decision to be made regarding trial continuation in an individual participant.

Participants who complete the randomized period will continue in a 2-part extension period, where all participants will receive ARO-APOC3. In Part A of the extension period, participants will remain blinded to their original treatment assignment and will initially receive open-label ARO-APOC3 at the dose corresponding to their study treatment dose in the randomized period. Thus, participants who received ARO-APOC3 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (ie, ARO-APOC3 25 mg Q3M or 50 mg Q3M).

In Part B of the extension period, after the last participant has completed the randomized period, all participants will switch to ARO-APOC3 25 mg Q3M until the last dose at Month 33. The timing of

this switch may vary for each participant, based on when the participant entered Part A of the extension period and when the dose for Part B of the extension period is selected.

For any participant experiencing acute pancreatitis, all TG levels will be provided by the central laboratory to the Investigator and Medical Monitor. The participant will be unblinded to their assigned treatment allocation, and from that point forward the participant will be transitioned to the Open Label Extension Period of the study. This will be documented via the Interactive Web Response System (IWRS).

- If the participant had been assigned to receive placebo, they will be re-assigned to receive active ARO-APOC3 in the Open Label Extension Period of the study. Their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor. Once considered clinically stable, the participant will follow the Open Label Extension Schedule of Activities from that point onwards, starting from the Day 360/Month 12 visit.
- If the participant had been assigned to receive ARO-APOC3, they will be assigned to receive active ARO-APOC3 in the Open Label Extension Period of the study. Their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and until at least 3 months have passed since receiving the last dose of study drug. Once these criteria have been met, the participant will follow the Open Label Extension Schedule of Activities from that point onwards, starting from the Day 360/Month 12 visit.

Treatment modification guidelines are provided in the Appendices for participants with elevated AST or ALT (Appendix 2) and poor glycemic control (Appendix 3).

Postprandial Substudy at Selected Sites in Australia, Canada, and the United States:

FCS is a rare, inherited lipid disorder characterized by high levels of plasma triglycerides and chylomicrons, which may cause life-threatening acute pancreatitis. (Williams 2018). Currently, the therapeutic management relies solely on a very low-fat diet (<20 g fat/day), which is difficult to maintain long term and can impose a significant clinical and psychosocial burden on patients and caregivers. With the restricted diet, TGs may remain elevated. Following competent authority approval, a postprandial substudy will be performed to evaluate the impact of ARO-APOC3 on postprandial serum TG levels in approximately 12 participants who received at least 2 consecutive doses of ARO-APOC3 in the Open Label Extension Period, have had 30 days elapse since being administered their most recent ARO-APOC3 dose, and have fasting serum triglycerides levels ≤500 mg/dL. Refer to Appendix 6 for postprandial substudy details including eligibility criteria, design, methodology, schema, statistics, and schedule of activities.

Sample Size Justification:

A total of 72 participants randomly assigned 2:1:2:1 to the dose cohorts (ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively) results in a 1:1 allocation for comparing each study treatment dose to pooled placebo. The study will have about 99% power to detect a statistically significant global or conjunctive difference in percentage change from baseline in TG between any active treatment group and pooled placebo using a 2-sided test and Holm's step-down multiple-comparison procedure, with a 2.5% level of significance for each test. These estimates assume an average of 75% and 80% reduction from baseline in fasting TG at Month 10 in participants receiving ARO-APOC3 25 mg and 50 mg, respectively, and a 5% reduction in participants receiving placebo. The standard deviation is assumed to be 40%. The Wilcoxon (Mann-Whitney) rank-sum test for continuous outcome is used for sample size estimation and 10% to 15% dropout rate is estimated.

Of the 72 planned participants, approximately 12 will be recruited in Japan. The sample size for participants in Japan was selected based on a combination of target enrollment of 10% to 20% of the total study population in Japan and the anticipated availability of eligible participants in Japan.
Number of Participants (Planned): A total of approximately 72 participants will be enrolled in the study, including approximately 12 participants in Japan.
Diagnosis and Main Criteria for Inclusion: The study will enroll men and nonpregnant women, ≥18 years of age (or ≥19 years of age, where applicable according to the local regulation), with fasting TG ≥10 mmol/L (≥880 mg/dL) that is refractory to standard lipid-lowering therapy, and with a diagnosis of FCS as defined in the inclusion criteria. Key exclusion criteria are recent use of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule, active pancreatitis, elevated ALT or AST (≥3×ULN), elevated total bilirubin (≥1.5×ULN), glycated hemoglobin (HbA1c) ≥9.0% (or ≥75 mmol/mol International Federation of Clinical Chemistry [IFCC] units) or glomerular filtration rate <30 mL/min/1.73 m^2.
Investigational Product, Dosage, and Mode of Administration: The test formulation is active ARO-APOC3 administered SC. The active pharmaceutical ingredient contained in ARO-APOC3 is a synthetic, double-stranded, siRNA duplex conjugated to an N-acetylgalactosamine targeting ligand to facilitate hepatocyte delivery. Dosage information: ARO-APOC3 (25 mg or 50 mg) on Day 1, then Q3M.
Duration of Treatment: The duration of the study is approximately 164 weeks from screening to the End of Study (EOS) examination. The screening period will last up to 8 weeks (Day -56 to Day -1). The treatment period will last up to 156 weeks (52 weeks in the randomized period and 104 weeks in the extension period).
Reference Therapy, Dosage, and Mode of Administration: The reference formulation is placebo: normal saline (0.9%) administered SC, volume-matched to the corresponding ARO-APOC3 dose volume.
Criteria for Evaluation: Efficacy: Change from baseline in TG and other parameters. The primary efficacy evaluation will be based on the estimate median difference in change from baseline between each ARO-APOC3 dose and pooled placebo at Month 10. Safety: Incidence of TEAEs.
Statistical Methods: The primary analysis will include data from the randomized period. The final analysis will include data from the randomized and extension periods. The primary analysis is planned when all randomized participants complete the randomized period or discontinue from study, whichever is earlier. The final analysis is planned when all participants complete the extension period or discontinue from study, whichever is earlier. Placebo groups will be pooled for descriptive summary and statistical analysis. The hypothesis testing procedure from the primary efficacy endpoint to the key secondary endpoints will use a fixed-sequence stepping-down procedure. When performing the efficacy analysis for an endpoint, the adjustment for multiplicity of testing 2 ARO-APOC3 treatment groups versus placebo will be carried out using Holm's step-down procedure. The sequence of hypotheses testing is as follows:

Endpoint	Testing Order
Percent change in fasting TG at Month 10 (primary endpoint)	1
Percent change in fasting TG at Month 10 and Month 12 (averaged)	2
Percent change in fasting APOC3 at Month 10	3
Percent change in fasting APOC3 at Month 12	4

The primary efficacy analysis will be based on Hodges-Lehmann estimator with pattern-mixture model imputation based on the Full Analysis Set (FAS). The pattern-mixture model will be used as the primary imputation method as part of the primary analysis for the percent change in fasting TGs from baseline to Month 10. This imputation model will include factors such as patient demographics, disease status, and baseline TG, as well as adherence to therapy. For participants who do not adhere to therapy and who do not have a Month 10 measurement, the missing data imputation method will use patients in the same treatment arm who do not adhere to therapy and have Month 10 measurements or wash out imputation will be used if there are no or very few patients in the same treatment arm who do not adhere to therapy and have Month 10 measurements. The estimand of interest is the difference in means of percent change from baseline in fasting TG at Month 10 in the adult FCS population (as defined by the inclusion/exclusion criteria), regardless of treatment compliance or other intercurrent events post-baseline. Tipping-point analyses with Multiple Imputation and analysis using the Mixed-Model Repeated Measures approach based on a missing-at-random assumption will be conducted as sensitivity analyses.

All key secondary endpoints will be analyzed in a similar manner to the primary endpoint. The Wilcoxon rank-sum test with the Hodges-Lehmann method will be used to test and evaluate the primary endpoint and key secondary endpoints. The same test will also be used to test other continuous secondary endpoints but will only be considered exploratory. The same sensitivity analyses of the primary endpoint will be applied to these 3 key secondary endpoints and other secondary endpoints as well.

For the analysis of exploratory endpoints, descriptive summaries will be provided, as applicable, and any inferential statistics (ie, p-values) will be considered only as exploratory.

All participants in the FAS who have sufficient plasma concentration data to facilitate determination of PK parameters will be used for PK analyses.

Analyses of baseline characteristics, efficacy, safety, PK, pharmacodynamics (PD), and immunogenicity conducted on the results from all participants in Japan will be compared with results for non-Japanese participants, as well as results for all study participants, to assess similarities and differences across these populations.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study protocol.

Table 2: Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	Adverse Events of Special Interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
API	active pharmaceutical ingredient
APOA-I or APOA1	apolipoprotein A-I
APOA-V or APOA5	apolipoprotein A-V
APOB	apolipoprotein B
APOB-100	apolipoprotein B 100
APOB-48	apolipoprotein B 48
APOC2	apolipoprotein C2
APOC3	apolipoprotein C3
ARO	Arrowhead Pharmaceuticals, Inc
ARO-APOC3	short name for ARO-APOC3 Injection
ARO-APOC3 Injection	clinical drug product solution ready for SC injection
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
CBC	complete blood cell count
CECT	contrast-enhanced computed tomography
cGMP	current Good Manufacturing Practice
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
COVID	coronavirus disease
CRA	clinical research associate
CRO	contract research organization
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events

DSC	Data Safety Committee
ECG	electrocardiogram
eCRF	electronic case report form
EORTC QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of Study
EQ-5D-5L	EuroQol 5-dimension instrument
ET	early termination
FAS	Full Analysis Set
FCS	familial chylomicronemia syndrome
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPIHBP1	Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1
HbA1c	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment for insulin resistance
HR	heart rate
HTG	hypertriglyceridemia
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDL-C	intermediate density lipoprotein cholesterol
IEC	Independent Ethics Committee
IFCC	International Federation of Clinical Chemistry
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
IWRS	interactive web response system

kDa	kilodalton
LDL-C	low-density lipoprotein cholesterol
LISR	local injection site reaction
LMF1	lipase maturation factor 1
LPL	lipoprotein lipase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NAG	N-acetylgalactosamine
NCA	non-compartmental analysis
NHV	normal healthy volunteer
NLME	nonlinear mixed effect
NOAEL	no adverse effect level
non-HDL-C	non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
OTC	over-the-counter
PD	pharmacodynamic
PFS	prefilled syringe
PI	Principal Investigator
PK	pharmacokinetics
PT	preferred term
Q3M	once every 3 months
Q12W	every 12 weeks
Q24W	every 24 weeks
QTcF	Fridericia-corrected QT interval
RISC	RNA-induced silencing complex
RNA	ribonucleic acid
RNAi	RNA interference
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SHTG	severe hypertriglyceridemia
siRNA	small interfering RNA oligonucleotide

SOA	schedule of activities
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TG	triglyceride(s)
TRL	triglyceride-rich lipoprotein
ULN	upper limit of normal
VAS	visual analog scale
VLDL-C	very-low-density lipoprotein cholesterol

4. INTRODUCTION

4.1. Overview of Familial Chylomicronemia Syndrome and APOC3

4.1.1. Familial Chylomicronemia Syndrome

Familial chylomicronemia syndrome (FCS) is a severe and ultrarare genetic disease, with a prevalence of approximately 1 in 1,000,000. FCS is often caused by various monogenic mutations (eg, null mutations in the genes coding for lipoprotein lipase [LPL], glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 [GPIHBP1], apolipoprotein C2 [APOC2], apolipoprotein A5 [APOA5], or lipase maturation factor 1 [LMF1]). FCS leads to extremely high fasting triglyceride (TG) levels, typically over 900 mg/dL, representing the top 0.1% of TG levels. Such severe elevations in TG lead to various serious signs and symptoms including acute pancreatitis (which can be fatal), chronic daily abdominal pain, type 2 diabetes mellitus, hepatic steatosis, and cognitive issues (aka "brain fog"). In the recent years, step-wise-, algorithm-, and score-based approaches have been proposed for the clinical diagnosis of FCS (Falko 2018; Moulin 2018; Stroes 2017). Genetic testing is increasingly becoming a common consideration in the clinical care of patients with dyslipidemia. FCS is amongst the dyslipidemias for which genetic testing could be clinically useful; however, no clinical practice guidelines currently exist for genetic testing in patients with possible hereditary dyslipidemia (Brown 2020). Currently, the therapeutic options for adequately treating FCS are very limited, with only one antisense oligonucleotide inhibitor of apolipoprotein C3 (APOC3, APOC-III) approved in Europe and Brazil.

The only effective treatment is a diet extremely low in fat (approximately 20 g per day). This diet does not normalize TG levels but does reduce the risk of pancreatitis. However, dietary compliance is a major hurdle to reducing pancreatitis risk. Available therapies commonly used to lower TG exert effect through the LPL pathway, which is usually dysfunctional in patients with FCS, rendering these therapies mostly ineffective. Patients with FCS are also at risk for large (often >500 mg/dL) increases in postprandial TG that often lead to severe abdominal pain and place patients at risk for postprandial pancreatitis, which often requires hospitalization. Pancreatitis is a major life-threatening complication of FCS caused by digestion of large amounts of chylomicron TG by pancreatic lipases. Pancreatitis has an estimated 10% per episode mortality rate and may lead to other life-threatening conditions such as sepsis, acute respiratory distress syndrome, hypovolemic shock, and renal failure.

Acute pancreatitis, a condition known to be associated with severe hypertriglyceridemia (SHTG), including FCS, is characterized by severe and persistent upper abdominal pain and elevated serum lipase and/or amylase levels that may result in organ failure, frequent emergency room visits, hospitalizations, chronic abdominal pain, and even death. The recurrence of acute pancreatitis can lead to chronic pancreatitis whereby patients develop pancreatic failure and chronic abdominal pain, and associated pancreatic endocrine dysfunction such as diabetes mellitus. Mortality associated with an attack of acute pancreatitis can range from 3% in mild cases to 30% in severe cases. Morbidity and mortality of acute pancreatitis associated with hypertriglyceridemia (HTG) is greater than for other etiologies (FDA 2018). The risk of acute pancreatitis increases relative to the elevation in serum TG levels, with the incidence of acute pancreatitis increasing 3% to 4% for every 100 mg/dL (1.13 mmol/L) increase in TG level (Gelrud 2017; Scherer 2014).

4.1.2. Apolipoprotein C3

APOC3 is an 8.8 kilodalton (kDa) protein component of triglyceride-rich lipoproteins (TRLs) such as very-low-density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL-C), chylomicrons, high-density lipoprotein cholesterol (HDL-C), and remnant particle lipoproteins. APOC3 is synthesized predominantly in hepatocytes (approximately 80% hepatocyte, 20% enterocyte), and inhibits the hydrolysis of TG on TRLs at the muscle and adipose tissue capillary level through inhibition of LPL. APOC3 also delays clearance of lipoprotein remnants by the liver by inhibiting hepatocyte receptor-mediated uptake. It functions as a key regulator of fasting and postprandial plasma TG levels (Crosby 2014).

Insights gained from studies in transgenic mice overexpressing APOC3 and in *APOC3* knockout mice have shown that APOC3 delays VLDL-C hydrolysis in vivo and may delay the catabolism of TRL remnants by the liver and other tissues (Aalto-Setala 1992; Aalto-Setala 1996; Gerritsen 2005; Jong 2001; Khetarpal 2015). *APOC3* knockout models in rabbits also exhibited significantly lower plasma levels of TG, VLDL-C, and IDL-C, as well as greater TG clearance, compared with wild-type animals. Both aortic and coronary atherosclerosis was significantly reduced in knockout rabbits compared with wild-type controls (Yan 2020).

Two 2014 reports, published concurrently, used complementary genetic approaches to demonstrate that loss-of-function mutations in *APOC3* are robustly associated with lower TG and decreased incidence of coronary artery disease, and do not demonstrate significant hepatic steatosis (Crosby 2014; Jorgensen 2014). *APOC3* homozygous-deficient individuals demonstrate APOC3 reductions of 88% and TG reductions of 59% compared with noncarriers (Lek 2016; Saleheen 2017). Additionally, *APOC3* homozygote-deficient patients (“human knockouts”) also appear to be without adverse phenotypes (Lek 2016; Proctor 2003). Given the important role of APOC3 in serum TG level modulation and its primary source of synthesis in hepatocytes, APOC3 is an ideal target for hepatocyte-targeted RNA interference (RNAi)-mediated gene silencing.

Reduction of APOC3 through a hepatocyte-targeted RNAi strategy is likely to reduce circulating TGs, benefiting several patient populations, including patients with FCS, that are at considerable risk for HTG-induced pancreatitis despite the current standard of care.

4.2. Overview of ARO-APOC3 Development

A brief overview of existing information on ARO-APOC3 is provided below; a comprehensive review of available data is contained in the Investigator’s Brochure (IB), which should be reviewed prior to initiating the study.

4.2.1. Mechanism of Action and Therapeutic Rationale

ARO-APOC3 works through a mechanism of RNAi. RNAi-based therapeutics have the potential to silence the expression of any specific target gene. RNAi is a naturally occurring phenomenon by which small interfering RNA oligonucleotides (siRNAs) trigger a sequence-specific down-regulation of gene expression. RNAi triggers refer to synthetic oligonucleotides designed to target for silencing specific gene expression (Fire 1998). The RNAi trigger is a short, double-stranded siRNA conjugated to a hepatocyte-targeted N-acetylgalactosamine (NAG) targeting moiety, acting as a ligand for the highly expressed, hepatocyte-specific

asialoglycoprotein receptor. Available nonclinical and clinical pharmacokinetics (PK) data show rapid absorption and clearance of all NAG-conjugated triggers from the blood stream within 24 to 48 hours after subcutaneous (SC) administration.

ARO-APOC3 is a synthetic, double-stranded, hepatocyte-targeted RNAi trigger designed to specifically silence messenger RNA (mRNA) transcripts from the *APOC3* gene using an RNAi mechanism. Preclinical distribution studies show that ARO-APOC3 is primarily distributed to the liver, where the trigger molecule is taken up by hepatocytes via receptor-mediated endocytosis. Introduction of the double-stranded RNAi trigger into the cytoplasm of hepatocytes results in its association with the protein components of the RNA-induced silencing complex (RISC), resulting in "on target" highly sequence-specific degradation of mRNA complementary to the antisense strand of the RNAi trigger. Active RISC is a multiple turnover enzyme complex; therefore, incorporation of a single RNAi trigger into RISC can result in the degradation of many mRNA molecules. The prolonged reduction of the expression of the corresponding protein can result in the persistence of pharmacologic activity significantly beyond the period of plasma exposure.

Silencing of hepatic *APOC3* using ARO-APOC3 is expected to lower serum TG by preventing APOC3-mediated inhibition of LPL, thus allowing enhanced peripheral LPL activity. Additionally, *APOC3* silencing removes the steric blockade of APOC3 at the hepatocyte, leading to enhanced clearance of TRLs from circulation by the liver.

4.2.2. Preclinical Studies

The Sponsor is conducting a comprehensive preclinical program to support the SC administration of ARO-APOC3. Studies of potential clinical significance and relevance to this protocol are summarized below.

Proof-of-concept studies in animal models support the use of siRNA against *APOC3* as a potential treatment of SHTG and FCS. Findings of potential clinical significance and relevance to this protocol are summarized below. Additional details regarding preclinical pharmacology, PK, and toxicology results are provided in the IB.

- Preclinical pharmacology of ADS-005, the active pharmaceutical ingredient (API) in ARO-APOC3, showed that ADS-005 treatment in transgenic mice (TgAPOC3) resulted in dose-dependent reduction of hepatic *APOC3* mRNA levels, which correlated with reduced serum APOC3 of >90%. Reductions in serum APOC3 were associated with reductions in serum lipids (maximum mean reduction of 91% in TG, 45% in total cholesterol, and 64% in low-density lipoprotein C [LDL-C]).
- Similar reductions in serum APOC3 were also observed after ADS-005 doses in a diet-induced dyslipidemic rhesus monkey model. ARO-APOC3 was well tolerated in toxicology studies of rats and nonhuman primates.
- Results of non-Good Laboratory Practice (GLP) in vitro toxicology studies indicate that, for ADS-005 exposure at concentrations up to 250 μg/mL (which far exceeds the blood concentrations anticipated at the doses to be used clinically):
  - There is minimal potential for induction of the innate immune system.

  - There is no potential for complement activation, mitochondrial toxicity/cytotoxicity, or platelet aggregation in whole blood.

- ADS-005 was shown to be nongenotoxic and had no adverse effects on the central nervous, respiratory, or cardiovascular systems as demonstrated by the results of the International Council for Harmonisation (ICH)-recommended battery of genetic toxicity and safety pharmacology studies.
- Multiple-dose GLP toxicity studies with SC administration of ADS-005 in rats and cynomolgus monkeys indicate ADS-005 was well tolerated, and the no adverse effect level (NOAEL) was 300 mg/kg in both species.
- In both rat and cynomolgus monkey studies, the prominent histopathologic findings were consistent with those described for other SC-administered NAG-siRNA drugs.

4.2.3. Clinical Studies

The Sponsor is conducting a comprehensive program of clinical studies investigating ARO-APOC3 as a potential therapeutic candidate for the treatment of SHTG and FCS.

4.2.3.1. Phase 1 Study AROAPOC31001

The Sponsor has completed a Phase 1, single and multiple dose-escalating study (AROAPOC31001) to evaluate the safety, tolerability, PK, and pharmacodynamic (PD) effects of ARO-APOC3 in adult healthy volunteers as well as in patients with HTG. Interim results from Study AROAPOC31001 show that in healthy volunteers, treatment with ARO-APOC3 reduces hepatic production of APOC3 via RNAi, leading to reductions in serum TG, LDL-C, and apolipoprotein B (APOB), and increases in HDL-C. Doses of 10, 25, 50, and 100 mg all demonstrated durable PD activity lasting beyond Month 3. Aside from mild and transient local injection site reactions (LISRs), and transient and self-limited alanine aminotransferase (ALT) elevations, single and repeat doses of ARO-APOC3 were well tolerated in healthy volunteers, and the safety profile based on Phase 1 data warrants additional later-stage clinical evaluation. Preliminary data from participants with chylomicronemia also demonstrated substantial reductions in APOC3 and TG levels with repeat doses (at baseline and on Day 29) of ARO-APOC3 25 mg and 50 mg. Additional information regarding results of Study AROAPOC31001 can be found in the IB.

Results from the Phase 1 study provided information for the design of randomized, double-blind, placebo-controlled Phase 2 studies in participants with SHTG (AROAPOC3-2001) or mixed dyslipidemia (AROAPOC3-2002), and an open label extension study for participants from either of those studies (AROAPOC3-2003). Results from the Phase 1 study also provided information justifying the dosing levels and interval as well as other design aspects of this Phase 3 study.

4.2.3.2. Phase 2b Study AROAPOC3-2001 (SHASTA-2) in Subjects with Severe Hypertriglyceridemia

The AROAPOC3-2001 (SHASTA-2) study was a Phase 2b, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ARO-APOC3 in adults with SHTG. A total of 226 subjects were treated with at least 1 of 2 planned doses of study treatment (ARO-APOC3 or placebo). Evaluation of key PD parameters showed that all doses of ARO-APOC3

(10 mg, 25 mg, and 50 mg) provided robust and sustained efficacy over 24 weeks compared with placebo. At Week 24, ARO-APOC3 significantly decreased mean serum APOC3 levels by 69% to 78% (P<0.0001). ARO-APOC3 significantly decreased median serum TGs by 75% to 80% (P<0.0001) at Week 24. Importantly, >90% of subjects in the 25 and 50 mg dose groups achieved TGs <500 mg/dL (<5.65 mmol/L) as early as Week 4 that were sustained through Week 24, and between 50% to 72% achieved normalization of TGs (<150 mg/dL [<1.69 mmol/L]) from Week 4 through Week 24.

As of 13 October 2023, treatment-emergent adverse events (TEAEs) were reported in 43 out of 54 subjects in the ARO-APOC3 10 mg cohort, 36 out of 55 subjects in the ARO-APOC3 25 mg cohort, and 49 out of 56 subjects in the ARO-APOC3 50 mg cohort versus 43 out of 61 subjects in the pooled placebo cohort.

Evaluation of key PD parameters showed that all doses of ARO-APOC3 (10 mg, 25 mg, and 50 mg) provided robust and sustained efficacy over 24 weeks compared with placebo. At Week 24, ARO-APOC3 significantly decreased mean serum APOC3 levels by 69% to 78% (P<0.0001). ARO-APOC3 significantly decreased median serum TGs by 75% to 80% (P<0.0001) at Week 24. Importantly, >90% of subjects in the 25 and 50 mg dose groups achieved TGs <500 mg/dL (<5.65 mmol/L) as early as Week 4 that were sustained through Week 24, and between 50% to 72% achieved normalization of TGs (<150 mg/dL [<1.69 mmol/L]) from Week 4 through Week 24.

As of 13 October 2023, TEAEs were reported in 43 out of 54 subjects in the ARO-APOC3 10 mg cohort, 36 out of 55 subjects in the ARO-APOC3 25 mg cohort, and 49 out of 56 subjects in the ARO-APOC3 50 mg cohort versus 43 out of 61 subjects in the pooled placebo cohort.

4.2.3.3. Phase 2b Study AROAPOC3-2002 (MUIR) in Subjects with Mixed Dyslipidemia

The AROAPOC3-2002 (MUIR) study is a completed Phase 2b, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ARO-APOC3 in adults with mixed lipidemia. A total of 353 subjects were treated with at least 1 of 2 planned doses of study treatment (ARO-APOC3 or placebo).

Evaluation of key PD parameters showed that all doses of ARO-APOC3 provided robust and sustained efficacy over 24 weeks compared with placebo. For those cohorts receiving their second dose at Week 12, ARO-APOC3 significantly decreased mean serum APOC3 levels by 59% to 80% (P<0.0001) at Week 24. For those subjects dosed at Day 1 and Week 12, median serum TGs were significantly decreased by 46% to 64% (P<0.0001) at Week 24 compared to placebo.

As of 19 September 2023, TEAEs were reported in 46 out of 67 subjects in the ARO-APOC3 10 mg cohort, 45 out of 67 subjects in the ARO-APOC3 25 mg cohort, 47 out of 66 subjects in the ARO-APOC3 50 mg every 12 weeks (Q12W) cohort, and 49 out of 66 subjects in the ARO-APOC3 50 mg every 24 weeks (Q24W) cohort versus 55 out of 87 subjects in the pooled placebo cohort.

Treatment-emergent serious adverse events (SAEs) were reported in 2 out of 67 subjects in the ARO-APOC3 10 mg cohort, 5 out of 67 subjects in the ARO-APOC3 25 mg cohort, 7 out of 66 subjects in the ARO-APOC3 50 mg Q12W cohort, and 5 out of 66 subjects in the ARO-APOC3 50 mg Q24W cohort versus 5 out of 87 subjects in the pooled placebo cohort. There was 1 SAE

of lacunar infarction reported as possibly related to study treatment and considered not related by the Sponsor. There were 4 SAEs with outcome of death reported and all were considered not related to the study treatment. There was 1 subject in the ARO-APOC3 50 mg Q12W cohort with study drug discontinuation due to a treatment-emergent SAE of myocardial infarction, which was considered not related to the study treatment.

An increase in HbA1c levels was observed in ARO-APOC3 cohorts in subjects who had pre-existing diabetes at baseline. In subgroup analyses, increases in HbA1c changes were most notable in a subset of subjects receiving the 50 mg dose Q12W of ARO-APOC3.

Additional details can be found in the IB.

4.3. Potential Risks of Study Participation

4.3.1. Embryo-Fetal

Limited GLP toxicology and clinical studies have been conducted. Accordingly, eligible participants enrolled in this study, both male and female (including partners), must agree to use a highly effective form of contraception in addition to a male condom during the study, or agree to abstinence (acceptable only if this method is in alignment with the normal lifestyle of the participant) (Appendix 1).

4.3.2. Liver Function

ARO-APOC3 targets the liver. siRNA literature has described ALT changes associated with off-target effects of the siRNA seed region on microRNAs in the hepatocyte (Janas 2018). The siRNA sequences of the ARO-APOC3 sense and antisense molecules have been screened for potential mRNA and microRNA homology, and sequences with homology were excluded from consideration. Thus, no such off-target effects are anticipated.

However, in the AROAPOC31001 study, transient mild-to-moderate elevations in ALT were occasionally seen without accompanying elevation in international normalized ratio (INR) or total bilirubin. In addition, mild-to-moderate elevations in ALT or AST have also been observed in the completed Phase 2 studies, AROAPOC3-2001 and AROAPOC3-2002 (see IB for details). However, no subject has been discontinued from the study due to liver injury and no subject has met Hy's Law criteria in any of the ARO-APOC3 clinical studies currently in progress.

To mitigate this risk, the proposed study protocol has built-in stopping rules for ALT and AST elevation (Appendix 2). Blood samples will be drawn as specified in the schedule of activities (SOA) (Table 3 and Table 4) to evaluate, among others, liver function and any potential liver injury. The Data Safety Committee (DSC) will review all available safety data including laboratory data periodically (Section 6.4.1).

4.3.3. Local Injection Site Adverse Events

Other SC-administered modified siRNA drug candidates evaluated in clinical studies have been associated with mild-to-moderate LISRs (eg, pain, erythema) (Appendix 4). Generally mild injection site AEs were reported in Study AROAPOC31001. LISRs have been reported in the completed Phase 2 studies (AROAPOC3-2001 and AROAPOC3-2002). All of these AEs have

been mild in severity and resolved with no intervention, and no action taken with the study drug. No other subjects had LISRs.

In this study, steps will be taken to minimize LISRs, such as rotating injection sites and allowing the ARO-APOC3 solution to come to room temperature prior to injection. Subcutaneously administered siRNA agents in clinical studies have been associated with mild to moderate LISRs (eg, pain, erythema). Below are essential tips for Clinical Trial Site staff administering subcutaneous injections of study medications to minimize the risk of LISRs:

- Follow best practices for SC administration.
- Stabilize medication at room temperature.
- Assess injection sites before administration.
- Rotate injection sites to avoid developing lumps or nodules or absorption issues.
- Apply a cold compress or ice pack if needed before and after the injection.
- Hydrate the subject.
- Use good hand hygiene.

If a study subject experiences an LISR:

- Monitor the subject for any signs of adverse reactions, such as redness, swelling, pain, or itching at the injection site. If any reactions occur, assess their severity and provide appropriate care.
- Documentation and follow-up: Document the site of injection, the exact timing of the study medication administration, and any adverse reactions in the electronic case report form (eCRF). Follow up with the patient to ensure that any LISRs are resolved. Record onset of each LISR, resolution state, and time.
- AEs, including LISRs, are reported according to Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT) (Section 13.5.3 and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 (Section 12.6.1) and (NIH 2017).

Note: For SC administration, moderate LISRs are reactions with erythema, induration, swelling >5 cm, or associated with pain >24 hours that interfere with daily activity and require the use of non-narcotic pain management (FDA 2007).

By following the guidelines, best practices and tips provided above, study staff can help minimize the risk of LISRs when administering subcutaneous study drugs, thereby ensuring the safety and comfort of clinical trial patients.

4.3.4. Glycemic Control

The completed Phase 2 ARO-APOC3 clinical trials indicated an increase in HbA1c in the ARO-APOC3 treatment group versus placebo group. The increased HbA1c values were observed in a small group of subjects who had pre-existing diabetes at baseline, particularly in a subset of subjects in the highest (50 mg) ARO-APOC3 dose group.

To mitigate the risk of worsening glycemic control, investigators are encouraged to evaluate diabetes status, take frequent measurement of glycemic status, and adjust diabetes treatment according to local clinical practice and diabetes care institutional guidelines.

In addition, any subject with worsening diabetic control may return for an unscheduled visit for evaluation of HbA1c prior to the next planned dose to confirm continued treatment eligibility.

For those subjects who, despite diabetes treatment adjustments, remain with elevated HbA1c above the protocol pre-established level, a number of criteria for study drug discontinuation have been established (Appendix 3).

Routine monitoring of serum HbA1c and fasting blood glucose concentrations will be assessed as part of the clinical laboratory panels to monitor glycemic control, as specified in the SOA (Table 3 and Table 4).

4.4. Benefit Assessment

ARO-APOC3 has been shown from numerous clinical trial data to have a favorable benefit-risk profile to date with an acceptable and manageable safety profile. Final data from the Phase 1 Study AROAPOC31001 showed that administration of ARO-APOC3 at doses from 10 to 100 mg resulted in significant and durable reduction of serum APOC3 when compared with placebo in healthy volunteers, together with meaningful reduction in TG in patients with HTG and chylomicronemia.

Cumulative pharmacodynamic data from clinical studies showed silencing of APOC3 led to substantial reductions in the levels of serum TG with plozasiran compared to placebo.

Upon administration of plozasiran, results from the Phase 1 study in normal healthy volunteers (NHVs) demonstrated reductions from baseline of serum APOC3 in a dose-dependent manner of up to -94%. There were also reductions in TG (up to -66%), non-HDL-C (up to -31%) and increases in serum high-density lipoprotein cholesterol (HDL-C) (up to +74%) with a dose response generally correlating to APOC3 serum level reductions in participants receiving active drug. Results for repeat doses of ARO-APOC3 in NHVs demonstrated consistent reductions of APOC3 (up to -94%), TGs (up to -75%), and non-HDL-C (up to -39%) and increases in HDL-C (up to +75%). These responses were sustained through Week 16 (12 weeks after the last dose).

Results from the Phase 1 study in subjects with HTG and/or chylomicronemia demonstrated similar or even larger effects of ARO-APOC3 at similar doses. Reduction in serum APOC3 (up to -98%), serum TGs (up to -88%), and non-HDL-C (up to -55%) and an increase in HDL-C (up to +122%) were observed. The effects of ARO-APOC3 treatment on these and other key lipid parameters were sustained through Week 16 (12 weeks after the last dose).

The Phase 2 study (AROAPOC3-2001) in subjects with SHTG demonstrated reductions in serum TG (up to -74%) and serum APOC3 (up to -78%) with ≥90% of subjects achieving the therapeutic goal of TG levels <500 mg/dL (<5.65 mmol/L) at Week 24. In AROAPOC3-2001, a numerical decrease in AP events was observed in subjects treated with plozasiran (1 subject each for the 3 plozasiran groups) versus placebo (3 subjects) at Week 48.

In general, ARO-APOC3 was well tolerated and has an acceptable safety profile that was manageable.

In the course of the review, an apparent increase in the level of HbA1c was observed when comparing subjects receiving ARO-APOC3 to those in the placebo group. The increase in HbA1c was observed mostly in subjects with pre-existing diabetes and was most notable in the ARO-APOC3 50 mg dose cohort. There is overall clinical benefit given the meaningful improvement in lipids and lipoprotein metabolism, particularly a decrease in triglycerides, which minimizes the risk of pancreatitis, which is the goal of therapy in this patient population.

Nevertheless, this observed HbA1c increase does not impose an immediate health risk, although, well controlled diabetes is required to minimize long term diabetes-related complications. However, worsening of glycemic control can be managed with diet, treatment adjustments, and compliance to treatment.

Therefore, in light of the risk mitigation strategies put in place to address the increased HbA1c (see Appendix 3) and the clinically meaningful decreases in triglycerides, likely reducing the risk for pancreatitis, the benefit-risk assessment remains positive in this patient population.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Objectives

The objectives of the study are to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS.

5.2. Endpoints

5.2.1. Primary Endpoint

The primary endpoint in this study is as follows:

- Percent change from baseline at Month 10 in fasting TG

5.2.2. Key Secondary Endpoints

Key secondary endpoints in this study are as follows:

- Percent change from baseline at Months 10 and 12 (averaged) in fasting TG
- Percent change from baseline at Month 10 in fasting APOC3
- Percent change from baseline at Month 12 in fasting APOC3

5.2.3. Secondary Endpoints

The following secondary endpoints are for the randomized period only, except as noted:

- Percent change from baseline at Month 10 in non-high-density lipoprotein cholesterol (non-HDL-C) and HDL-C
- Percent change from baseline at Month 12 in fasting TG, non-HDL-C, and HDL-C
- Proportion of participants achieving TG of <500 mg/dL at Month 10
- Proportion of participants achieving TG of <500 mg/dL at Month 12
- Change and percent change from baseline at each scheduled assessment in fasting TG up to Month 12
- Participant incidence of TEAEs (either period)
- Incidence of positively adjudicated events of acute pancreatitis (either period)

  Note: All AEs and SAEs reported by the Investigator during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the 2013 Atlanta definition meeting 2 of the following 3 criteria:

  1. Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
  2. Serum lipase activity (or amylase activity) ≥3 times the upper limit of normal (×ULN)

3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography

5.2.4. Exploratory Endpoints

The following exploratory endpoints are for both the randomized period and the extension period, except as noted:

- Change and percent change from baseline at each scheduled assessment in fasting lipid parameters (total cholesterol, LDL-C, HDL-C, non-HDL-C, VLDL-C, total APOB, APOB-48, lipoprotein(a) [LP(a)], APOB-100, APOC2, APOC3, apolipoprotein A-I [APOA1], and APOA5), with all values drawn after at least a 10-hour fast; LDL-C will be measured using ultracentrifugation methodology, preferentially, as well as Martin-Hopkins methodology.
- Changes from baseline at each scheduled assessment in fasting serum blood glucose, glycated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide
- Change and percent change from baseline at each scheduled assessment in TG, APOC3, non-HDL-C, and HDL-C (extension period only)
- Proportion of participants reaching TG of <500 mg/dL at each scheduled assessment
- Incidence of hospitalizations for abdominal pain
- Participant incidence of emergent apheresis
- Population PK of ARO-APOC3, with assessment of the covariates of Country (Japan) and Race (Asian) for any significant effect on ARO-APOC3 PK (randomized period only)
- Incidence of anti-drug antibodies (ADA) to ARO-APOC3
- Change from baseline at each scheduled assessment in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 score
- Change from baseline at each scheduled assessment in EORTC QLQ-PAN26 score
- Change from baseline at each scheduled assessment in EuroQol 5-dimension instrument (EQ-5D-5L) score

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

6.1.1. Overview of Study Design

This study will be conducted in adult participants with FCS. Participants who have signed an informed consent form (ICF) previously approved by an Independent Ethics Committee (IEC) or

Institutional Review Board (IRB) may initiate Screening, during which eligibility assessments will be completed. Eligible participants with a diagnosis of FCS will first initiate a treatment stabilization period for at least 4 weeks, during which diet, lifestyle, and medication regimen will be stabilized at the PI's discretion and in accordance with the local standard of care. All other eligibility criteria assessments and laboratory sample collections required to confirm subject's eligibility must be completed within 6 weeks prior to Day 1.

During the randomized period, approximately 72 participants who have met all protocol eligibility criteria during Screening will be randomized in a double-blinded fashion to receive 4 total doses of ARO-APOC3, or matching placebo, administered SC once every 3 months (Q3M; Figure 1). Of the 72 total participants in this study, approximately 12 participants will be enrolled at sites in Japan. Blinding will be preserved to the extent possible; however, treatment unblinding may occur at the PI's or medical monitor's discretion when deemed necessary for treatment of an AE, for a safety-related decision, or for a decision regarding trial continuation in an individual participant.

In Part A of the extension period, participants will remain blinded to their treatment assignment from the randomized period and will initially receive open-label ARO-APOC3 at the dose corresponding to their study treatment dose in the randomized period. Thus, participants who received ARO-APOC3 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (ie, ARO-APOC3 25 mg Q3M or 50 mg Q3M).

In Part B of the extension period, after the last participant has completed the randomized period, all participants will switch to ARO-APOC3 25 mg Q3M, which will be introduced as a PFS, upon approval of global Protocol Amendment 7 by the relevant regulatory authorities and IECs/IRBs, until the last dose at Month 33. The timing of this switch may vary for each participant, based on when the participant entered Part A of the extension period and when the dose for Part B of the extension period is selected.

All enrolled participants will be counseled starting at Screening and throughout the study to remain on a diet comprising ≤20 g of fat per day and stable treatment regimen throughout the study, as recommended by the PI and in accordance with local standard of care. The specifics of the diet will be at the discretion of the PI. Dietary counseling will begin with the initiation of the dietary diet/treatment stabilization period, followed by dietary counseling performed at each subsequent study visit to facilitate compliance, and diet assessments will be conducted as per the SOA (Table 3 and Table 4) and Section 11.4.

For any participant experiencing acute pancreatitis, all TG levels will be provided by the central laboratory to the Investigator and Medical Monitor. The participant will be unblinded to their assigned treatment allocation, and from that point forward the participant will be transitioned to the Open Label Extension period of the study. This will be documented via the Interactive Web Response System (IWRS).

- If the participant had been assigned to receive placebo, they will be re-assigned to receive active ARO-APOC3 in the Open Label Extension Period of the study. Their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor. Once considered

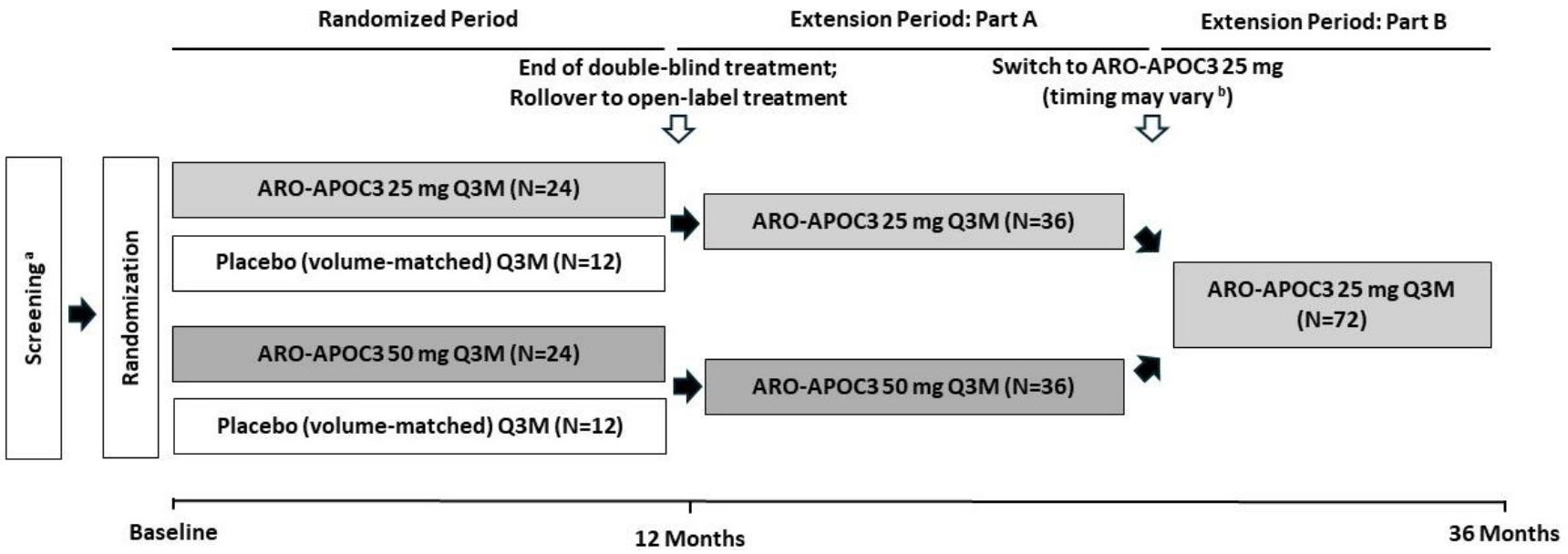
clinically stable, the participant will follow the Open Label Extension Schedule of Activities from that point onwards, starting from the Day 360/Month 12 visit.

- If the participant had been assigned to receive ARO-APOC3, they will be assigned to receive active ARO-APOC3 in the Open Label Extension Period of the study. Their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and until at least 3 months have passed since receiving the last dose of study drug. Once these criteria have been met, the participant will follow the Open Label Extension Schedule of Activities from that point onwards, starting from the Day 360/Month 12 visit.

6.1.1.1. Postprandial Substudy at Selected Sites in Australia, Canada, and the United States

FCS is a rare, inherited lipid disorder characterized by high levels of plasma TGs and chylomicrons, which may cause life-threatening acute pancreatitis (Williams 2018). Currently, the therapeutic management relies solely on a very low-fat diet (<20g fat/day), which is difficult to maintain long term and can impose a significant clinical and psychosocial burden on patients and caregivers. With the restricted diet, TGs may remain elevated. A postprandial substudy will be performed to evaluate the impact of ARO-APOC3 on postprandial serum TG levels in approximately 12 participants who received at least 2 consecutive doses of ARO-APOC3 in the Open Label Extension Period, have had 30 elapse since being administered their most recent ARO-APOC3 dose, and have fasting serum TGs levels ≤500 mg/dL. Refer to Appendix 6 for postprandial substudy details including eligibility criteria, design, methodology, schema, statistics, and the SOA.

Figure 1: Study Schema



Abbreviations: N=sample size; Q3M=every 3 months.
[a] Screening: review and stabilization of diet, medications, and laboratory values
[b] The duration of Parts A and B depend on when the participant entered Part A and when the dose was selected for Part B.

Table 3: Schedule of Activities: Randomized Period

Study Visit	Screening	Randomized Period														
					Months											
					1	2	3		4	5	6	7	8	9	10	11	12
Study Day	Day -56 to -1	Day 1[a]	Day 2	Day 15 (±2 Days) (Japan Only)	Days (Each ±5 Days, Except at Day 91)												
					30	60	90[b]	91[c]	120	150	180[b]	210	240	270[b]	300	330	360[b,o]
Informed consent	X																
Dietary counseling / maintain diet	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Review with participant signs and symptoms of pancreatitis and when to seek medical care	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Eligibility criteria[d]	X	X															
Height and weight[e]	X	X					X				X			X			X
Vital signs (BP, temperature, respiratory rate, heart rate)	X	X		X			X				X			X			X
Demographics	X																
Medical history	X	X															
Physical examination (symptom-directed after screening)	X	X		X			X				X			X			X
Single 12-Lead ECG[f]	X										X			X			X
Triplicate 12-Lead ECG[g]		X					X										
HBV/HCV serology screen	X																

Study Visit	Screening	Randomized Period														
					Months											
					1	2	3		4	5	6	7	8	9	10	11	12
Study Day	Day -56 to -1	Day 1[a]	Day 2	Day 15 (±2 Days) (Japan Only)	Days (Each ±5 Days, Except at Day 91)												
					30	60	90[b]	91[c]	120	150	180[b]	210	240	270[b]	300	330	360[b,o]
FSH (women not of childbearing potential to confirm postmenopausal status)	X																
Pregnancy test in women of childbearing potential (predose on dosing days)[h]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genotype (new sample or record from source documents, if available)[d]	X																
Clinical laboratory tests (predose on dosing days)[h]	X	X		X	X	X	X				X			X			X
Liver function tests (ALP, ALT, AST, total bilirubin), HbA1c, and CBC[i]					X	X	X		X	X	X	X	X	X	X	X	X
Lipid parameters (predose on dosing days)[j]	X	X			X	X	X		X	X	X	X	X	X	X[k]	X	X
Child-Pugh score (predose)	X[l]																
Anti-drug antibodies (predose on dosing days)		X			X		X				X			X			X
Full PK Subset[m]		X	X				X	X									

Study Visit	Screening	Randomized Period														
					Months											
					1	2	3		4	5	6	7	8	9	10	11	12
Study Day	Day -56 to -1	Day 1[a]	Day 2	Day 15 (±2 Days) (Japan Only)	Days (Each ±5 Days, Except at Day 91)												
					30	60	90[b]	91[c]	120	150	180[b]	210	240	270[b]	300	330	360[b,o]
Sparse PK Subset[n]		X					X										
IMP administration (Vial or PFS)[o]		X					X				X			X			X[p]
Injection site assessment (all sites)[q]		X					X				X			X			X
2-hour postdose observation (Japan only)		X[r]					X[r]										
24-hour postdose follow-up (all sites)			X					X									
Diet assessment[s]		X					X				X			X			X
Quality of Life Assessment (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-PAN26)		X					X				X			X			X
Concomitant medications/ therapies	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; CBC=complete blood cell count; COVID=coronavirus disease; ECG=electrocardiogram; EORTC QLQ=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire;

EQ-5D-5L=EuroQol 5-dimension instrument; FSH=follicle-stimulating hormone; HbA1c= glycated hemoglobin HBV=hepatitis B virus; HCV=hepatitis C virus; IEC=Independent Ethics Committee; IMP=investigational medicinal product; IRB=Institutional Review Board; PFS=prefilled syringe; PI=Principal Investigator; PK=pharmacokinetics; TG=triglyceride.

a. If a participant discontinues study participation early, then the Month 36 assessments (see Table 4) should be completed at the time of early discontinuation, if possible.
b. Assessments completed on dosing days are to be done predose, unless otherwise specified.
c. At Month 3, the 24-hour postdose visit will only occur for participants in the Full PK Subset at designated PK sites.
d. If required, sample for genotype analysis should be collected as soon as possible after informed consent is obtained. Review of medical history, concomitant medications, and diet assessment, as well as collection of laboratory samples for confirmation of all other eligibility criteria may occur up to 42 days (6 weeks) prior to Day 1. The sample used to confirm a qualifying baseline TG should be drawn after the site has confirmed the participant has maintained a stable diet for ≥4 weeks and stable background medications (see Table 5).
e. Height (cm) at screening visit only; weight (kg) at all indicated visits.
f. Single 12-lead ECG will be performed in the supine position after the participant has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.
g. Triplicate 12-lead ECG will be performed using validated ECG services equipment from a central facility approximately time-matched to whole blood PK collections for all participants. Triplicate measurements should be separated by approximately 1 minute with the patient in the supine or semi-supine position after resting comfortably for at least 5 minutes. At all timepoints, ECG assessments must be done prior to drawing the blood sample for PK assessments within 5 minutes prior to the PK blood collections at the 0.25 hour (15 min) postdose PK assessment, and within 10 minutes prior to all other PK collection times. For the prespecified "Full PK Subset", the triplicate ECGs are to be collected at predose, and the PK assessments at 0.25, 1, 3, 6, and 24 hours postdose at Day 1 and Month 3 after study treatment administration (ARO-APOC3 or placebo). For the prespecified "Sparse PK Subset", the triplicate ECGs are to be collected at predose and 2 hours postdose at Day 1 and Month 3 after study treatment administration (ARO-APOC3 or placebo).
h. Blood and urine samples will be collected at screening after obtaining informed consent. With prior written consent, a separate blood sample will be collected and stored for future research at Day 1 and Month 3. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, lab samples may be collected at alternative location (eg, home health [except in countries where this not allowed], local laboratory) using the central laboratory kit and shipped to the central laboratory for analysis. If central laboratory kit collection is not available, local laboratory safety testing may be permitted only in limited circumstances and only with prior Sponsor approval. Beginning on Day 1, at study visits with blood draws for clinical laboratory tests or lipid parameter measurements, participants will have fasted for at least 10 hours prior to blood draw unless otherwise specified. Samples collected on Month 1 and 2 will be analyzed for HbA1c only. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Appendix 3).
i. Any elevation in ALP, ALT, AST, or total bilirubin test results will be evaluated and followed as described in the consensus guidelines for suspected drug-induced liver injury during clinical trials (Appendix 2). HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Appendix 3). The CBC will be used to monitor platelet counts. If a participant does not enter the extension period, then continue monthly assessments of liver function tests and CBC for 12 months after the last dose of IMP.
j. Whole blood for PD lipid analysis will be drawn after the site has confirmed the participant has maintained a stable diet for ≥4 weeks and stable background medications (see Table 5). Only TGs are required at screening. Lipid parameter testing must be done after the participant has fasted for ≥10 hours before collection at each study visit.
k. At Month 10, collect lipids twice, 2 to 7 days apart, for calculation of study endpoints. The second collection at Month 10 may be done through home health (except in countries where this is not allowed).
l. Child-Pugh score will be determined based upon standard of care clinical evaluations by the Investigator and predose Day 1 baseline laboratory values.
m. Full PK Subset: Whole blood for plasma PK samples will be drawn in approximately 36 participants (24 active and 12 placebo) enrolled at designated PK sites, including all participants enrolled at sites in Japan. PK collection time points (time window) are at predose, 0.25 hour (±5 minutes), 1 hour (±5 minutes), 3 hours (± 10 minutes), 6 hours (± 30 minutes), and 24 hours (± 1 hour) postdose at Day 1 and Month 3. For postdose samples that require next-day collection, participants may return to the clinical facility to have their blood drawn or they may opt to have their PK samples collected through home health (except in countries where this is not allowed).
n. Sparse PK Subset: Participants not in the Full PK Subset will have whole blood for plasma PK samples drawn predose and at 2 hours (± 10 minutes) postdose at Day 1 and Month 3 after study treatment administration (ARO-APOC3 or placebo).
o. Upon approval of global Protocol Amendment 6 by the relevant regulatory authorities and IECs/IRBs, the PI (or appropriately trained and qualified clinical staff designated by the PI) will administer IMP using a PFS to participants assigned to the 50 mg dose cohort (ARO-APOC3 50 mg or volume-matched placebo), once available at the study site. A PFS will not be introduced in the 25 mg dose cohort in the randomized period.

p. At Month 12, all participants will receive the first open-label dose of ARO-APOC3 at the dose corresponding to their study treatment dose in the randomized period. Thus, participants who received ARO-APOC3 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (ie, ARO-APOC3 25 mg Q3M or 50 mg Q3M).
q. For all participants, the injection site will be assessed for any signs of localized reaction after IMP administration by the PI (or appropriately trained and qualified clinical staff designated by the PI).
r. The injection site will be assessed for any signs of localized reaction after administration. At these visits, participants enrolled in Japan will remain at the study site for 2 hours after completion of dosing, for observation and the following assessments: vital signs, triplicate 12-lead ECG and plasma PK sample at 1h (±5 minutes) post dose (as per the Full PK Subset collection schedule), and documentation of any adverse events. All participants enrolled in Japan will also have plasma PK samples and triplicate ECG monitoring through 6 hours after the first and second doses; see footnotes (g) and (m) for additional details.
s. Diet will be recorded on at least 3 of the past 5 days before the study visit.
.

Table 4: Schedule of Activities: Extension Period

	Extension Period									
	Months									
Study Visit	**13**	**14**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36/ EOS/ ET[a]**
	Days (Each ±5 Days)									
Study Day	**390**	**420**	**450[b]**	**540[b]**	**630[b]**	**720[b]**	**810[b]**	**900[b]**	**990[b]**	**1080**
Dietary counseling / maintain diet	X	X	X	X	X	X	X	X	X	X
Review with participant signs and symptoms of pancreatitis and when to seek medical care	X	X	X	X	X	X	X	X	X	X
Weight			X	X	X	X	X	X	X	X
Vital signs (BP, temperature, respiratory rate, heart rate)			X	X	X	X	X	X	X	X
Physical examination (symptom-directed)			X	X	X	X	X	X	X	X
Single 12-Lead ECG[c]			X	X	X	X	X	X	X	X
Pregnancy test in women of childbearing potential	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[d,e]	X	X	X	X	X	X	X	X	X	X
Liver function tests (ALP, ALT, AST, total bilirubin), HbA1c, and CBC[e]	X	X	X	X	X	X	X	X	X	X
Lipid parameters[f]	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies			X	X		X				X
IMP administration (Vial or PFS)[g]			X	X	X	X	X	X	X	
Injection site assessment (all sites)[h]			X	X	X	X	X	X	X	
Diet assessment[i]										X
Quality of Life Assessment (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-PAN26)										X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain, or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; CBC=complete blood cell count; ECG=electrocardiogram; EORTC QLQ=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EOS=end of study;

EQ-5D-5L=EuroQol 5-dimension instrument; ET=early termination; IEC=Independent Ethics Committee; IMP=investigational medicinal product; IRB=Institutional Review Board; PFS=prefilled syringe; PI=Principal Investigator.

a. If a participant discontinues study participation early, then the Month 36 assessments should be completed at the time of early discontinuation, if possible.
b. Assessments completed on dosing days are to be done predose, unless otherwise specified.
c. Single 12-lead ECG will be performed in the supine position after the participant has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.
d. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, lab samples may be collected at alternative location (eg, home health [except in countries where this is not allowed], local laboratory) using the central laboratory kit and shipped to the central laboratory for analysis. If central laboratory kit collection is not available, local laboratory safety testing may be permitted only in limited circumstances and only with prior Sponsor approval. At study visits with blood draws for clinical laboratory tests or lipid parameter measurements, participants will have fasted for at least 10 hours prior to blood draw unless otherwise specified. Samples collected on Month 13 and 14 will be analyzed for HbA1c only.
e. Any elevation in ALP, ALT, AST, or total bilirubin test results will be evaluated and followed as described in the consensus guidelines for suspected drug-induced liver injury during clinical trials (Appendix 2). HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Appendix 3). The CBC will be used to monitor platelet counts.
f. Lipid parameter testing must be done after the participant has fasted for ≥10 hours before collection at each study visit.
g. Upon approval of global Protocol Amendment 6 by the relevant regulatory authorities and IECs/IRBs, the PI (or appropriately trained and qualified clinical staff designated by the PI) will administer IMP using the 50mg PFS to participants in the ARO-APOC3 50 mg cohort once it is available at the study site. Similarly, upon approval of global Protocol Amendment 7 by the relevant regulatory authorities and IECs/IRBs, the PI (or appropriately trained and qualified clinical staff designated by the PI) will administer IMP using the 25 mg PFS to all study participants once available at the study site. In addition, upon approval of global Protocol Amendment 7, subjects will be offered the option to self-administer the study drug at the study site under supervision of the PI or designated staff.
h. For all participants, the injection site will be assessed for any signs of localized reaction after IMP administration by the PI (or appropriately trained and qualified clinical staff designated by the PI).
i. Diet will be recorded on at least 3 of the past 5 days before the study visit.

6.1.2. Informed Consent

Prior to commencement of any screening procedures, the PI or designee will inform the participant about the nature and purpose of the study, including the risks and benefits involved, possible AEs, the fact that their participation is voluntary, and will provide a copy of the IRB/IEC-approved ICF for review. Each participant will acknowledge receipt of this information by giving written informed consent for their involvement in the study in the presence of the PI or designee, who will also sign and date the ICF. Time of consent will be recorded in the site's source document for each participant. The original signed consent form will be retained by the PI and a copy of the original will be given to the participant.

Informed consent will be performed per the principles of the ICH Good Clinical Practice (GCP) procedures. Documentation of the participant's fulfillment of the entry criteria, for all participants considered for the study and subsequently included or excluded, is to be completed by the PI, or medically qualified designee. Documentation of screening failure details will be recorded using eligibility screening forms or a participant screen failure log. Procedures outlined in the SOA (Table 3) will be performed. Timing will abide by fasting restrictions outlined in Section 8.2.1.

No study assessment or procedure will occur before the participant has signed the ICF.

6.1.3. Screening

The SOA for Screening is provided in Table 3. Confirmation of ≥4 weeks diet, lifestyle, and medication regimen stabilization will precede qualifying fasting lipid parameter laboratory assessments. Enrolled participants will be counseled to remain on a diet comprising ≤20 g of fat per day throughout the study, as recommended by the PI and in accordance with local standard of care. For example, in the United States, PIs may refer to the guidelines established by the American Heart Association and American College of Cardiology (Van Horn 2016). The specifics of the diet will be at the discretion of the PI based on each individual's specific diagnosis and medical needs. Dietary assessment and counseling will begin during the screening period, with dietary counseling performed throughout the study to facilitate compliance. This diet may vary at the PI's discretion.

All other eligibility criteria assessments and laboratory sample collections required to confirm participant`s eligibility (Section 7) must be completed within 42 days (6 weeks) prior to Day 1. Lipid parameters assessed during the screening period for eligibility and throughout the study will be collected from participants in a fasted state (no food or drink except water and required medication for at least 10 hours).

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

6.1.4. Treatment Period

Participants who successfully pass the eligibility requirements at screening will be enrolled into the study. All dose cohorts will enroll in parallel, with participants randomly assigned 2:1:2:1 to the dose cohorts (ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively).

In the 12-month randomized period (Table 3), each participant will receive SC injection of double-blinded active treatment or placebo Q3M, as follows:

- ARO-APOC3 25 mg (n=24) or volume-matched placebo (n=12) Q3M; or
- ARO-APOC3 50 mg (n=24) or volume-matched placebo (n=12) Q3M

In the 24-month extension period (Table 4), each participant will receive open-label active treatment Q3M. See Section 6.3 for a discussion of dosing in these parts of the study.

Each participant will present to the clinical facility on Day 1 (baseline). Study dose administration is on Day 1, which must occur within 8 weeks of initiating screening assessments. On arrival at the clinical facility, the PI or designee will meet with the participant to reiterate all study procedures and encourage participants to ask any questions. All participants will undergo a check-in procedure during which questions will be asked regarding protocol compliance and safety monitoring. Participants will return to the clinical facility for visits as per the SOA, with each visit generally lasting approximately 2 hours, unless additional monitoring is needed at the PI's discretion for safety reasons.

All visits will be conducted at the clinical study site. At the discretion of the PI and with prior Sponsor approval, use of home health care services to conduct study assessments at non-dosing visits is permissible (except in countries where this is not allowed). Use of home health care services is contingent upon compliance with local laws and regulations, and the capability of the PI to adequately monitor participant safety. In cases where home health care services are to be used, this approach, and any specific risks associated with it, must be clearly outlined in the IEC/IRB-approved ICF.

Some participants enrolling into this study may have baseline elevations in transaminases. Refer to Appendix 2 for treatment modification guidelines in participants with elevated ALT.

Parameters to be assessed and the timing of assessments are provided in the SOA in Table 3 and Table 4. At regular intervals during the study, participants will undergo the following evaluations: medical history review, physical examinations, vital sign measurements (blood pressure, temperature, heart rate, respiratory rate), weight measurement, AE monitoring, ECGs, pregnancy test (females of childbearing potential), laboratory assessments, and concomitant medication review. Blood samples will be collected for HDL-C, LDL-C, VLDL-C, TG, and other specified lipid or metabolic parameters, hematology, serum lipase and insulin, HbA1c, C-peptide, coagulation, and chemistry analysis. Urinalysis will include spot urine creatinine and spot urine protein. Participants will have fasted for at least 10 hours.

Clinically significant changes including AEs will be followed until resolution is achieved or events are considered medically stable.

6.1.5. Pharmacokinetics Subset

All participants will have a predose and postdose PK sample collected at Day 1 and Month 3.

In a subset of participants undergoing full PK (24 active, 12 placebo), including all participants enrolled at sites in Japan, PK will be measured predose and up to 24 hours serially postdose on Day 1 and Month 3. Pharmacokinetic time points (time window) on Day 1 and Month 3 are at predose and at 0.25 hour (±5 minutes), 1 hour (±5 minutes), 3 hours (±10 minutes), 6 hours (±30 minutes), and 24 hours (±1 hour) postdose. If the recommended time window is missed, every attempt should be made to collect this PK sample as soon as possible within the same study visit. Only samples collected from participants receiving active treatment will be included in the PK analysis. For postdose samples that require next-day collection, participants may return to the clinical facility to have their blood drawn or they may opt to have their PK samples collected through home health (except in countries where this is not allowed).

6.1.6. Adverse Event Monitoring

Safety assessments will include AEs and SAEs, physical examinations, vital sign measurements (blood pressure, heart rate, temperature, and respiratory rate), ECGs, clinical laboratory tests, concomitant medications/therapy, and reasons for treatment discontinuation. Safety assessments will be performed at the time points specified in the SOA from informed consent through the Month 36/EOS visit, including a 2-hour observational period after dosing on Day 1 and Day 90 in participants enrolled in Japan (Table 3 and Table 4). The Sponsor will perform periodic review/monitoring of safety data, including safety laboratory results, on a monthly basis, at a minimum.

TEAEs and SAEs are defined as AEs that occur following investigational medicinal product (IMP) administration or a pre-existing condition exacerbated following IMP administration. The TEAE reporting period begins after the first dose and extends until 6 months after the last dose or the EOS visit is complete, whichever is later. All SAEs that occur during the reporting period, in addition to reporting via eCRFs, must also be reported to the Sponsor via the SAE report form immediately upon being notified. All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event causality is otherwise explained, or until the participant is lost to follow-up. If the PI learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the IMP, the PI will promptly notify the Sponsor. Laboratory or diagnostic assessment (eg, ECG) abnormalities will be reported as AEs if considered clinically significant by the PI. Laboratory or diagnostic assessment abnormalities not reported as AEs are not to be reported as clinically significant in the study database.

6.1.7. Early Termination

If a participant discontinues from the study prematurely, every reasonable effort will be made to perform the Month 36/EOS/ET visit within 30 days of the decision to terminate a participant's study participation. The reason for early termination will be documented in source documents

and eCRF. Participants who discontinue ARO-APOC3 due to an SAE will be encouraged to remain available for follow-up for medical monitoring until resolution.

6.2. Number of Participants

Approximately 72 participants will be enrolled in the study. This will include approximately 12 participants enrolled in Japan.

6.3. Treatment Assignment

All dose cohorts will enroll in parallel with participants randomly assigned 2:1:2:1 to the dose cohorts (ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively).

In the randomized period, each participant will receive SC injection of double-blinded active treatment or placebo Q3M, as follows:

- ARO-APOC3 25 mg (n=24) or volume-matched placebo (n=12) Q3M; or
- ARO-APOC3 50 mg (n=24) or volume-matched placebo (n=12) Q3M

In the extension period, each participant will receive open-label active treatment Q3M, as follows:

- In Part A, participants will remain blinded to their treatment assignment from the randomized period and will initially receive open-label ARO-APOC3 at the dose corresponding to their study treatment dose in the randomized period. Thus, participants who received ARO-APOC3 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (ie, ARO-APOC3 25 mg Q3M or 50 mg Q3M).
- In Part B, after the last participant completes the randomized period, all participants will switch to ARO-APOC3 25 mg Q3M prepared as a PFS.

6.4. Dose Adjustment Criteria

There will be no dose escalation or dose reduction.

6.4.1. Data Safety Committee and Safety Criteria for Adjustment or Stopping Doses

An independent DSC will be assembled to review safety data after approximately 10 participants have received at least 1 dose of IMP and after half of the total number of participants planned for enrollment have received at least 1 dose of IMP. This group may also be asked by the study Sponsor to meet on an ad hoc basis to review safety data and make recommendations related to the study. Planned safety reviews will include evaluations for imbalances between active and placebo groups for AEs and SAEs. The DSC may be asked to review safety data at additional unscheduled meetings should a potential safety signal be detected. The DSC may also make recommendations to the Sponsor for any follow-up actions as well as modifying, stopping, or continuing the study as planned. The DSC will review blinded data initially in open session, with Sponsor present. At the open session, the Sponsor will provide updated information on

enrollment and conduct of the study and advise the DSC of any pertinent information regarding the study, which may be relevant to DSC deliberations, including safety concerns based on blinded data. The open session will be followed by a closed session in which unblinded data will be reviewed by the DSC without Sponsor presence, as described in the DSC charter. The DSC members will take all necessary and appropriate steps to safeguard the confidentiality of unblinded treatment information.

The DSC **may** recommend to the Sponsor to pause additional dosing to allow for time to evaluate safety data and recommend the action to be taken, which may include, but is not limited to, one of the following:

- The study may continue without modifications
- The study may continue with modifications
- The study should be terminated
- The study should be temporarily suspended
- Other changes

The Sponsor or PI can discontinue any participant at any time.

A decision to modify the study or pause/suspend dosing in an individual participant or group of participants, or to halt enrollment temporarily or permanently may be indicated based on any of the following:

- Any confirmed pregnancy in the study will lead to permanent discontinuation of IMP dosing of that participant.
- Elevated ALT may require interruption of study treatment (Appendix 2).
- Participants needing apheresis or other emergent interventions indicated to lower TG should have their next dose postponed until they are clinically stable based on the assessment of the PI in consultation with the medical monitor.
- Participants experiencing bouts of acute pancreatitis should have their next dose postponed until they are clinically stable based on the assessment of the PI in consultation with the medical monitor. The PI will assess the patient and decide on a therapeutic plan with regards to the episode of acute pancreatitis as per the local standard of care; this may include referral to the participants clinician or other specialists when required. For any participant experiencing acute pancreatitis, all TG levels will be provided by the central laboratory to the Investigator and Medical Monitor. The participant will be unblinded to their assigned treatment allocation, and from that point forward the participant will be transitioned to the Open Label Extension period of the study. This will be documented via the IWRS.
  - If the participant had been assigned to receive placebo, they will be re-assigned to receive active ARO-APOC3 in the Open Label Extension Period of the study. Their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor. Once considered clinically stable, the participant will follow the Open Label Extension

Schedule of Activities from that point onwards, starting from the Day 360/Month 12 visit.

  - If the participant had been assigned to receive ARO-APOC3, they will be assigned to receive active ARO-APOC3 in the Open Label Extension Period of the study. Their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and until at least 3 months have passed since receiving the last dose of study drug. Once these criteria have been met, the participant will follow the Open Label Extension Schedule of Activities from that point onwards, starting from the Day 360/Month 12 visit.

- Participants who meet IMP discontinuation criteria based on HbA1c criteria during the study (Appendix 3) will discontinue from IMP and will be asked to continue with study follow-up assessments until 6 months following the participant's last dose.

6.5. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study at any time. The circumstances under which the study may be terminated include:

- Discontinuation of the study is in the interest of the health of participants.
- Continuation of the clinical trial no longer serves a scientific purpose.

Reasons will be provided in the event of this happening. The PI reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.

6.6. Discussion of Study Design, Including Choice of Control Group

The objectives of the study are to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS.

Participants with diagnosis of FCS, as per study inclusion criteria, who are confirmed to be on a stable diet and on stable regimen of lipid-lowering and diabetes mellitus therapy, as applicable (Section 6.1.3), will complete all remaining eligibility assessments in accordance with the SOA (Table 3). The treatment period will begin on Day 1 and will continue for 36 months. Dietary counseling will commence at the start of the screening period and will be reinforced at intervals throughout the treatment period. This approach is necessary to minimize the potential effects of dietary changes that can alter TG levels and confound interpretation of study results.

A placebo-controlled design was chosen for the randomized period because it would have been impractical to maintain blinding with an active control. All participants in active and placebo groups on lipid-lowering therapies should remain on a stable regimen during the study.

In response to diabetes evaluations, adjustments to treatment medication are allowed at the discretion of the PI (refer to Section 8.2.3). Compared with the potent effect of ARO-APOC3 in lowering TG levels, other first-line therapies have modest effects on TG. For example, patients with SHTG receiving omega-3 fatty acids had only a 33% placebo-adjusted reduction in TG (Bays 2011), and patients with mild TG elevations receiving gemfibrozil had a 31% reduction in TG (Rubins 1999). Thus, additional TG and lipid-lowering effects are expected when

ARO-APOC3 is used with an optimal lipid-lowering therapy. In this Phase 3 study, concomitant use of optimal statin therapy, nicotinic acid/niacin, omega-3 fatty acids (prescription or over-the-counter [OTC]), or fibrates or other lipid management regimens will be permitted as long as the participants have had a stable regimen for at least 4 weeks prior the screening laboratory assessments and will agree to stay on this baseline regimen during the treatment period. Randomization will be stratified by level of TG at screening (≥2000 mg/dL vs <2000 mg/dL).

An open label design without a control group was chosen for the extension period to allow all participants to receive active treatment. The duration of treatment and assessment is intended to ensure adequate exposure to ARO-APOC3 to evaluate the efficacy and safety for its long-term use.

6.7. Rationale for Dose and Schedule of Administration

In the Phase 1 study evaluating ARO-APOC3 in healthy volunteers, doses of 10, 25, and 50 mg consistently reduced serum APOC3 and TG levels through Week 16. A gradual rise in these PD parameters occurred in several healthy volunteers after Week 16, and an increase from nadir levels occurred after approximately Week 8 in the 50 mg cohorts. A clearer dose response was seen with HDL-C levels, with dose-dependent HDL-C increases demonstrated with increasing doses. While a limited number of participants were enrolled in the Phase 1 study, data available for patients with HTG and chylomicronemia showed that ARO-APOC3 50 mg administered on Days 1 and 29 maintained APOC3 and TG reduction through Week 12 after the second dose. Additional analyses from the Phase 1 Study AROAPOC31001 indicate that participants with genetically confirmed FCS achieved similar percent reductions from baseline in APOC3 and TG, compared with participants with chylomicronemia without genetically confirmed FCS.

Dose simulations of serum APOC3 and TG responses using a population PD model developed from the data collected in Phase 1 Study AROAPOC31001 indicate that there probably will be only modest incremental improvement in further TG reduction comparing 100 mg vs 50 mg Q3M dosing regimens. Therefore, limiting the dose to 50 mg Q3M in this Phase 3 study should help optimize the benefit-to-risk ratio for participants with FCS. Direct clinical observation and modeling results also suggested that participants with chylomicronemia including FCS may have a shorter duration of ARO-APOC3 effect, potentially requiring higher doses for patients with FCS as compared to the general SHTG population. Therefore, a dose lower than 25 mg Q3M is not recommended for patients with FCS. An examination of the limited data from study AROAPOC31001 did not reveal a major difference in the safety profile between the 25 mg and 50 mg doses, suggesting that the benefit-to-risk ratio should be further studied in more patients with FCS for these 2 dose levels. The recommended doses to be studied in this Phase 3 trial are therefore 25 mg Q3M and 50 mg Q3M.

The observations regarding an increase in HbA1c in subjects treated with ARO-APOC3 made during an administrative analysis from the Phase 2 studies have been addressed by updated risk mitigation strategies as delineated in Appendix 3. It is important to also note that these observations were limited to a subset of patients with diabetes (especially those with poorly controlled diabetes) and therefore the majority of subjects in the AROAPOC3-3001 study would not be impacted by the study drug discontinuation criteria outlined in the risk mitigation strategy. In addition, these observations are based on an interim data cut and hence incomplete and may be confounded by multiple other factors such as baseline HbA1c, background concomitant

medications including insulin and lipid-lowering therapies (statins and niacin) and anti-hypertensives (diuretics). The results of the administrative analysis also demonstrate a robust and clinically relevant PD profile for ARO-APOC3 in a similar patient population (SHTG) and, given the risk mitigation strategy proposed, the benefit from continuing the ARO-APOC3 50 mg dose cohort (such as reduced risk of pancreatitis) outweigh the noted risk. Therefore, both doses 25 mg and 50 mg dose cohorts will continue into the OLE study until further evidence from FCS subjects is provided.

The higher dose of 50 mg is approximately 1/420th of the NOAEL (300 mg/kg) from 4-week/3-dose GLP toxicology studies in both rats and monkeys, assuming weight-based conversion and an average 70-kg participant. In chronic GLP toxicity studies, the NOAEL was 15 mg/kg in the rat and 180 mg/kg in monkeys. Assuming a 70-kg participant, this translates into a safety margin of approximately 20-fold for the proposed dose of 50 mg in this study based on the rat NOAEL, and 250-fold based on the monkey NOAEL. It should also be noted that the dose frequency in this proposed study is Q3M, whereas the dose frequency in chronic toxicology studies (6-month rat and 9-month monkey) was every 4 weeks. Therefore, there is a wide margin of safety between the planned clinical doses and animal toxicology study NOAELs.

As of the database lock date (16 May 2024) for the primary analysis, an analysis of the topline results from the double-blind period of the AROAPOC3-3001 Phase 3 trial has been completed. ARO-APOC3 25 mg or 50 mg administered SC Q3M demonstrated significant and durable reductions in APOC3, TGs, and atherogenic lipids and lipoproteins in subjects with genetically confirmed or clinical FCS. These therapies were generally well tolerated and were associated with a significantly lower incidence of acute pancreatitis, which is the most serious complication regularly faced by FCS patients. Based on population PK and PD analyses, ARO-APOC3 25 mg Q3M is appropriate for adult patients with FCS, with no adjustment recommended based on patient body weight, body mass index, sex, age, race/ethnicity, baseline TG level, mild or moderate renal impairment, or mild hepatic impairment. Population PD analysis also supported the use of ARO-APOC3 25 mg Q3M for all patients with FCS, regardless of pathogenic variants, concomitant TG-lowering or lipid. Global Protocol Amendment 7 is being issued to consolidate the implementation of this selected dose during the Open Label Extension Part B.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Participant Inclusion Criteria

To be eligible for enrollment, participants must meet all the following inclusion criteria:

1. Males or nonpregnant (who do not plan to become pregnant), nonlactating females ≥18 years of age (or ≥19 years of age, where applicable according to the local regulation)
2. Able and willing to provide written informed consent prior to the performance of any study-specific procedures
3. Fasting TG ≥10 mmol/L (≥880 mg/dL) at screening, that is refractory to standard lipid-lowering therapy (sample drawn after at least the minimum time on stable lipid-lowering regimen described in Table 5). Two repeat tests are allowed to qualify.

4. A diagnosis of FCS based on a documented history of fasting TG levels in excess of 1000 mg/dL on repeated testing (for at least 3 prior occasions), **and at least one** of the following:
    a. A supportive genetic test (from a source-verifiable medical record or based on screening genotype). Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including *LPL*, *APOC2*, *APOA5*, *GPIHBP1*, *GPD1*, or *LMF1*; or evidence of low LPL activity (<20% of normal) based on source-verifiable documentation; or
    b. Documented history of recurrent episodes of acute pancreatitis, not caused by alcohol or cholelithiasis; or
    c. Documented history of recurrent hospitalizations for severe abdominal pain without other explainable cause; or
    d. Documented history of childhood pancreatitis; or
    e. Family history of hypertriglyceridemia-induced pancreatitis.
5. Willing to follow dietary counseling as per PI judgment based on local standard of care, consistent with an intake of ≤20 g of fat per day during the study
6. If on medications for management of type 2 diabetes, or other medications specified in Table 5 (see Section 8.2.3), the dosing regimen must be stable before collection of qualifying lipid parameter at screening.
7. Participants with a medical history of clinical atherosclerotic cardiovascular disease (ASCVD) or those with elevated 10-year ASCVD risk (eg, ≥7.5% per American Heart Association / American College of Cardiology risk calculator) must be on appropriate lipid-lowering therapy as per local standard of care (ie, including moderate to high intensity statin, as indicated) prior to collection of qualifying TG levels.
8. Participants of childbearing potential must agree to use a highly effective form of contraception in addition to a male condom (Appendix 1), during the study and for at least 24 weeks after the last dose of IMP. Women of childbearing potential on a hormonal contraceptive must be stable on the medication for ≥2 menstrual cycles prior to Day 1. Men must not donate sperm during the study and for at least 24 weeks after the last dose of IMP.

NOTE: All laboratory tests used as inclusion criteria will be assessed by a central laboratory and may be repeated once (except for fasting TG required per Inclusion Criterion #3, which can be repeated twice), and the repeat value may be used for inclusion purposes. Local laboratory testing may be permitted in limited circumstances and only with prior Sponsor approval.

7.2. Participant Exclusion Criteria

A potential participant will be excluded from the study if any of the following criteria apply:

1. Current use or use within the last 365 days from Day 1 of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule
2. Diabetes mellitus with any of the following:
    a. Newly diagnosed within 12 weeks of screening

   b. HbA1c ≥9.0% (or ≥75 mmol/mol International Federation of Clinical Chemistry [IFCC] units) at screening

3. Active pancreatitis within 12 weeks before Day 1
4. History of acute coronary syndrome events (myocardial infarction or unstable angina) or procedures (coronary revascularization, angioplasty, or stenting) within 24 weeks of Day 1
5. History of major surgeries within 12 weeks of Day 1 (including cardiac and vascular surgeries, eg, coronary artery bypass graft)
6. Any of the following laboratory values at screening:
   a. ALT or AST ≥3×ULN at screening
   b. Total bilirubin ≥1.5×ULN (if the participant has a prior diagnosis and documentation of Gilbert's syndrome, then total bilirubin must be ≤3 mg/dL at screening)
   c. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 at screening, using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (Levey 2009)
   d. Spot urine protein/spot urine creatinine ratio greater than 3 grams per day
   e. Clinically significant abnormality in prothrombin time, partial thromboplastin time, or INR
7. Uncontrolled hypertension (blood pressure >160/100 mmHg at screening); if untreated, participant may be rescreened once hypertension is treated and controlled
8. Use of any of the following:
   a. Systemic use of corticosteroids or anabolic steroids within 4 weeks prior to Day 1 or planned use during the study
   b. GLP-1 receptor agonists
   c. Plasma apheresis within 4 weeks prior to Day 1 or planned during the study
   d. Blood donation of 50 to 499 mL within 4 weeks of collection of qualifying lipid parameter collection or of >499 mL within 8 weeks of qualifying lipid parameter collection
9. On treatment with HIV antiretroviral therapy (Note: determination of HIV status is not a required study procedure)
10. Seropositive (hepatitis B surface antigen [HBsAg] +) for hepatitis B virus (HBV) or hepatitis C virus (HCV) (HCV seropositivity requires positive test for antibodies confirmed with positive test for HCV RNA)
11. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%
12. Clinical evidence of primary hypothyroidism (screening TSH > ULN and free T4<LLN), primary subclinical hypothyroidism (screening TSH > ULN and free T4 WNL), or secondary hypothyroidism (screening TSH < LLN and free T4< LLN)
13. History of stroke, transient ischemic attack, or peripheral artery disease within 24 weeks of first dose

14. History of bleeding diathesis or coagulopathy
15. Current diagnosis of nephrotic syndrome
16. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week for women and men (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)
17. History of malignancy within the last 2 years prior to the date of consent requiring systemic treatment except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Currently receiving systemic cancer treatment(s) or, in the PI's opinion, at risk of relapse for recent cancer.
18. Use of an investigational agent or device within 30 days or within 5 half-lives, based on plasma PK (whichever is longer) prior to Day 1 or current participation in an interventional investigational study. Participants previously exposed to ARO-APOC3 or ARO-ANG3 will require a washout period of at least 1 year from last dose.
19. Any concomitant medical or psychiatric condition or social situation or any other situation that, in the PI's judgment, would make it difficult to comply with protocol requirements or put the participant at additional safety risk.
20. Clinical evidence of Cushing's syndrome.

All laboratory tests used as exclusion criteria may be repeated once and the repeat value may be used for exclusion purposes.

7.3. Participant Withdrawal Criteria

Participants will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the PI, medically trained designee, or Sponsor may withdraw a participant from the study, per the following criteria, to protect the participant's health:

- The need to take medication that may interfere with study measurements
- Intolerable/unacceptable adverse experiences
- Major violation of or deviation from study protocol procedures
- Noncompliance of participant with protocol
- Participant is unwilling to proceed, or consent is withdrawn
- Withdrawal from the study if, in the PI's judgment, it is in the participant's best interest

The reasons for withdrawal will be recorded on the eCRF and included in the final clinical study report (CSR), along with any AEs and any necessary medical treatment.

If a participant is withdrawn from the study due to significant AE or SAE, the PI, or medically trained designee, will evaluate the urgency of the event. If the situation warrants, the PI, or medically trained designee, will take appropriate diagnostic and therapeutic measures. If the situation is not an immediate emergency, the PI, or medically trained designee, at the clinical study facility will attempt to contact the medical monitor or medically qualified designee for consultation. No medical help, diagnosis, or advice will be withheld from the participant due to

an inability to contact the medical monitor. The participant will be encouraged to remain available for follow-up medical monitoring. The Sponsor will be notified as soon as possible of any participant withdrawals.

8. TREATMENT OF PARTICIPANTS

8.1. Description of Study Drug

There will be 2 study treatments; one active (test formulation) and one placebo (reference formulation), both administered by SC injection.

Test Formulation: The test formulation is active ARO-APOC3 Injection (also referred to as ARO-APOC3) administered SC. The API contained in ARO-APOC3 is a synthetic, double-stranded, siRNA duplex conjugated to a NAG-targeting ligand to facilitate hepatocyte delivery.

Reference Formulation: The reference formulation is placebo: normal saline (0.9%) administered SC, volume-matched to the corresponding ARO-APOC3 dose volume.

Refer to Section 9 for additional information about study drug materials and management.

8.2. Restrictions and Concomitant Medications

8.2.1. Fasting

On the day of dosing or on other days with blood draws for lipid parameter measurement, participants will have fasted for at least 10 hours prior to blood draw unless otherwise specified.

8.2.2. Recreational Drugs or Alcohol

Participants will be instructed to abstain from consuming alcohol for at least 48 hours prior to their clinic visit on dosing days and during the clinic visit. In addition, participants will be instructed to refrain from regular use of alcohol (ie, 14 units per week for women and men [1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol]) for the study duration. Participants must abstain from use of recreational drugs throughout the study.

8.2.3. Concomitant Medications

Use of optimal statin therapy, nicotinic acid/niacin, omega-3 fatty acids (prescription or OTC), or fibrates or other lipid management regimens, is acceptable if the participant has been on a stable regimen for the period specified in Table 5 before the screening qualifying laboratory assessments and if the participant is willing to maintain a constant dosing regimen during the treatment period. During the study, use of any concomitant medications, including lipid-lowering therapies, hormonal contraceptives, insulin regulating therapies, and glucose lowering therapies, should only be used in accordance with local standard of care.

Adjustments to medication regimens during the study, including lipid-lowering and diabetes mellitus therapies, are only allowed if, at the discretion of the PI, they are needed to provide adequate supportive care. These changes must be documented in the eCRF no later than at the

next study visit. Participants will be instructed to inform the PI of the details (indication, dose, and dates of administration) if they do take any medication, and these details will be recorded in the eCRF. Before making any changes to a participant's prescription lipid-lowering therapy, the medical monitor or designee should be notified. Use of apheresis during the study will also be recorded in the eCRF.

Table 5: Restricted Concomitant Medications

Restricted Background Medications	Time on Stable Regimen Before Qualifying Screening Laboratory Assessments
Lipid-lowering therapies (including statins)	> 4 weeks
Fibrates	> 6 weeks
PCSK9 inhibitors	> 8 weeks
Beta-blockers, Thiazide diuretics	> 4 weeks
Retinoids	> 8 weeks
Atypical antipsychotics	> 12 weeks
Diabetes mellitus medications	> 12 weeks
Oral estrogens, tamoxifen, raloxifene	> 16 weeks
Immunosuppressants	> 24 weeks

Abbreviation: PCSK9= proprotein convertase subtilisin/kexin type 9

8.2.4. Central Laboratory Lipid Testing

Some laboratory results may potentially unblind treatment assignment to ARO-APOC3. Central laboratory results of fasting serum TG and other lipid parameters (LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, APOB-48, LP[a], APOB-100, total APOB, APOC-III, APOC-II, APOA-I, and APOA-V) will not be reported to the PI and will be blinded after Day 1. After Day 1, PIs should not perform local non-protocol testing of these analytes during a participant's study participation from the first dose of IMP until after the participant's Month 13 visit.

Between the Month 10 and Month 13 visits, in cases where a participant with a baseline LDL-C ≥130 mg/dL (≥3.37 mmol/L) experiences an increase from baseline ≥25% at 2 consecutive visits, LDL-C values for this participant will be unblinded for the remainder of the study and the central laboratory will notify a designated independent unblinded medical monitor for medical follow-up. Between the Month 10 and Month 13 visits, in cases where a participant with a baseline LDL-C <130 mg/dL (<3.37 mmol/L) subsequently experiences an increase to ≥130 mg/dL (≥3.37 mmol/L) at 2 consecutive visits, LDL-C will be unblinded for this participant and the central laboratory will notify the PI and medical monitor for medical follow-up. For all such cases, the PI will contact the participant to provide appropriate medical follow-up including dietary and medication compliance counseling, which may also include modification to the participant's lipid-lowering regimen according to country-specific guidelines (eg, initiate statin therapy or increase the statin dose for participants who are already on treatment).

If a participant with a history of pancreatitis within the past 1 year prior to Day 1 has a treatment-emergent TG increase >40% from baseline, or a participant has an absolute TG level >4000 mg/dL (45 mmol/L) on any of the laboratory measurements, the central laboratory will immediately notify the unblinded clinician from the CRO. The unblinded CRO clinician will contact the Investigator and discuss next steps regarding the participant in order to determine appropriate monitoring and follow-up.

After completion of the Month 13 visit, through the Month 36/EOS Visit, the central laboratory will provide available lipid parameter results to the PI for each participant.

8.2.5. Notification of General Practitioner

It is the responsibility of the PI or designee to notify, where applicable and with the consent of the participant, the general practitioner of the participant's participation in the trial, by sending a letter stating the nature of the trial, treatments, expected benefits, or AEs and concomitant drugs to be avoided.

8.3. Treatment Compliance

All study treatment will be administered at the study site. The IMP will be dispensed by clinical study site staff on the day of dosing and recorded in the drug accountability records. The date, time, and duration of study treatment administration will be recorded on the eCRF on dosing days.

8.4. Treatment Stopping Rules

A decision to pause/suspend dosing in an individual participant **may** be indicated based on any of the following:

- Any confirmed pregnancy in the study will lead to permanent discontinuation of IMP dosing of that participant.
- A need for apheresis or other emergent interventions indicated to lower TG
- In participants with normal (per central laboratory reference range) AST and ALT on Day 1, treatment-emergent elevations ≥3× ULN at least possibly related to IMP per study Investigator must confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 2 for specific guidelines regarding treatment discontinuation or interruption for participants with any of the below findings:
  - ALT or AST ≥5×ULN (permanently discontinue IMP dosing for that participant, per Appendix 2; the participant will be permitted to remain on study follow-up visits until the EOS Visit, per the SOA [Table 3 and Table 4])
  - ALT or AST ≥3× ULN with a total bilirubin ≥2×ULN
  - ALT or AST ≥3×ULN with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
  - ALT or AST ≥3×ULN with a treatment-emergent INR >1.5 (must be confirmed on repeat) and which is not explained by another plausible cause *

* if Gilbert's syndrome or hemolysis: doubling of direct bilirubin if baseline >0.5 mg/dL

- Some participants enrolling into this study may have baseline elevations in transaminases. In participants with elevated (per central laboratory reference range) AST or ALT on Day 1, treatment-emergent elevations >2× baseline at least possibly related to IMP per study Investigator, as specified below, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 2 for specific guidelines regarding treatment discontinuation or interruption for participants with any of the below findings:
- ALT or AST ≥300 U/L (permanently discontinue IMP dosing for that participant, per Appendix 2; the participant will be permitted to remain on study follow-up visits until the EOS Visit, per the SOA [Table 3 and Table 4])
- ALT or AST ≥2×baseline with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
- ALT or AST ≥2×baseline with a total bilirubin ≥2×ULN
- ALT or AST ≥2×baseline with a treatment-emergent INR >1.5 (must be confirmed on repeat) and which is not explained by another plausible cause *

  * if Gilbert's syndrome or hemolysis: doubling of direct bilirubin if baseline >0.5 mg/dL

Treatment modification guidelines for participants with elevated ALT/AST are provided in Appendix 2.

8.5. Study Drug Discontinuation Criteria for Increased HbA1c

Regarding HbA1c study drug discontinuation criteria, participants should discontinue IMP if they meet the following criteria (refer to Appendix 3):

- HbA1c measurement >10% (or >86 mmol/mol IFCC units) at the last visit prior to the next dose; or
- An increase from baseline HbA1c >2% (or > 17 mmol/mol IFCC units) at the last visit prior to the next dose; or
- In participants with a baseline HbA1c >7.5% (or >58 mmol/mol IFCC units), an increase in HbA1c from baseline >1% (or >8.6 mmol/mol IFCC units) at repeat study visits with the last one being the visit prior to the next dose.

Participants who discontinue IMP due to HbA1c determinations will be followed for 6 months after their last dose per the Schedule of Activities.

8.6. Randomization, Blinding, and Open-Label Treatment

8.6.1. Randomization

All potential participants who sign an informed consent at screening will receive a unique identifier (ie, a screening number). For participants who are deemed eligible, this unique screening number will become the participant's permanent study ID number.

Eligible participants will be allocated a unique randomization number, in accordance with the randomization schedule. Each participant will be randomly assigned 2:1:2:1 to the dose cohorts (ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively). Treatments will be administered per the randomized sequence generated by an IWRS. The allocation of active treatment or placebo will be performed using a block randomization algorithm. Randomization will be stratified by level of TG at screening (≥2000 mg/dL vs <2000 mg/dL).

8.6.2. Blinding

Treatment assignment (active vs placebo) is blinded in this clinical study. Dose group assignment is not blinded, due to required injection volume differences dictated by the respective dose group. Therefore, participants will receive an injection of either active or placebo volume-matched to the assigned dose group (Section 9.5). To mask for slight color differences between active and placebo, syringes will be blinded in the pharmacy with translucent wrapping to mask the blinded staff and participants to the treatment assignment in accordance with instructions provided in the Pharmacy Manual. During the extension period, participants will receive open-label treatment, but blinding of the initial treatment assignment from the randomized period will be maintained.

Blinding of IMP /placebo assignment is critical to the integrity of this clinical study. It is expected that in most cases, AEs can be properly managed without the need for unblinding. However, in the event of a medical emergency in which knowledge of an individual participant's assignment is considered critical to the participant's well-being and management, the PI or documented designated treating physician or the medical monitor can unblind the treatment assignment. For any participant experiencing acute pancreatitis, the participant will be unblinded to their assigned treatment allocation.

If the situation is not an immediate emergency, the Investigator should contact the responsible medical monitor to discuss the participant and circumstances requiring the unblinding. The blind will be broken only for the specific participant under discussion. The unblinding will be documented in the IWRS. The study monitor should be informed promptly.

The randomization schedules will be maintained under controlled access. Staff involved in the dispensing of IMP will be accountable for ensuring compliance with randomization schedules. The nonblinded clinical research associate (CRA) will verify correct randomization.

If the PI considers an AE to be of such severity as to require immediate specific knowledge of the identity and dose of the relevant product, unblinding will be completed via the IWRS system. Medical emergency unblinding in IWRS is only accessible to the designated unblinded pharmacist, PI, and sub-Investigator. The medical monitor should be informed promptly.

If a participant requires emergency unblinding (with or without a discussion between the PI and the medical monitor preceding the unblinding), the PI may also be required to complete a 'Drug Safety Unblinding Request/Notification Form' to document the medical rationale necessitating the unblinding. This form is then forwarded to the medical monitor.

Blinding of central laboratory results for TG and lipid assessments is discussed in Section 11.1.

8.6.3 Open-Label Treatment

Upon completion of the double-blind randomized treatment period, subjects may enter Part A of the open-label treatment period. Subjects will remain on their assigned dose level (either 25 mg or 50 mg) until the final study dose is selected by the Sponsor. Subjects assigned to the 50 mg dose cohort will be administered the IMP using a PFS, while subjects assigned to the 25 mg dose cohort will continue to receive IMP prepared from vials.

With the selection of the optimal, final dose level of 25 mg, which was determined by the Sponsor and communicated to all investigative sites on 06 June 2024, Part B of the OLE was initiated. All subjects were transitioned to the 25 mg dose of ARO-APOC3 prepared from vials. Upon approval of AROAPOC3-3001 global Protocol Amendment 7 by the relevant regulatory authorities and IECs/IRBs, IMP will be administered using a PFS ARO-APOC3 solution (25 mg/0.5 mL; 50 mg/mL) once it is available at the study site. Once a participant is administered IMP using a 25 mg PFS, this mode of IMP administration must be used throughout the remainder of the study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

The Sponsor is responsible for the supply of ARO-APOC3 together with detailed instructions (in a Pharmacy Manual) describing preparation of ARO-APOC3. Accordingly, ARO-APOC3 will be supplied as single sterile 2-mL vials containing ARO-APOC3, with the correct dose of ARO-APOC3 prepared by the Pharmacy prior to dosing participants.

Upon approval of global Protocol Amendment 6 by the relevant regulatory authorities and IECs/IRBs, IMP for the 50 mg dose cohort will be provided as a PFS. Similarly, upon approval of global Protocol Amendment 7 by the relevant regulatory authorities and IECs/IRBs, IMP for the 25 mg dose cohort will be provided as a PFS. Refer to Section 8.6.2 for additional details.

Placebo (normal saline 0.9%) will be supplied for the double-blind treatment period by the clinical site or may be provided by the Sponsor upon request. Upon implementation of the PFS, placebo (normal saline 0.9%) for the 50 mg dose cohort must be supplied by the Sponsor.

9.2. Study Drug Packaging and Labeling

During the double-blind randomized period of the study, ARO-APOC3 will be supplied as a sterile Type-1 glass 2.0-mL vial (0.7 mL nominal volume, 0.5 mL withdrawable volume).

Upon approval of global Protocol Amendment 6 by the relevant regulatory authorities and IECs/IRBs, IMP for the 50 mg dose cohort will also be provided in a single dose PFS. Refer to Section 8.6.2 for additional details.

Upon approval of the global Protocol Amendment 7 by the relevant regulatory authorities and IECs/IRBs, ARO-APOC3 will be supplied as a 25 mg PFS and will have a different formulation. Refer to Section 8.6.2 for additional details.

The IMP vials and PFSs will be labeled per current Good Manufacturing Practice (cGMP)/GCP.

The table below summarizes attributes of the IMP:

Table 6: Characteristics of ARO-APOC3

IMP	ARO-APOC3 25 or 50 mg vial	ARO-APOC3 50 mg PFS	ARO-APOC3 25 mg PFS
Implementation	Original Protocol	Global Protocol Amendment 6	Global Protocol Amendment 7
Strength	200 mg/mL	200 mg/mL	50 mg/mL
Appearance	Clear, colorless to light yellow solution		
Inactive ingredients	0.5 mM sodium phosphate monobasic, 0.5 mM sodium phosphate dibasic in water for injection		
Shipment and Storage	Refrigerated, 2 ºC to 8 ºC		

Each 25 mg or 50 mg PFS supplied to sites will be packed individually and include the drug name, batch number, expiration date (as applicable), and storage conditions. The label will also include a unique syringe ID number, which should match the ID number listed on the IWRS dispensation transaction confirmation.

9.3. Study Drug Storage

The IMP supplies will be stored at clinical sites securely under the appropriate conditions. The IMP must be stored in a secure area with access limited to the PI and authorized staff and under the physical conditions that are consistent with the IMP-specific requirements.

9.4. Study Drug Preparation

ARO-APOC3 will be prepared, per the Pharmacy Manual, by a pharmacist or qualified staff at the clinical sites. Aseptic technique will be used to ensure sterility of the solution to be injected. The time of preparation for active drug must be documented and tracked to demonstrate administration within prepared drug stability boundaries. Please refer to the Pharmacy Manual for more detailed instructions.

The Sponsor will provide the PI with a sufficient quantity of clinical drug supplies. The PI must ensure that deliveries of IMP from the Sponsor are correctly received by a responsible person, that all receipts of drug shipments are recorded on the appropriate drug accountability forms prepared by the pharmacy at the clinical site, and that the products are stored in a secure area under recommended storage conditions. It is also the responsibility of the PI to ensure that the integrity of packaged study product not be jeopardized prior to dispensing.

Only participants enrolled in the study may receive IMP, in accordance with all applicable regulatory requirements. An authorized and trained staff member at each clinical study site will

dispense the IMP per predefined drug dispensing requirements. The dispensing will be verified by a second member of site staff.

When preparing the 25 mg dose of plozasiran using the vial presentation, Protocol Section 9.4, Study Drug Preparation, requires a double verification step to confirm the appropriate dose volume has been withdrawn into the syringe. This two-step verification process is required until the 25 mg plozasiran prefilled syringe presentation has been implemented at the site following approval of Protocol Amendment 7 (dated 13-Sep-2024) by the applicable regulatory authority and IEC/IRB. With the introduction of the prefilled syringe presentation there will no longer be the need for a verification step by a second staff member in order to confirm the correct volume is in the syringe. A single member of the site staff will be able to document the dispensation of the 25 mg PFS in the dispensation log, according to the number assigned for dispensation in 4G IRT.

9.5. Administration

Appropriately trained and qualified clinical staff at the study site will administer the IMP. Each dose will be administered as a single SC injection (Table 7). The site of injection will be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites include the upper arms (fatty tissue over the triceps area in the back of the arms) and thighs (either the top or outer part of the thigh). Note that the upper arms are not intended for self-administration. Further instructions on self-administration of study drug is provided in the ARO-APOC3 25mg PFS – Subject Instructions for Self-administration

Table 7: Injection Number and Volume Per Dose Cohort

ARO-APOC3 Dose[a]	Concentration	Total Injection Volume	No. of Injections per Planned Dose	Total No. of Study Injections
25 mg	200 mg/mL	0.13 mL	Single	8
50 mg	200 mg/mL	0.25 mL	Single	8

[a] Placebo injections of normal saline for the first 4 study injections will be volume-matched.

Upon approval of the global Protocol Amendment 7 by the relevant regulatory authorities and IECs/IRBs, ARO-APOC3 will be supplied as a 25 mg PFS, containing ARO-APOC3 in a different formulation (refer to Table 7).

Table 8: Injection Number and Volume Per Dose Cohort (OLE – Part B)

ARO-APOC3 Dose	Concentration	Total Injection Volume	No. of Injections per Planned Dose	Approximate No. of Study Injections
25 mg	50 mg/mL	0.5 mL	Single	4-6[a]

Abbreviation: IMP = investigational medicinal product

[a] Depending on when the protocol is approved in each region and depending upon the number of study visits remaining for individual subjects, the number of IMP administrations in Part B may range from a minimum of 4 to a maximum of 6 administrations.

Each dose of either active drug (ARO-APOC3) or placebo (normal saline 0.9%), will be administered by SC injection by the PI or appropriately trained and qualified clinical staff designated by the PI Upon approval of the AROAPOC3-3001 global Protocol Amendment 7 by

the relevant regulatory authorities and IECs/IRBs, subjects will be offered the option to self-administer the study drug at the study site under direct supervision of the PI or designated staff. Self-administration by study participants will be recorded on the eCRF.

Injections will be made into the SC tissue at an appropriate site (eg, abdomen, thigh, upper arm) using a 25- to 30-Gauge, ½-inch needle. The abdomen is the preferred site. The injection site is to be varied (no multiple injections into the same exact site, but alternating various locations on the abdomen is acceptable). The injection site location is to be recorded in the eCRF. Prior to dose administration, IMP must be allowed sufficient time to come to room temperature. Small air bubbles in the PFS are considered acceptable. Subcutaneous injections with a small amount of air in the PFS is harmless and adds no additional risks to study participants. Furthermore, the small amount of air in the PFS does not impact the volume of IMP administered. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

9.6. Study Drug Accountability

All material supplied is for use only in this clinical study and should not be used for any other purpose. The PI is responsible for the IMP accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the PI or designated site staff must maintain IMP accountability records throughout the course of the study. This person will document the amount of IMP received from the Sponsor and the amount administered to participants. A nonblinded CRA will perform initial and ongoing IMP kit and placebo accountability. The nonblinded CRA will protect the integrity of the assignment blind and will not participate in data review for study participants. Used vials of ARO-APOC3/placebo will be retained sequestered per participant (where allowable by local policy) and made available to the nonblinded CRA during IMP and placebo reconciliation. Following dispensation and administration, PFS will be disposed of in a puncture-resistant biohazard container and in accordance with local policy. The PFS label will have a tear-off portion that will include the information required to be documented in the Subject Dispensing Log. The tear-off portion of the label must be attached to the Subject Dispensing Log.

A Subject Dispensing Log must be kept current and will contain the following information:

- The identification of the participant to whom the drug was dispensed
- The date(s), quantity, lot number(s), and expiration date(s) of the IMP dispensed to the participant

The date and time of dose preparation, dispensation, and administration will be contemporaneously recorded to support administration and accountability of IMP. The authorized pharmacist or qualified staff will be unblinded to treatment assignment (ie, active or placebo). The pharmacy will dispense the study medication and the study center will administer the study medication only to participants included in this study following the procedures set out in the study protocol and the Pharmacy Manual. Each participant will be given only the IMP as assigned by the IWRS. IMP administration will be documented and recorded on the eCRFs. The inventory must be available for inspection by the CRA during the study. Drug supplies will either be collected at the end of the study by the study monitor or returned by the PI or designee to the Sponsor or the designated the Sponsor-approved depot.

9.7. Study Drug Handling and Disposal

For this study, used and partially used drug vials will be retained for an adequate period to allow accountability where permitted by local policy. All other unused vials or unused PFSs must be retained for accountability to be performed by the Sponsor. No additional IMP samples will be retained.

Used PFSs will be disposed of, and the tear-off portion of the label will be attached to the Subject Dispensing Log. Refer to Section 9.6 for additional details.

10. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

10.1. Pharmacokinetic Assessments

10.1.1. Sample Collection

In a subset of approximately 36 participants (24 active, 12 placebo), including all participants enrolled at sites in Japan (Section 6.1.5), plasma PK samples for the analysis of ARO-APOC3 will be collected through an indwelling cannula or through a fresh vein puncture before and after IMP administration at regular intervals up to 24 hours postdose at Day 1 and Month 3 (Table 3). All other participants will provide a predose PK sample and 1 additional sample 2 hours postdose at Day 1 and Month 3.

For postdose samples that require next-day collection, participants may return to the clinical facility to have their blood drawn or they may opt to have their PK samples collected through home healthcare visits (except in countries where this is not allowed) if this is an option at their study site.

10.1.2. Sample Analysis

Whole blood will be collected and processed per the Laboratory Manual. Plasma samples will be assayed by a validated hybridization-ligation method. The criteria for repeat analysis, as defined in the respective in-house procedure, will be followed. The validation study conducted by the appointed bioanalytical laboratory to establish validity including accuracy, precision, reproducibility, specificity, recovery, and frozen stability of the analytical method will be appended to the final report.

11. ASSESSMENT OF EFFICACY

Assessments of efficacy will occur at time points following IMP administration as outlined in the SOA (Table 3 and Table 4).

Efficacy assessments required to be performed at dosing visits, the Month 10 visit, and the Month 36/EOS visit will occur at the investigational site. At all other post-Day 1 study visits, in the event of logistical disruptions (eg, coronavirus disease [COVID]-related) where a participant does not have direct access to the site, assessments may be performed at an alternative location

(eg, home health [except in countries where this is not allowed], local laboratory) using the central laboratory kit and shipped to a central laboratory for analysis.

11.1. Serum Triglycerides and Other Lipid Parameters

Blood samples for lipid parameters will be collected from participants through an indwelling cannula or through a fresh vein puncture. The actual blood collection time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections for the actual time of sample collection will be incorporated at the time of data analysis. Blood samples will be collected at time points outlined in the SOA (Table 3 and Table 4). The actual sample times (times samples are taken) will be recorded in the eCRF and will be entered at the time of or as soon as possible after sampling. All times must be recorded in the 24-hour format. An explanation must be given for any blood sample taken outside of the set sampling times.

Fasting serum TG and other lipid parameters (LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, APOB-48, LP[a], APOB-100, total APOB, APOC3, APOC2, APOA1 and APOA5) will be collected at the screening visit and on Day 1 prior to dosing after at least a 10-hour fast. The Day 1 values will be used as each participant's baseline value for data analysis purposes. Fasting serum TG will be measured as per the SOA (Table 3 and Table 4) and assessed by a central laboratory standard method. LDL-C will be measured as per the SOA and assessed by a central laboratory, preferentially using an ultracentrifugation methodology, with direct measurement method and Martin-Hopkins calculation as a backup.

At Month 10, fasting lipid samples will be collected twice, 2 to 7 days apart, for calculation of study endpoints. The second collection at Month 10 may be done through home health (except in countries where this is not allowed). After completion of the Month 13 visit, the central laboratory will provide available lipid parameter results to the PI through the Month 36/EOS Visit.

11.2. Glucose Metabolism

Serum samples will be collected at screening and on Day 1 after at least 10 hours of fasting and prior to dosing. The Day 1 values will be used as each participant's baseline value for data analysis purposes. Fasting serum blood glucose, HbA1c, HOMA-IR, and C-peptide will be measured as per the SOA (Table 3 and Table 4) and assessed by a central laboratory.

11.3. Acute Pancreatitis Events

All treatment-emergent AEs and SAEs reported by the Investigator through Month 36/EOS that are consistent or possibly represent an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the 2013 Atlanta definition meeting 2 of the following 3 criteria:

1. Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
2. Serum lipase activity (or amylase activity) ≥3×ULN

3. Characteristic findings of acute pancreatitis on CECT, MRI, or transabdominal ultrasonography

This committee will meet to review and assess the blinded data as described in the independent adjudication committee charter.

11.3.1. Detecting and Reporting Pancreatic Events

During each study visit, the PI and clinical staff will be responsible for educating and/or reminding study participants on the signs and symptoms of acute pancreatitis and when to seek care. The PI or medically qualified designee will also be responsible for detecting, recording, and reporting pancreatic events that meet the criteria and definition of acute pancreatitis (according to the 2013 Atlanta definition) and events that possibly represent pancreatitis. AEs terms that could signal a potential case of pancreatitis are listed below according to the MedDRA PT. These PTs represent possible pancreatitis events but are not limited to the following:

Any PTs that includes pancreatitis	Abdominal rigidity
Amylase increased	Acute abdomen
Blood bilirubin increased	Ascites
Lipase increased	Gastrointestinal pain
Hyperamylasaemia	Intra-abdominal pressure increased
Hyperbilirubinaemia	Jaundice
Hyperlipasaemia	Nausea
Pancreatic enzymes increased	Pancreatic duct rupture
Ultrasound pancreas abnormal	Peripancreatic fluid collection
Abdominal distension	Vomiting
Abdominal pain	Vomiting projectile
Abdominal rebound tenderness	

After the initial AE of pancreatitis or possible pancreatitis events, the PI will follow each participant and provide further information on the participant's condition as deemed appropriate.

The PI will follow all pancreatic or possible pancreatic AEs until resolution until the condition stabilizes, or until the event is otherwise explained. Once resolved, the PI or medically qualified designee will update the appropriate AE eCRF page and SAE report form (if the event is serious). The PI, or medically qualified designee, will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the possible pancreatic AE or SAE.

New or updated information regarding an SAE will be recorded on a new SAE report form marked as follow-up with the appropriate follow-up number added to the report. The follow-up report will be signed and dated by the PI or medically qualified designee.

11.4. Diet

Participant diet will be recorded as per the SOA (Table 3 and Table 4). At these study visits, the participant will be asked to report their dietary management of FCS for at least 3 of the past 5 days.

11.5. Patient-Reported Outcomes

Participants will complete the EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-PAN26 questionnaires as per the SOA (Table 3 and Table 4).

11.5.1. EuroQoL 5-Dimension Questionnaire

The EQ-5D-5L comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman 2011). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also includes a visual analog scale (VAS) to record the participant's self-rated health, where the endpoints are labeled "The best health you can imagine" and "The worst health you can imagine." The VAS can be used as a quantitative measure of health outcome that reflects the participant's own judgment.

11.5.2. EORTC QLQ-C30 Questionnaire

The EORTC QLQ-C30 instrument consists of 30 questions: 28 questions about specific aspects of quality of life, and 2 questions about overall health and overall quality of life. It has been translated and validated into more than 100 languages. The EORTC QLQ-C30 was initially developed and validated in patients with lung cancer (Aaronson 1993), and subsequently shown to be useful for the assessment of quality of life in patients with chronic pancreatitis (Fitzsimmons 2005) and in patients with LPL deficiency (Johnson 2015).

11.5.3. EORTC QLQ-PAN26 Questionnaire

The EORTC QLQ-PAN26 instrument consists of 26 items related to disease symptoms, treatment side effects, and specific emotional issues such as abdominal pain, gastrointestinal symptoms, or anxiety. It focuses on patient-reported outcomes among patients with pancreatic cancer (Fitzsimmons 1999) and subsequently shown to be useful for the assessment of quality of life in patients with chronic pancreatitis (Fitzsimmons 2005) and in patients with LPL deficiency (Johnson 2015).

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The following safety assessments will be obtained at the time points outlined in the SOA (Table 3 and Table 4).

Safety assessments required to be performed at dosing visits, the Month 10 visit, and the Month 36/EOS visit will occur at the investigational site. At all other post-Day 1 study visits, in the event of logistical disruptions (eg, coronavirus disease [COVID]-related) where a participant

does not have direct access to the site, assessments may be performed at an alternative location (eg, home health [except in countries where this is not allowed], local laboratory) using the central laboratory kit and shipped to a central laboratory for analysis.

12.1.1. Demographic/Medical History

Participant demographics (eg, date of birth, race and ethnicity, sex) and medical history will be collected during the screening period. Medical History will include medication use over the previous 30 days, including vitamins, OTC medications, prescription drugs, recreational drugs, or supplements and alcohol and tobacco use.

Potential participants who do not have a previous genetic test result for FCS will be asked to consent for genetic testing specific to identification of genetic mutations associated with FCS only. Participants who consent will have a blood sample drawn for this test at the Screening visit. Potential participants who do not have a previous genetic test result evaluating for the presence of genetic mutations associated with FCS and who do not consent to genetic testing to assess for the FCS genotype will not be eligible to join the study.

Participants will also have the option to consent for having additional blood samples collected at Day 1 and Month 3 for future analyses. Participants who do not consent for this optional substudy will be allowed to participate in the main study. Pharmacogenetic analysis will not be performed on samples collected for future research.

12.1.2. Vital Signs

Systolic/diastolic blood pressure (mm Hg), temperature (degrees Celsius [°C]), heart rate (beats/minute), and respiratory rate (breaths/minute) will be obtained after the participant is semi-supine or sitting for at least 3 minutes. Vitals signs will be obtained prior to venipuncture and other invasive procedures.

12.1.3. Physical Examination

A complete physical examination will be performed at screening, including height (centimeters, without shoes) and weight (kilograms, without shoes). At all other time points outlined in the SOA (Table 3 and Table 4), a symptom-directed physical examination will be performed as indicated.

12.1.4. Electrocardiogram

Standard single 12-lead ECG, which will be recorded at Screening and the timepoints outlined in the SOA (Table 3 and Table 4), can be performed on local ECG equipment.

Triplicate 12-lead ECG measurements approximately time-matched to PK blood collections will be obtained using validated ECG services equipment from a central facility at Day 1 and Month 3. Any abnormal and clinically significant ECGs, as per the PI's medical judgment, will be repeated in triplicate, with each measurement approximately 1 minute apart. For all triplicate ECGs, the ECGs must be acquired using centralized ECG service equipment and results should be interpreted at a central laboratory.

The participant should be supine or semi-supine for at least 5 minutes before each ECG is obtained. ECGs will be performed prior to venipuncture and any other invasive procedures. More details of ECG collections are available in Table 3 and Table 4.

The electrophysiological parameters assessed will be heart rate (HR), overall ECG waveforms, PR interval, QRS duration, QT interval, and Fridericia-corrected QT interval (QTcF) among other ECG parameters.

12.1.5. Laboratory Assessments

Blood and urine samples will be collected at the site and shipped to the central laboratory for analysis. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, lab samples may be collected at alternative location (eg, home health [except in countries where this is not allowed], local laboratory) using the central laboratory kit and shipped to the central laboratory for analysis. If central laboratory kit collection is not available, local laboratory safety testing may only be permitted in limited circumstances and only with prior Sponsor approval. Blood and urine samples will be collected for the laboratory tests detailed below, to establish baseline data and eligibility for enrollment. One repeat screening laboratory sample collection is allowed per laboratory assessment to establish eligibility (except for fasting TG required per Inclusion Criterion #3, which can be repeated twice). The results will be assessed by the PI or medically qualified designee before study enrollment. Any abnormality in laboratory values (that are confirmed on repeat) deemed clinically significant by the PI or a medically qualified designee (ie, those that would jeopardize the safety of the participant or impact on the validity of the study results), will result in exclusion of that participant.

Any abnormal and clinically significant laboratory result, as per the PI's medical judgment, should be documented as an AE or SAE, as applicable.

Refer to the Laboratory Manual for additional details on clinical laboratory tests.

12.1.5.1. Hematology

The following will be assessed: hemoglobin, red blood cell count, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

12.1.5.2. Blood Chemistry

The following will be assessed: sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, creatine kinase, uric acid, phosphate, total calcium, anion gap, albumin, globulins, protein, total bilirubin, amylase, lipase, HbA1c, serum insulin, C-peptide, conjugated bilirubin, gamma glutamyltransferase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, and C-reactive protein.

12.1.5.3. Coagulation

The following will be assessed: partial thromboplastin time, prothrombin time with INR, and fibrinogen.

12.1.5.4. Urine Testing

The following will be assessed: leukocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose. Microscopic urinalysis will be performed if indicated, including white blood cells, red blood cells, epithelial cells, and bacteria. Spot urine creatinine and spot urine protein will also be performed.

12.1.5.5. Virus Serology

The following will be assessed: HBsAg and hepatitis C antibody screen. If necessary, participants will be counseled by the PI, or medically trained designee, concerning the blood tests for HBsAg, and hepatitis C antibody, and their subsequent results.

12.1.5.6. Pregnancy Screen

Postmenopausal status will be confirmed by follicle-stimulating hormone (FSH) level consistent with postmenopausal state. Serum pregnancy tests (for patients enrolled in South Korea) and urine qualitative pregnancy tests will be conducted for women of childbearing potential at specified visits (see Table 3 and Table 4).

12.1.6. Anti-Drug Antibodies

Anti-drug antibodies will be assessed from serum samples.

12.1.7. Early Termination Procedures

If a participant discontinues from the study prematurely, every reasonable effort will be made to perform the early termination visit within 30 days of the decision to terminate a participant's study participation. The reason for early termination will be documented in source documents and eCRF. Procedures as outlined for Month 36/EOS in the SOA (Table 4) will be completed. Participants who discontinue the study due to SAE will be encouraged to remain available for follow-up for medical monitoring until resolution.

12.2. Adverse Events

The PI and clinical facility staff are responsible for detection, recording, and reporting of events that meet the criteria and definition of various AEs as listed below. Adverse events will be recorded from time of signed consent through to the EOS visit; only AEs that occur postdose will be considered treatment-emergent. The PI and clinical facility staff are responsible for detection, recording, and reporting of pregnancy and appropriate follow up. Any known pregnancy that occurs within 24 weeks after the last dose of IMP or EOS (whichever is later) should be reported by the participant to the PI. Information regarding any reported pregnancy should be collected up to 1 year after birth or until the end of the pregnancy.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign

(including an abnormal laboratory finding or diagnostic test), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether related to this product or not (refer to ICH E2a: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 27 October 1994).

Treatment-emergent AEs will be defined as AEs with onset after administration of the study drug, or when a pre-existing medical condition increases in severity or frequency after study drug administration.

AEs will not include:

- A medical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE)
- A pre-existing disease or condition present at the start of the study that does not worsen during the study
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or "social" admissions)
- An overdose of either the IMP or a concurrent medication without any resulting signs or symptoms

12.2.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the IMP or placebo, that fulfills one or more of the following:

- Results in death
- Is immediately life-threatening (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the participant was at immediate risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require medical or surgical intervention to prevent one of the other serious outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events

Abnormal assessments (eg, ECGs and vital signs) that are judged by the PI as clinically significant or result in clinical sequelae will be recorded as AEs. Laboratory abnormalities will be reported by the PI as AEs if the abnormality is considered clinically significant or results in clinical sequelae. Laboratory abnormalities or other abnormal assessments not reported as AEs are not to be reported as Clinically Significant (CS) in the study database.

Clinically significant abnormal laboratory findings or other clinically significant abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs.

The PI (or medically qualified designee) will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

12.4. Timing, Frequency, and Method of Detecting Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a participant prior to the start of the study (ie, before informed consent) should be recorded as Medical/Surgical History.

All AEs occurring after informed consent and on or before the final visit must be reported as AEs; only AEs that occur postdose will be considered treatment-emergent. All AEs must be recorded irrespective of whether they are considered drug-related. AEs will be collected through the EOS visit or through 30 days after the last dose whichever is longer.

At each visit/assessment in the period defined above, AEs will be evaluated by the PI (or medically qualified designee) and recorded.

12.5. Recording Adverse Events

When an AE occurs, it is the responsibility of the PI or medically qualified designee to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The PI or medically qualified designee will then record the AE on the AE eCRF. Additional reporting requirements for an AE meeting serious criteria are discussed in Section 12.8.

The PI or medically qualified designee will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In all cases, when available, the diagnosis should be reported as the event and not the individual signs/symptoms. It is not acceptable for the PI to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the appropriate AE eCRF pages.

12.5.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) include hypersensitivity/anaphylaxis, ISRs, and potential hepatotoxicity events. The PI and delegated clinical staff are responsible for detecting, recording, and reporting these events. AESIs that occur after first dose of IMP will be considered treatment emergent. AESI should be recorded on specifically designated electronic case report

form. A list of MedDRA PTs or search strategies for the AESI categories is provided in Appendix 4.

The criteria used for the assessment or grading of the AESI are provided below.

A. **Hypersensitivity/Anaphylaxis**: The assessment of hypersensitivity and anaphylactic reaction will be based on the Sampson criteria (refer to Appendix 4).

B. **Injection site reactions**: ISRs are graded based on the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0:

- Mild: Tenderness with or without associated symptoms (eg, warmth, erythema, itching), mild pain or mild edema
- Moderate: Pain with associated phlebitis or lipodystrophy and edema
- Severe: Tissue ulceration or necrosis with associated severe tissue damage or if operative intervention is indicated.

C. **Potential Hepatotoxicity Events**: abnormal liver function tests that may indicate potential hepatotoxicity events are graded based on the latest version of CTCAE Version 5.0. Specifically, laboratory test results that indicate an increase in the level of ALT and AST in a blood specimen are graded as follows:

- Grade 1: >ULN – 3.0 × ULN if baseline was normal; 1.5-3.0 × baseline if baseline was abnormal
- Grade 2: 3.0-5.0 × ULN if baseline was normal; >3.0–5.0 × baseline if baseline was abnormal
- Grade 3: >5.0 to 20 × ULN if baseline was normal; >5.0 – 20 × baseline if baseline was abnormal
- Grade 4: >20 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal

12.6. Evaluating Adverse Events

12.6.1. Assessment of Severity

The PI or medically qualified designee will assess severity for each AE reported during the study. The assessment will be based on the PI's (or medically qualified designee's) clinical judgment. The severity of all AEs should be graded using the latest version of the National Cancer Institute CTCAE Version 5.0 assigned to one of the following categories:

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. Medical intervention not indicated.
- **Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities. Noninvasive medical intervention indicated.
- **Severe**: An event that prevents normal everyday activities but not immediately life-threatening.

- **Life-Threatening:** An event that places the participant at immediate risk of death or is disabling.
- **Death:** An event that results in death.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the severity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the predefined outcomes as described in Section 12.2.1.2.

12.6.2. Assessment of Causality

The PI (or medically qualified designee) is obligated to assess the relationship between IMP and the occurrence of each AE. The PI (or medically qualified designee) will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IMP will be considered and investigated. The PI (or medically qualified designee) will also consult the IB in the determination of his/her assessment.

Some situations may arise when an SAE has occurred and the PI has minimal information to include in the initial SAE report. However, it is very important that the PI (or medically qualified designee) always assess causality for every event prior to transmission of the SAE report form. The PI (or medically qualified designee) may change his/her opinion of causality considering follow-up information, amending the SAE report form accordingly. The causality assessment is one of the criteria used when determining global regulatory reporting requirements.

The PI (or medically qualified designee) will provide the assessment of causality using three possible categories: Not Related, Possibly Related, or Probably Related.

An AE will be considered "not related" to the use of the product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the product and the onset of the AE (eg, the event occurred either before, or too long after administration of the product for it to be considered product-related)
- A causal relationship between the product and the AE is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

An AE will be considered "possibly related" when an event follows a reasonable temporal sequence from administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals, or an event that follows a known or expected response pattern to the drug but that could have been produced by a number of other factors.

An AE will be considered "probably related" when an event follows a reasonable temporal sequence from administration of the IMP, unlikely to be attributed to concurrent disease or other drugs or chemicals. Other examples include an event that follows a known or expected response pattern to the IMP, or that is confirmed by stopping or reducing the dosage of the IMP and that could not reasonably be explained by known characteristics of the participant's clinical state.

12.7. Follow-up of Adverse Events

After the initial AE, the PI is required to proactively follow each participant and provide further information on the participant's condition as deemed appropriate.

All AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the appropriate AE eCRF page and SAE report form (if event is serious) will be updated. The PI, or medically qualified designee, will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. In the event of a fatal outcome in an SAE, the PI, or medically qualified designee, will attempt to obtain postmortem findings, including histopathology, and provide all additional information in a follow up SAE report.

New or updated information regarding an SAE will be recorded on a new SAE report form marked as follow-up with the appropriate follow-up number added to the report. The follow-up report will be signed and dated by the PI.

12.8. Prompt Reporting of Serious Adverse Events

Any AE meeting serious criteria MUST be reported promptly to the Sponsor's designated Pharmacovigilance Contract Research Organization (CRO), and the IRB/IEC in accordance with applicable local/institutional requirements.

12.8.1. Completion and Transmission of the Serious Adverse Event Reports

Once an PI becomes aware that an SAE has occurred in a study participant, she/he will report the information on an SAE report form to the designated Pharmacovigilance CRO immediately. The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the PI (or medically qualified designee). If the PI does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The SAE report form will be updated when additional information is received.

The PI (or medically qualified designee) will always provide an assessment of causality at the time of the initial report as described in Section 12.6.2. However, as new information becomes available, causality may be modified.

Email transmission of the SAE report form is the preferred method to transmit this information to the designated Pharmacovigilance CRO. Facsimile is acceptable if email is unavailable. In rare circumstances, notification by telephone is acceptable, with a copy of the SAE report sent by overnight mail. Initial notification via the telephone does not replace the need for the PI, or medically qualified designee, to complete and sign the SAE report form within the outlined time frames.

The Sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses. Any event that in the opinion of the PI may be of immediate or potential concern for the participant's health or well-being will be reported to the Sponsor emergency contact listed in Table 1.

12.8.2. Pregnancy Reporting

Pregnancy occurring in a participant or in the female partner of a male participant during the study must be reported on a pregnancy reporting form or on an SAE form to the designated Pharmacovigilance CRO immediately and not later than 24 hours of initially becoming aware of the pregnancy by the PI.

Any known pregnancy that occurs within 24 weeks after the last dose of IMP or EOS (whichever is later) should also be reported by the participant to the PI.

Pregnancies are not SAEs. However, pregnancy data will be collected at the initial notification, birth/termination of pregnancy, and for at least 1 year after birth or until the end of the pregnancy.

Any SAE that occurs during pregnancy (eg, serious maternal complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth etc.) must be reported in accordance with the procedure for reporting SAEs.

12.8.3. Serious Adverse Event Reports to the IRB

The PI, or responsible person per local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the appropriate IEC/IRB.

12.8.4. Regulatory Requirements for Reporting of Serious Adverse Events

The PI (or medically qualified designee) will promptly report all SAEs in accordance with the procedures detailed in Section 12.8.1. Prompt notification of SAEs by the PI is essential so that the Sponsor may comply with its regulatory obligations.

Any SAEs requiring expedited reporting will be reported by the Sponsor to relevant regulatory authorities, PIs, and IRBs/IECs in accordance with the Sponsor's procedures and local regulatory requirements, as applicable.

Serious adverse events will be reported if either the PI or the Sponsor deems that the event is related to the IMP. Furthermore, medication errors, pregnancies, and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

Special attention should be given to the subjects' underlying disease, concomitant medications, drug mechanistic factors, and other contributing factors when considering whether any given event is associated with a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence, similar events, drug class effect, and the totality of available safety data and reference safety information.

In the case where limited information that informs causal attributions is provided by the reporting investigator, the Sponsor will issue queries directly or via the contract research organization to the reporting investigator to collect sufficient clinical data and medical information about the study participant to inform causality.

If the Arrowhead Global Safety Reviewer/Officer disagrees with the investigator's causality assessment, the opinion of both the investigator and the Sponsor shall be provided with the report and the case will be reported to EU Health Authorities in accordance with REGULATION (EU) No 536/2014) and local and global reporting regulations.

12.8.4.1. Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

For countries within the European Economic Area (EEA), the Sponsor or its authorized representative will report in an expedited manner to concerned Regulatory Authorities and Ethics Committees suspected unexpected serious adverse reactions (SUSARs) in accordance with REGULATION (EU) No 536/2014 and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor shall report electronically to the EudraVigilance database all relevant information about the following SUSARs:

- All SUSARs related to an IMP that occurred in any of the countries participating in the study, even if the Sponsor is aware of it only after the end of the study.
- All SUSARs related to the same active substance that occurred in a study conducted in third countries by the same Sponsor or by another sponsor within the same parent company or who develops the medicinal product jointly.

Regarding fatal or life-threatening SUSARs, the reporting period begins the day the Sponsor becomes aware of the reactions. The Sponsor will report them as soon as possible and no later than 7 days.

For non-fatal or non-life-threatening SUSARs, the reporting period begins the day the Sponsor becomes aware of the reactions. The Sponsor will report them as soon as possible and no later than 15 days.

12.8.5. Post-study Adverse Events

A post-study AE is defined as any event that occurs outside of the AE detection period defined in Section 12.4. Investigators are not obligated to actively seek AEs in former study participants. However, if the PI learns of any SAE at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the IMP, the PI will promptly notify the Sponsor.

12.8.6. Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly (Section 12.6).

13. STATISTICS

13.1. General Considerations

Statistical analyses and descriptive summaries will be presented for primary, secondary, and exploratory endpoints using appropriate methods. Any proposed amendments to the Statistical Analysis Plan (SAP) will only occur prior to database lock. Descriptive statistics will be presented for all analyses unless otherwise specified. For continuous variables, data will be presented as number (n), mean, median, standard deviation, minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percent. Data will be analyzed by treatment group: ARO-APOC3 25 mg, ARO-APOC3 50 mg, or pooled placebo.

The treatment difference in efficacy and safety for participants dosed or not with a PFS will be explored.

Additional details of all planned analyses for this study will be provided in the SAP.

13.2. Analysis Populations

The following study sets are defined in this study:

- Full Analysis Set (FAS): All randomized participants will be included in FAS. All efficacy analyses will be performed using the FAS. Participants will be analyzed according to the treatment assigned at randomization.
- Safety Analysis Set: All participants who receive at least 1 dose of IMP. All safety and tolerability analyses will be performed using this set. Participants will be analyzed according to the treatment they received.
- Per-Protocol Set: All randomized participants who completed the study without major protocol deviations.
- PK Analysis Set: All FAS participants who have sufficient plasma concentration data to facilitate determination of PK parameters.

13.3. Sample Size Considerations

A total of 72 participants randomly assigned 2:1:2:1 to the dose cohorts (ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively) results in a 1:1 allocation for comparing each study treatment dose to pooled placebo. The study will have about 99% power to detect a statistically significant global or conjunctive difference in percentage change from baseline in TG between any active treatment group and pooled placebo using a 2-sided test and Holm's step-down multiple-comparison procedure, with a 2.5% level of significance for each test between ARO-APOC3 dose level vs. placebo. These estimates assume an average of 75% and 80% reduction from baseline in fasting TG at Month 10 in participants receiving ARO-APOC3 25 mg and 50 mg, respectively, and a 5% reduction in participants receiving placebo. The standard deviation is assumed to be 40% (Witztum 2019). The Wilcoxon (Mann-Whitney) rank-sum test is used with the assumption of $p_1=P(X<Y)$=0.108. The dropout rate is estimated to be 10% to 15%.

Of the 72 planned participants, approximately 12 will be recruited in Japan. The sample size for participants in Japan was selected based on a combination of target enrollment of 10% to 20% of the total study population in Japan and the anticipated availability of eligible participants in Japan.

13.4. Stratification

Randomization will be stratified by level of TG at screening (≥2000 vs <2000 mg/dL). The same stratification factor will be applied in the randomization of participants in Japan.

13.5. Analysis Methods

The primary analysis will include data from the randomized period. The final analysis will include data from the randomized and extension periods. The primary analysis is planned when all randomized participants complete the randomized period or discontinue from study, whichever is earlier. The final analysis is planned when all participants complete the extension period or discontinue from study, whichever is earlier.

13.5.1. Baseline Data

Demographics will be tabulated by participant and summarized by treatment group. Eligibility assessments at baseline, including medical/surgical history data, physical examination data (including height and weight), and FCS genotype completed at screening or from a source-verifiable document, will be listed for each participant.

Medical history will be summarized and listed by participant. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and Concomitant Medications will be coded using the World Health Organization Drug Dictionary into drug class (Anatomical Therapeutic Chemical level 4) and PT. PTs will be summarized and listed, and verbatim terms will be listed by participant.

13.5.2. Efficacy

To control the family-wise Type I error at a 0.05 level, a fixed sequential testing procedure will be implemented in a hierarchical step-down manner. The hypothesis testing procedure from primary efficacy endpoint to key secondary endpoints will use a fixed-sequence stepping-down procedure. That is, only if the primary efficacy analysis of primary endpoint proves significantly in favor of active treatment groups will the key secondary endpoints be tested.

To strongly control the family-wise overall Type I error, inferential conclusions about these efficacy endpoints will require statistical significance from both dose levels of the previous one. Within each endpoint, there are two tests, ARO-APOC3 25 mg vs placebo and ARO-APOC3 50 mg vs placebo. When performing the efficacy analysis for an endpoint, the adjustment for multiplicity of testing 2 ARO-APOC3 treatment groups vs placebo will be carried out using Holm's step-down procedure.

The sequence of hypotheses testing is as follows:

Endpoint	Testing Order
Percent change in fasting TG at Month 10 (primary endpoint)	1

Endpoint	Testing Order
Percent change in fasting TG at Month 10 and Month 12 (averaged)	2
Percent change in fasting ApoC3 at Month 10	3
Percent change in fasting ApoC3 at Month 12	4

The objectives of this study are to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS. The primary endpoint is the percent change from baseline at Month 10 in fasting TG levels. The primary analysis of the primary endpoint will evaluate the difference in means between each ARO-APOC3 dose cohort and pooled placebo cohort and will be conducted in all randomized participants (FAS). The estimand of interest is the difference in means of percent change from baseline in fasting TG at Month 10 in adults with FCS (as defined by the inclusion/exclusion criteria), regardless of treatment compliance or other intercurrent events post-baseline.

For endpoint analysis based on Month 10 data, the laboratory value will be the arithmetic mean of two values taken during Month 10. If only one value is available during Month 10, then this value will be used for endpoint analysis. For data analysis purposes, baseline will be defined as the arithmetic mean of Day 1 predose assessment and the last fasting assessment prior to Day 1. If only one predose value is available, the predose value closest to the first dose will be used.

The primary efficacy analysis will be based on Hodges-Lehmann estimator with pattern-mixture model imputation based on the FAS. The pattern-mixture model will be used as the primary imputation method as part of the primary analysis for the percent change in fasting TGs from baseline to Month 10. This imputation model will include factors such as patient demographics, disease status, and baseline TG, as well as adherence to therapy. The imputation model will impute missing Month 10 TG values as follows:

- For participants who do not adhere to therapy and who do not have a Month 10 measurement, the missing data imputation method will use patients in the same treatment arm who do not adhere to therapy and have a Month 10 measurement; and
- If there are no participants in the same treatment arm who do not adhere to therapy and have a Month 10 measurement, missing Month 10 TG values will be imputed as follows:
  - For the ARO-APOC3 treatment groups, the treatment effect is considered washed out and baseline TG values from these participants (no intermediate measures will be used) and data from placebo group will be used to impute the Month 10 TG values; and
  - For the placebo arm, missing Month 10 TG values will be imputed assuming missing-at-random, including patient demographics, disease status, and baseline and post-baseline efficacy data, using observed data from all participants in the placebo arm.

After the multiple imputation step, each imputed dataset will be analyzed by the nonparametric Hodges-Lehmann method and the Hodges-Lehmann estimator and standard error will be combined to produce treatment difference estimate and 95% CI and p-value. The method provided by Rubin and a modified macro from (Mogg 2007) will be used to combine and derive

overall p-value for the imputation procedure. The ANCOVA model with treatment as a factor and baseline TG as a covariate will be used as sensitivity analysis only if the normality assumption is not violated.

Tipping-point analyses with Multiple Imputation will be conducted as a supportive sensitivity analysis to assess how severe the departure from missing-at-random assumption must be in order to overturn the conclusion of the primary analysis. The analysis using the Mixed-Model Repeated Measures approach based on a missing-at-random assumption will be conducted as a sensitivity analysis to test the robustness of primary efficacy analysis results.

Similar to the primary analysis of Month 10 fasting TG (the primary endpoint), the Wilcoxon rank-sum test with the Hodges-Lehmann method will be used to test and evaluate the key secondary endpoints listed above, with testing order 2 to 4. Wilcoxon rank-sum test with Hodges-Lehmann method will also be used to test other continuous secondary endpoints but will only be considered exploratory. The same sensitivity analyses of the primary endpoint will be applied to these 3 key secondary endpoints and other secondary endpoints as well.

For the analysis of exploratory endpoints, descriptive summaries will be provided, as applicable, and any inferential statistics (ie, p-values) will be considered only as exploratory. Descriptive statistics will be provided for all endpoints.

For long-term efficacy endpoints such as change and percent change from baseline in TG, APOC3, non-HDL-C, and HDL-C and other lipid parameters in the extension period, descriptive statistics will be provided by active dose received. For participants who receive placebo in the randomized period, baseline of long-term endpoints will be rederived using the value of the last assessment prior to receiving first dose of active IMP in the extension period. For participants who receive active drug in the randomized period, baseline is the value of last assessment prior to first dose of active IMP in the randomized period.

13.5.3. Safety

In general, safety analyses will be performed, and the results summarized by treatment group. TEAEs will be coded using MedDRA version 24.0 or later by System Organ Class (SOC) and PT. Overall Summaries of TEAEs will be tabulated by seriousness, severity, and relationship to IMP. The incidence and frequency of TEAEs, TEAEs related to ISR, serious TEAEs, and serious TEAEs leading to discontinuation, will be summarized by cohort per SOC, PT, and severity. Treatment-related TEAEs will also be summarized in a similar manner. All AEs will also be presented in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome. The incidence of laboratory abnormalities will be assessed using descriptive summary statistics. Shift tables may be provided. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Abnormal physical examination findings will be summarized by time point and presented in participant listings. ECG parameters, changes from baseline, and qualitative assessments will be summarized. Pregnancy and FSH test results will be listed.

For long-term safety endpoints, descriptive statistics will be provided by active dose received similar to long-term efficacy endpoints.

13.5.4. Pharmacokinetics and Pharmacodynamics

For participants assigned to the "full PK" subgroup, including all participants in Japan, PK parameters from Non-Compartmental Analysis (NCA) will be generated when feasible. Analysis of variance (ANOVA) of primary ARO-APOC3 plasma exposures (C_{max} and AUC [dose-normalized if supported by data]) will be attempted to ascertain the degree of difference between Japanese and non-Japanese participants, and between Asian and non-Asian participants.

Derived change and percentage change from Day 1 will be summarized for fasting APOC3, APOC2, and APOA5.

Population PK and PD analyses of ARO-APOC3 will be performed using Nonlinear Mixed Effect (NLME) methods and appropriate software (eg, Phoenix NLME or NONMEM). If there is sufficient diversity in demographics and other baseline characteristics in the study population, an attempt will be made to evaluate the baseline characteristics (eg, age, weight, sex, race, renal and hepatic function) as potential covariates of ARO-APOC3 PK and PD. This analysis will specifically evaluate the covariates of Country (Japan) and Race (Asian) for any potential significant effect on ARO-APOC3 PK or PD. The PK and PD data collected in this study may be combined with those from study AROAPOC31001 to develop an integrated population PK and population PD model.

13.5.5. Immunogenicity (Anti-Drug Antibodies)

The number of participants to test positive for ADA at baseline and post-treatment will be summarized. Maximum ADA titer and range of titer values will be presented. ARO-APOC3 treatment-induced ADA formation, if any, will be analyzed to ascertain if the ADA response duration is transient or persistent using the definitions in the white paper by (Shankar 2014). The effect of ADA formation on ARO-APOC3 PK, PD, efficacy, and safety will be analyzed.

13.5.6. Subgroup Analysis of Participants in Japan

Analyses of baseline characteristics, efficacy, and safety will be conducted on all participants from Japan and compared with results for all study participants to assess similarities and differences. For the primary efficacy endpoint and key secondary efficacy endpoints, descriptive results from participants from Japan will be visually compared with the results from all study participants. Due to the small sample size, the study will define regions with considerations of race, geography, and number of participants. Japan will be defined as an independent region. Regional differences will be assessed visually with forest plots or other supportive figures/graphs. Subgroups of randomization strata (TG at screening ≥2000 mg/dL vs <2000 mg/dL) may be explored in participants from Japan, if data permit.

Cochran's Q heterogeneity statistic will be used to test consistency for key efficacy endpoints (TG, non-HDL-C, HDL-C, and ApoC3) across Japan and non-Japan regions. Higgins I^2 will be used to measure the degree of inconsistency across regions. Regression models adding a treatment-by-region interaction term will be considered. The treatment difference between participants from Japan and those in the whole study will be calculated as the ratio π. The threshold of π will be set as 0.5 (ie, the treatment effect in participants from Japan will be at least half that of the overall study).

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Arrowhead is responsible for assuring the proper conduct of the study about protocol adherence and validity of the data recorded on the eCRFs. Participant confidentiality will be maintained.

In accordance with applicable regulations, GCP, and Arrowhead procedures, Arrowhead will be responsible for assigning a study monitor (CRA) who will contact the site to organize a visit prior to participant enrollment to review the protocol and data collection procedures with site staff. In addition, the assigned study monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these site visits, the study monitor will perform the following:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution
- Check IMP accountability
- Review blood and urine samples and ensure they are labeled and stored correctly

This will be done to verify the following:

- Data are authentic, accurate and complete
- Safety and rights of participants are being protected
- The study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The PI agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, a study monitor will conduct the following activities in conjunction with the PI or site staff as appropriate:

- Return of all study data to Arrowhead
- Data queries
- Accountability, reconciliation, and arrangements for unused IMP
- Inventory and final disposition (eg, destruction, shipping to repository)
- Review of site study records for completeness

14.2. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. The PI will conduct the study in compliance with the approved protocol and will not implement any deviation from or changes to the protocol, except where necessary to eliminate an immediate hazard to study participants.

Deviations may result from the action or inaction of the participant, PI, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc. – either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, failure to obtain IRB/IEC approvals for the protocol, and ICF revisions

Protocol deviations impacting participant safety or eligibility will be reported to the Sponsor or CRO within 2 business days of occurrence and to the IRB/IEC/competent regulatory authority per local regulatory requirements.

The PI is responsible for ensuring that any known protocol deviations are recorded and reported as agreed. The nature and reasons for protocol deviations will be recorded.

14.3. Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the PI or designee will obtain a copy of the certification form, with certification number and expiration date for all clinical laboratories (excluding central laboratories) used in the study. Reference ranges for each clinical laboratory test used in this study will be obtained from the appropriate central laboratory, which will perform the test for the study. In the event of COVID-related restrictions prohibiting participant site visits, local laboratories with associated local lab reference ranges may be utilized with prior Sponsor approval.

14.4. Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, Arrowhead may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the PI and clinical site agree to notify the Sponsor as soon as possible following awareness of an impending regulatory inspection. The

PI and clinical site agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

14.5. Institutional Review Board/Independent Ethics Committee Approval

Prior to initiation of the study, written IRB/IEC approval of the protocol and ICFs, based on the principles of ICH GCP procedures, will be received. A copy of the signed and dated letter of approval will be provided to the clinical site and Arrowhead prior to study commencement. Any written information or advertisements to be used for patient recruitment will be approved by the IRB/IEC prior to use. A list of the IRB/IEC voting members, their titles or occupations, Federal Wide Assurance number (where applicable), and their institutional affiliations will be requested before study initiation.

Protocol modifications that may impact participant safety or the validity of the study will be approved by the IRB/IEC, following written agreement from the Sponsor.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 14.4 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The PI must submit written approval to the Sponsor before enrolling any patient/participant into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the IMP. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice

(GCP), 21 Code of Federal Regulations (CFR), European Union (EU) Clinical Trial Regulation 536/2014 (EU-CTR), and the applicable regulatory requirement(s).

The protocol will be submitted for approval to the IRB/IEC, and written approval obtained before patients are enrolled. The composition of the IRB/IEC will also be provided to the Sponsor. If approval is suspended or terminated by the IRB/IEC, the PI will notify the Sponsor immediately.

Where applicable, the clinical site and Arrowhead agree to abide by the local compensation guidelines for injury resulting from participating in a company-sponsored research project.

16.3. Written Informed Consent

Informed consent will be obtained before the participant can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements. Study participation includes all screening procedures, as well as any wash out of excluded medications.

It is the responsibility of the PI or medically qualified designee to obtain a written informed consent from everyone participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The PI or medically qualified designee must also explain to the patients that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the PI or by Arrowhead.

For this study, each eligible participant will be required to provide written informed consent before participation in the study.

All eligible participants will have the study explained by the PI or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomforts, risks and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. During the consent process, the PI or designee will also review and discuss with each participant all currently approved therapies for the treatment of FCS that are commercially available in the respective region (eg, volanesorsen in the European Union). It will be pointed out that they can withdraw from the study at any time without prejudice. Each participant will acknowledge receipt of this information by giving written informed consent for participation in the study. The participant will be given a copy of the signed ICF to retain.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The PI agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

Following closure of the study, the PI must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. When permitted by local laws/regulations or institutional policy, some of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The PI must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the PI must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

Arrowhead will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Arrowhead standards/procedures; otherwise, the retention period will default to 15 years.

The material to be stored shall include, but is not limited to, the following:

- Signed and dated copy of the final study protocol and any amendments
- Signed and dated letter of IRB/IEC approval, letter of constitution of the IRB/IEC and copies of any other correspondence relevant to the study with the IRB/IEC or regulatory authorities
- The IRB/IEC-approved ICF
- Current curriculum vitae (signed and dated) of the PI and coworkers with major responsibilities in the trial
- Site Signature and Delegation of Responsibility Log
- Food and Drug Administration Form 1572 (where applicable)
- Financial Disclosure Form(s)
- Blank case report form (CRF)/eCRF
- Signed participant ICFs
- Laboratory reference ranges (signed and dated)
- The completed Clinical Trial Notification Application Form (where applicable)
- Clinical raw data including the source data forms, all clinical laboratory report forms, participant CRFs, drug accountability forms, and dispensing records, etc.

18. PUBLICATION AND DATA DISSEMINATION POLICIES

18.1. Publication

[redacted]

18.2. Ownership

[redacted]

18.3. Confidentiality

[redacted]

[redacted]

18.4. Submission of Results to CTIS Portal

The summary of results of the trial will be submitted to the Clinical Trials Information System (CTIS) portal no later than one year after the trial has ended.

18.5. Dissemination of Clinical Study Data

The data generated by this study are confidential information of the Sponsor. The Sponsor will use reasonable efforts to make the results of the study publicly available. Irrespective of the outcome, the Sponsor agrees to submit to any relevant database a summary of the results of the clinical study within 1 year from the end of the global clinical study.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual study site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

19. REFERENCES

Aalto-Setala K, Fisher EA, Chen X, Chajek-Shaul T, Hayek T, Zechner R, et al. Mechanism of hypertriglyceridemia in human apolipoprotein (apo) CIII transgenic mice. Diminished very low density lipoprotein fractional catabolic rate associated with increased apo CIII and reduced apo E on the particles. J Clin Invest. 1992;90(5):1889-900. Epub 1992/11/01. doi: 10.1172/JCI116066. PubMed PMID: 1430212; PubMed Central PMCID: PMCPMC443250.

Aalto-Setala K, Weinstock PH, Bisgaier CL, Wu L, Smith JD, Breslow JL. Further characterization of the metabolic properties of triglyceride-rich lipoproteins from human and mouse apoC-III transgenic mice. J Lipid Res. 1996;37(8):1802-11. Epub 1996/08/01. PubMed PMID: 8864964.

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76. doi: 10.1093/jnci/85.5.365. PubMed PMID: 8433390.

Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011;108(5):682-90.

Brown EE, Sturm AC, Cuchel M, Braun LT, Duell PB, Underberg JA, et al. Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. J Clin Lipidol. 2020;14(4):398-413. Epub 20200507. doi: 10.1016/j.jacl.2020.04.011. PubMed PMID: 32507592.

Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med. 2014;371(1):22-31. doi: 10.1056/NEJMoa1307095. PubMed PMID: 24941081; PubMed Central PMCID: PMCPMC4180269.

Falko JM. Familial Chylomicronemia Syndrome: A Clinical Guide For Endocrinologists. Endocr Pract. 2018;24(8):756-63. Epub 2018/09/06. doi: 10.4158/EP-2018-0157. PubMed PMID: 30183397.

FDA. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical.

FDA. Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009.

FDA. Meeting Transcript Endocrinologic and Metabolic Drugs Advisory Committee Meeting. May 10, 2018. Available from: https://www.fda.gov/media/116320/download. 2018.

Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature. 1998;391(6669):806-11. doi: 10.1038/35888. PubMed PMID: 9486653.

Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer. 1999;35(6):939-41. doi: 10.1016/s0959-8049(99)00047-7. PubMed PMID: 10533475.

Fitzsimmons D, Kahl S, Butturini G, van Wyk M, Bornman P, Bassi C, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol. 2005;100(4):918-26. doi: 10.1111/j.1572-0241.2005.40859.x. PubMed PMID: 15784041.

Gelrud A, Williams KR, Hsieh A, Gwosdow AR, Gilstrap A, Brown A. The burden of familial chylomicronemia syndrome from the patients' perspective. Expert Rev Cardiovasc Ther. 2017;15(11):879-87. Epub 2017/08/30. doi: 10.1080/14779072.2017.1372193. PubMed PMID: 28847199.

Gerritsen G, Rensen PC, Kypreos KE, Zannis VI, Havekes LM, Willems van Dijk K. ApoC-III deficiency prevents hyperlipidemia induced by apoE overexpression. J Lipid Res. 2005;46(7):1466-73. Epub 2005/05/03. doi: 10.1194/jlr.M400479-JLR200. PubMed PMID: 15863838.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36. Epub 20110409. doi: 10.1007/s11136-011-9903-x. PubMed PMID: 21479777; PubMed Central PMCID: PMCPMC3220807.

Janas MM, Harbison CE, Perry VK, Carito B, Sutherland JE, Vaishnaw AK, et al. The nonclinical safety profile of GalNAc-conjugated RNAi therapeutics in subacute studies. Toxicol Pathol. 2018;46(7):735-45.

Johnson C, Stroes ES, Soran H, Wierzbicki A, Moulin P, Bruckert E, et al. Issues Affecting Quality of Life and Disease Burden in Lipoprotein Lipase Deficiency (Lpld) – First Step Towards a Pro Measure in Lpld. Value Health. 2015;18(7):PA707.

Jong MC, Rensen PC, Dahlmans VE, van der Boom H, van Berkel TJ, Havekes LM. Apolipoprotein C-III deficiency accelerates triglyceride hydrolysis by lipoprotein lipase in wild-type and apoE knockout mice. J Lipid Res. 2001;42(10):1578-85. Epub 2001/10/09. PubMed PMID: 11590213.

Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med. 2014;371(1):32-41. Epub 2014/06/19. doi: 10.1056/NEJMoa1308027. PubMed PMID: 24941082.

Khetarpal SA, Rader DJ. Triglyceride-rich lipoproteins and coronary artery disease risk: new insights from human genetics. Arterioscler Thromb Vasc Biol. 2015;35(2):e3-9. Epub 2015/01/13. doi: 10.1161/ATVBAHA.114.305172. PubMed PMID: 25573854.

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536(7616):285-91. Epub 2016/08/19. doi: 10.1038/nature19057. PubMed PMID: 27535533; PubMed Central PMCID: PMCPMC5018207.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006. PubMed PMID: 19414839; PubMed Central PMCID: PMCPMC2763564.

Mogg R, Mehrotra DV. Analysis of antiretroviral immunotherapy trials with potentially non-normal and incomplete longitudinal data. Stat Med. 2007;26(3):484-97. Epub 2006/04/21. doi: 10.1002/sim.2555. PubMed PMID: 16625520.

Moulin P, Dufour R, Averna M, Arca M, Cefalu AB, Noto D, et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". Atherosclerosis. 2018;275:265-72. Epub 2018/07/07. doi: 10.1016/j.atherosclerosis.2018.06.814. PubMed PMID: 29980054.

NIH. National Institutes of Health, US Department of Health and Human Services. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5 2017 [June 12, 2024]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Proctor SD, Mamo JC. Intimal retention of cholesterol derived from apolipoprotein B100- and apolipoprotein B48-containing lipoproteins in carotid arteries of Watanabe heritable hyperlipidemic rabbits. Arterioscler Thromb Vasc Biol. 2003;23(9):1595-600. Epub 2003/07/05. doi: 10.1161/01.ATV.0000084638.14534.0A. PubMed PMID: 12842838.

Regev A, Palmer M, Avigan MI, Dimick-Santos L, Treem WR, Marcinak JF, et al. Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2019;49(6):702-13.

Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341(6):410-8.

Saleheen D, Natarajan P, Armean IM, Zhao W, Rasheed A, Khetarpal SA, et al. Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. Nature. 2017;544(7649):235-9. Epub 2017/04/14. doi: 10.1038/nature22034. PubMed PMID: 28406212; PubMed Central PMCID: PMCPMC5600291.

Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. J Clin Gastroenterol. 2014;48(3):195-203.

Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J. 2014;16(4):658-73. Epub 20140424. doi: 10.1208/s12248-014-9599-2. PubMed PMID: 24764037; PubMed Central PMCID: PMCPMC4070270.

Stroes E, Moulin P, Parhofer KG, Rebours V, Lohr JM, Averna M. Diagnostic algorithm for familial chylomicronemia syndrome. Atheroscler Suppl. 2017;23:1-7. Epub 20161218. doi: 10.1016/j.atherosclerosissup.2016.10.002. PubMed PMID: 27998715.

Van Horn L, Carson JA, Appel LJ, Burke LE, Economos C, Karmally W, et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. Circulation. 2016;134(22):e505-e29. Epub 20161027. doi: 10.1161/CIR.0000000000000462. PubMed PMID: 27789558.

Williams L, Rhodes KS, Karmally W, Welstead LA, Alexander L, Sutton L. Familial chylomicronemia syndrome: Bringing to life dietary recommendations throughout the life span. J Clin Lipidol. 2018;12(4):908-19. Epub 20180427. doi: 10.1016/j.jacl.2018.04.010. PubMed PMID: 29804909.

Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, et al. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. N Engl J Med. 2019;381(6):531-42. Epub 2019/08/08. doi: 10.1056/NEJMoa1715944. PubMed PMID: 31390500.

Yan H, Niimi M, Matsuhisa F, Zhou H, Kitajima S, Chen Y, et al. Apolipoprotein CIII Deficiency Protects Against Atherosclerosis in Knockout Rabbits. Arterioscler Thromb Vasc Biol. 2020;40(9):2095-107. Epub 20200806. doi: 10.1161/ATVBAHA.120.314368. PubMed PMID: 32757647; PubMed Central PMCID: PMCPMC7484272.

APPENDIX 1. CONTRACEPTION

Women not of childbearing potential must be either surgically sterile or postmenopausal (defined as cessation of regular menstrual periods for at least 12 months without an alternative medical cause) with supportive follicle-stimulating hormone (FSH) consistent with postmenopausal state based on laboratory reference ranges.

If a participant's serum or urine pregnancy test is positive, the participant will be referred to their primary care provider for follow-up. Female participants with a positive pregnancy test at screening or on Day 1 predose will not be enrolled in the study. Female participants who become pregnant during the study will not receive IMP but may otherwise continue in the study.

All participants (female participants of childbearing potential with male partners and male participants with female partners of childbearing potential) must consent to use a highly effective form of contraception in addition to a male condom during the study and for at least 24 weeks after the last dose of study treatment.

The following are acceptable methods of highly effective contraception:

- [In Japan only] Using twice the normal protection of birth control by using a male condom AND one other form of highly effective contraception: birth control pills (combined progesterone and estrogen), contraceptive implant associated with inhibition of ovulation (intrauterine system: IUS only), or intrauterine device; or
- [Other sites] Using twice the normal protection of birth control by using a condom AND one other form of contraception; either birth control pills (The Pill), injectable birth control, birth control patch, vaginal contraceptive ring, or contraceptive implant associated with inhibition of ovulation, or intrauterine device; or
- Surgical sterilization as a single form of birth control: ie, tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy, or equivalently effective surgical form of birth control; or
- True sexual abstinence for the duration of the study and for at least 24 weeks after the last dose of IMP is acceptable only when in line with the preferred and usual lifestyle of the participant.

The following are not considered "true" abstinence and are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only (not available in Japan), and lactational amenorrhea methods.

Note: The Investigator may need to recommend an alternative contraceptive method if hormonal contraceptive methods above are restricted by local regulation and/or guidelines or if a concomitant medication is contraindicated for the participant's selected method of contraception.

APPENDIX 2. LIVER-RELATED STUDY MODIFICATION AND FOLLOW-UP GUIDELINES

Treatment-Emergent ALT/AST	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
Normal baseline: ALT/AST ≥5×ULN Elevated baseline[a]: ALT/AST ≥300 U/L	Normal or elevated Participants with Gilbert's syndrome or hemolysis - no change in baseline TBL	None	Discontinue IMP. Confirm ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies.[b] Follow-up for symptoms.
Normal baseline: ALT/AST ≥3×ULN Elevated baseline[a]: ALT/AST ≥2×baseline	Normal Participants with Gilbert's syndrome or hemolysis - no change in baseline TBL	None	Confirm ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies.[b] Follow-up for symptoms.
Normal baseline: ALT/AST ≥3×ULN Elevated baseline[a]: ALT/AST ≥2×baseline	Normal Participants with Gilbert's syndrome or hemolysis - no change in baseline TBL	Symptoms of clinical hepatitis: severe fatigue, nausea, vomiting, right upper quadrant pain; or immunologic reactions (eg, rash, >5% eosinophilia)	Interrupt IMP. Confirm ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies.[b] IMP can be restarted only if an alternative etiology is identified, and liver enzymes return to baseline. IMP cannot be restarted if hepatic decompensation occurred. Follow-up for symptoms.
Normal baseline: ALT/AST ≥3×ULN Elevated baseline[a]: ALT/AST ≥2×baseline	TBL ≥2×ULN or increased INR to >1.5 (For participants with Gilbert's syndrome or hemolysis - doubling of direct bilirubin if baseline TBL >0.5 mg/dL)	None	Interrupt IMP. Confirm ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies.[b] IMP can be restarted only if an alternative etiology is identified, and liver enzymes return to baseline. IMP cannot be restarted if hepatic decompensation occurred.

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; IMP=investigational medicinal product; TBL=total bilirubin; ULN=upper limit of normal.

[a] Elevated baseline is defined as ALT/AST ≥1.5×ULN.

[b] Acute and chronic viral hepatitis (hepatitis A - E), cholelithiasis, alcohol, or other drugs (both prescribed and over-the-counter herbs and supplements). If needed, consider consultation with hepatologist for identification of alternative etiologies and follow-up.

Source: Adapted from the following guidelines (FDA 2009; Regev 2019).

Guidelines for Close Observation for Potential Drug-Induced Liver Injury

Within 72 hours, perform a complete history, physical, and liver biochemistries, including evaluation of:

- New or worsening signs and symptoms of clinical hepatitis such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

- Concomitant medications, including acetaminophen, dietary supplements, herbal remedies, over-the-counter (OTC) medications, recreational drug use, and special diets
- Alcohol consumption
- Exposure to environmental chemical agents
- Past medical history
- Complete review of systems
- Liver biochemistries including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin (TBL), and INR.

Evaluate participants 2 or 3 times a week for signs and symptoms of clinical hepatitis and obtain liver biochemistries until biochemistries stabilize.

If biochemistries stabilize and the participant is asymptomatic, monitor liver biochemistries once a week until they return to baseline.

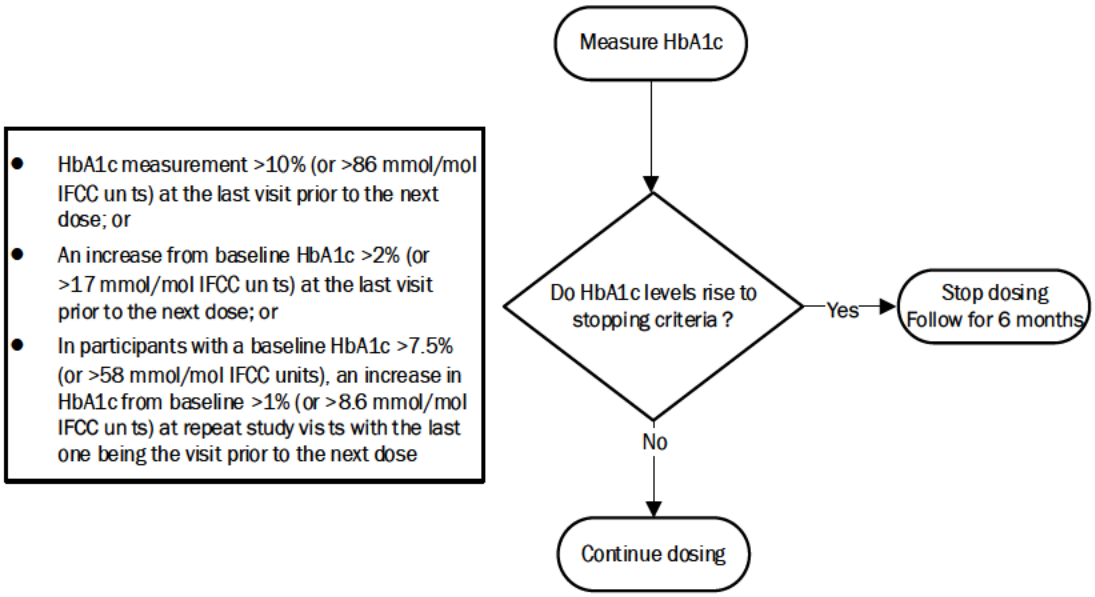
Participants who live far from study sites may be evaluated locally for history, physical exam, and laboratories, if the results are communicated promptly to the Principal Investigator.

APPENDIX 3. GLYCEMIC CONTROL-RELATED GUIDELINES

HbA1c Investigational Product Discontinuation Criteria

Participants should discontinue IMP if they meet the following criteria:

- HbA1c measurement >10% (or >86 mmol/mol IFCC units) at the last visit prior to the next dose; or
- An increase from baseline HbA1c >2% (or >17 mmol/mol IFCC units) at the last visit prior to the next dose; or
- For participants with a baseline HbA1c >7.5% (or >58 mmol/mol IFCC units) who had an increase from baseline >1% (8.6 mmol/mol IFCC units) at repeat study visits with the last one being the visit prior to the next dose.



Guidelines for Excessive Increases in HbA1c

The following guidelines should be followed for increases in HbA1c:

- Investigators are encouraged to evaluate diabetes status and adjust diabetes treatment according to clinical practice and diabetes care guidance.
- At the Investigator's discretion, any participants with worsening diabetic control may return for an unscheduled visit for evaluation of HbA1c prior to the next planned dose to confirm continued treatment eligibility.
- The participants who discontinue IMP due to the above criteria will be followed for 6 months after their last dose per the Schedule of Activities.

APPENDIX 4. ADVERSE EVENTS OF SPECIAL INTEREST - LIST OF MEDDRA PREFERRED TERMS OR SEARCH STRATEGY

INJECTION SITE REACTIONS:

As determined by the Sponsor's pharmacovigilance staff, the following the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms will be considered to represent injection site reaction:

Injection site discomfort	Injection site calcification
Injection site discoloration	Injection site cellulitis
Injection site erythema	Injection site dermatitis
Injection site irritation	Injection site erosion
Injection site inflammation	Injection site fibrosis
Injection site induration	Injection site indentation
Injection site pain	Injection site necrosis
Injection site edema	Injection site nodule
Injection site pruritus	Injection site ulcer
Injection site rash	Injection site bruising
Injection site urticaria	Injections site haematoma
Injection site reaction	Injection site hypersensitivity
Injection site swelling	Injection site infection
Injection site abscess	Injection site pallor
Injection site abscess sterile	Injection site paraesthesia
Injection site atrophy	Injection site warmth

HYPERSENSITIVITY/ANAPHYLAXIS EVENTS:

A participant is said to have an episode fulfilling Sampson criteria **if at least one** of the following criteria is met:

Criterion 1: The participant experienced an onset of both Condition 1 and Condition 2 up to 24 hours post dosing with study drug:

- Condition 1 - a skin or mucosal membrane AE
- Condition 2 - a respiratory compromise AE or an end-organ dysfunction/reduced blood pressure AE, or reduced systolic blood pressure under 90 mm Hg or greater than 30% decrease from baseline based on the vital signs data

Criterion 2: The participant experienced an onset of any 2 or more conditions up to 24 hours postdosing with study drug:

- Condition 1 – a skin or mucosal membrane AE

- Condition 2 – a respiratory compromise AE
- Condition 3 – an end-organ dysfunction/reduced blood pressure AE, or reduced systolic blood pressure
- Condition 4 – a gastrointestinal AE

Criterion 3: The participant experienced reduced systolic blood pressure up to 24 hours post dosing with study drug, and at least 1 qualifying event.*

*A qualifying event is defined as any of the following occurring during the study, after the first administration of the study drug associated with the current reduced systolic blood pressure event.

- Condition 1 – an event meeting Criterion 1
- Condition 2 – an injection site reaction
- Condition 3 – AE under Anaphylactic reaction Standardized MedDRA Query (SMQ) or the Angioedema SMQ or the Hypersensitivity SMQ considered to be related to the study drug.

POTENTIAL HEPATOTOXICITY EVENTS:

The following the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms will be considered to possibly represent hepatic events:

Drug-induced liver injury	Liver injury
Hepatoxicity	Hepatic enzyme increased
Acute hepatic failure	Alanine aminotransferase abnormal
Ascites	Alanine aminotransferase increased
Hepatic failure	Aspartate aminotransferase abnormal
Hepatic fibrosis	Aspartate aminotransferase increased
Hepatic necrosis	Bilirubin conjugated abnormal
Hepatic steatosis	Bilirubin conjugated increased
Hepatobiliary disease	Hepatic enzyme abnormal
Hepatocellular injury	Hepatic enzyme increased
Hyperbilirubinemia	Liver function test increased
Jaundice	Transaminase increased
Liver disorder	Hypertransminasaemia

APPENDIX 5. GUIDANCE FOR MANAGING LOCAL INJECTION SITE REACTIONS

I. Best Practices of SC Administration to Avoid the Risk of LISR

For the Clinical Trial Site staff involved in administering subcutaneous injections of the study medications, below are some key tips to help minimize the risk of injection site reactions:

1. Proper Injection Technique: Ensure that injections are administered properly. This includes rotating injection sites and injecting at the correct depth and angle.
    a. Sites to ensure study drug administration staff are properly trained in administering subcutaneous injections. This includes understanding the correct technique and angle (see #5 below) injection sites appropriate for SC administration.
2. Room Temperature Medication: allow the study medication to come to room temperature before administering the injection. Cold medication can be more painful and may increase the risk of a reaction.
3. Assess Injection Sites: Before administering the injection, assess the subject's skin for signs of bruising, swelling, or inflammation.
4. Educate on the importance of rotating injection sites to avoid developing lumps or nodules or absorption issues.
    a. Avoid injecting into the muscle, sensitive spots (around the umbilicus), or those close to blood vessels, joints, or areas with visible signs of inflammation, redness, or tenderness.
    b. Avoid overusing any one area. If the subject is on insulin or other subcutaneously administered drugs, ask about the locations of the most recent injections and avoid them, Also, ask the subject about the most convenient, least sensitive spots.
5. Injection Technique: Use the proper injection technique, including pinching the skin and inserting the needle at the correct angle, usually 45 degrees to 90 degrees (the angle depends on the length of the needle and the amount of subcutaneous tissue).
6. Inject the medication slowly to minimize discomfort and tissue trauma.
7. Cold Compress or Ice Pack (if needed): Applying an ice pack to the injection site before and after the injection can help reduce pain and inflammation.
8. Hydration: Ensure study subjects are well hydrated before and after the injection. Staying hydrated can help reduce the risk of an LISR
9. Hand Hygiene, Gloves and Cleanliness: Ensure that the injection site is clean before administering the injection. Clean the site with an alcohol swab (60–70% alcohol) and allow it to air dry (30 seconds) become sterile before inserting the needle. Do not allow the needle to be in contact of any nonsterile surface.
10. Monitor for Adverse Reactions: Monitor the subject for any signs of adverse reactions such as redness, swelling, pain, or itching at the injection site. If any reactions occur, assess their severity and provide appropriate care.

II. Documentation and Follow-Up: Document the injection site, the exact timing of the study medication administered, and any adverse reactions in the CRF. Follow up with the subject to ensure that any injection site reactions are resolved. Record the onset of the LISR, resolution state, and time. Note: Most LISR reported are mild, need no intervention or management, and resolve no later than 48 hours after onset.

As indicated in the Study protocol ALL AEs (and SAEs) are reported according to MedDRA Terms and are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 (NIH 2017). LISR are graded according to CTCAE as follows:

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	

Note: For SC administration, moderate LISRs are reactions with erythema, induration, swelling >5 cm, or associated with pain >24 hours that interfere with daily activity and require the use of non-narcotic pain management (FDA 2007).

By following the guidelines, best practices and tips provided above, study staff can help minimize the risk of LISRs when administering subcutaneous study drugs, thereby ensuring the safety and comfort of clinical trial subjects.

APPENDIX 6. POSTPRANDIAL SUBSTUDY AT SELECTED SITES IN AUSTRALIA, CANADA, AND THE UNITED STATES

Familial chylomicronemia syndrome (FCS) is a rare, inherited lipid disorder characterized by high levels of plasma triglycerides and chylomicrons, which may cause life-threatening acute pancreatitis (Williams 2018). Currently, the therapeutic management of this disorder relies solely on a very low-fat diet (<20g fat/day), which is difficult to maintain long term and can impose a significant clinical and psychosocial burden on patients and caregivers. A postprandial substudy will be performed at selected sites in Australia, Canada, and the United States in adults with FCS after the ingestion of a higher fat meal to evaluate the impact of treatment with ARO-APOC3 on postprandial serum TG levels in these participants when not following their usual low-fat diet.

Substudy Design:

Approximately 12 participants who have been administered at least 2 consecutive doses of ARO-APOC3 during the AROAPOC3-3001 Open Label Extension Period will be eligible to participate in the substudy. Day 1 of the substudy must occur 30 days after these participants have been administered their most recent ARO-APOC3 dose in the Open Label Extension Period of the AROAPOC3-3001 study.

Participants must not receive any ARO-APOC3 doses while participating in the AROAPOC3-3001 substudy.

The duration of the substudy is approximately 30 days from the Day 1 visit to the Day 30 End of Substudy (EOSS) telephone call.

The substudy schema is provided in Figure 2.

Substudy Eligibility:

To be eligible for the substudy, participants must:

- Have completed the double-blind period of the AROAPOC3-3001 study and transitioned to the Open Label Extension Period.
- Have received at least 2 consecutive doses of ARO-APOC3 in the ARO-APOC3-3001 study Open Label Extension Period and 30 days must have elapsed since their most recent ARO-APOC3 dose.
- Be willing to follow diet counseling and maintain a stable diet based on standard of care throughout the study (ie, consent through Day 30 [EOSS]).
- Have fasting TG levels ≤500 mg/dL at the most recent Open Label Extension visit.

Participants are not eligible for the substudy if they were discontinued from either the AROAPOC3-3001 study double-blind or open label extension periods, or if they met any AROAPOC3-3001 study or treatment discontinuation criteria.

Substudy Methodology:

After signing the informed consent form participants will be assessed for eligibility and those meeting the eligibility criteria will be enrolled. In addition to the Open Label Extension Period study assessments, these participants will undergo additional clinical and laboratory assessments for the substudy. The substudy SOA is provided in Table 9.

TG values, lipid parameters, fasting state (premeal) symptoms and assessments evaluated throughout the substudy will be collected from participants in a fasted state.

Participants will be counseled to remain on stable background medications and on a specified diet throughout the substudy (ie, from consent through Day 30 [EOSS]), as instructed by the principal investigator and per standard of care.

On Days 1, 2, and 3 participants will enter the clinic after an overnight fast of ≥10 hours. The following procedures will be completed on Days 1, 2, and 3 in the order listed:

- Day 1:
  - Perform 12-lead electrocardiogram (ECG) and clinical assessments including physical examination, weight, and vital signs
  - Fasting blood sample collection to assess serum TG, lipids, and lipoproteins levels, and other clinical parameters (glucose, insulin, C-peptide, free fatty acids, IL-1b, IL-6, TNFa).
  - Consume a standard FCS breakfast with content limited to 10% of daily caloric intake (≈7 grams of fat)
  - Post breakfast blood sample collection at 1, 2, 5, and 8 hours to assess serum TG, lipids, and lipoproteins levels, and other clinical parameters (glucose, insulin, C-peptide, free fatty acids, IL-1b, IL-6, TNFa)
  - Participants will be discharged from the clinic after the 8-hour blood sample collection
  - Consume a standard FCS lunch after the 8 hour blood sample collection
  - Consume a standard FCS dinner per the participant's standard schedule
- Day 2:
  - Perform clinical assessments including physical examination, weight, and vital signs
  - Fasting blood sample collection to assess serum TG, lipids, and lipoproteins levels, and other clinical parameters (glucose, insulin, C-peptide, free fatty acids, IL-1b, IL-6, TNFa).
  - Consume a higher-fat breakfast with dietary content increased to ≈26 grams fat content (dietary fat content increased to 20% of daily caloric intake [≈40 grams of fat per day])
  - Post breakfast blood sample collection at 1, 2, 5, and 8 hours to assess serum TG, lipids, and lipoproteins levels, and other clinical parameters (glucose, insulin, C-peptide, free fatty acids, IL-1b, IL-6, TNFa).
  - Participants will be discharged from the clinic after the 8-hour blood sample collection
  - Consume a standard FCS lunch after the 8 hour blood sample collection

  - Consume a standard FCS dinner per the participant's standard schedule

- Day 3:
  - Perform 12-lead ECG and clinical assessments including physical examination, weight, and vital signs
  - Fasting blood sample collection ≈24 hours after consuming the higher-fat breakfast to assess serum TG, lipids, and lipoproteins levels, and other clinical parameters (glucose, insulin, C-peptide, free fatty acids, IL-1b, IL-6, TNFa).
  - Participants will be discharged from the clinic when the laboratory and clinical assessments (ie, physical examination, weight, and vital signs) are completed

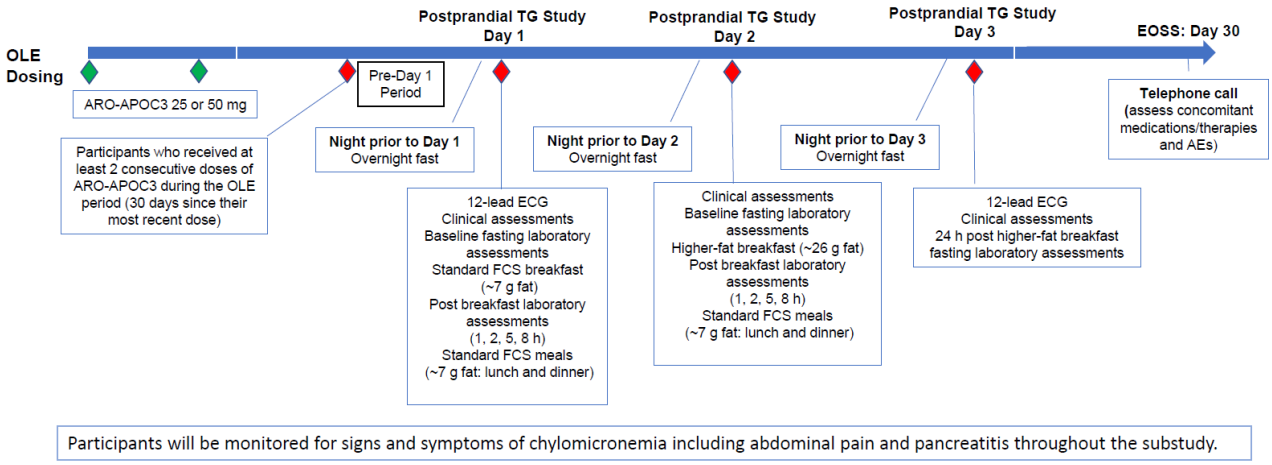
On Day 30 participants will have an EOSS telephone call to assess concomitant medications and therapies and potential AEs.

Participants will be monitored for signs and symptoms of chylomicronemia, including abdominal pain and pancreatitis throughout the substudy.

Statistics

Substudy data will be summarized descriptively.

Figure 2: Substudy Schema



Abbreviations: AE=adverse event; ECG=electrocardiogram; EOSS=End of Substudy; FCS=familial chylomicronemia syndrome; OLE=Open Label Extension; TBD=to be determined; TG=triglyceride.
Note: This substudy will enroll participants who received at least 2 consecutive doses of ARO-APOC3 during the AROAPOC3-3001 OLE period, have had 30 days elapse since being administered their most recent ARO-APOC3 dose, and have fasting serum triglycerides levels ≤500 mg/dL at the most recent OLE visit. Clinical assessments include physical examination, weight, and vital signs.

Table 9: Substudy Schedule of Activities

Assessment	Pre-Day 1	Day 1	Day 2	Day 3	Day 30 (EOSS)/ET[a]
(Visit Windows, Days)	**-30 to -1**	**--**	**--**	**--**	**±5**
Informed Consent	X				
Eligibility Criteria	X				
Enrollment		X			
Physical Exam[b]		X	X	X	
Weight		X	X	X	
Vital Signs (BP, temp, pulse ox, RR, HR)[c]		X	X	X	
Concomitant Meds/Therapies		X	X	X	X
Adverse Events		X	X	X	X
12-lead ECG[d]		X		X	
Lipid parameters[e]	X[f]	X[g]	X[g]	X	
Clinical Laboratory (glucose, insulin, C-peptide)		X[g]	X[g]	X	
FFA and lipoprotein particles		X[g]	X[g]	X	
Proinflammatory Panel (IL-1b, IL-6, TNFa)		X[g]	X[g]	X	
Regular FCS meal (≈7 g fat content) administered		X	X		
Higher-fat breakfast (≈26 g fat content) administered			X		

Abbreviations: BP=blood pressure; CBC=complete blood count; chem=blood chemistry; coag=coagulation; ECG=electrocardiogram; EOSS=End of Substudy; ET=early termination; FCS=familial chylomicronemia syndrome; FSH=follicle-stimulating hormone; heme=hematology; HIV=human immunodeficiency virus; HR=heart rate; meds=medications; LLN=lower limit of normal; PI=Principal Investigator; PK=pharmacokinetics; pulse ox=pulse oximetry; RR=respiratory rate; temp=temperature; TG=triglyceride; UA=urinalysis.

[a] The 30-day follow- up visit will be performed by telephone to assess concomitant medications/therapies and adverse events.

[b] A complete physical examination will be done at Day 1 period only, and afterwards a symptom-directed physical examination will be performed. Any physical exam should be performed prior to any blood draw.

[c] Vital signs should be collected prior to any blood draw.

[d] Single 12-lead ECG will be performed in the supine position after the participant has rested comfortably for 5 minutes. ECGs should be collected prior to any blood draws.

[e] Fasting lipid parameter testing must be done after the participant has fasted for ≥10 hours before collection at each study visit. The following lipid parameters will be evaluated: Total Cholesterol, Triglycerides, Calculated non-HDL-C, HDL-C, Calculated VLDL-C, Calculated LDL-C (Friedewald & Hopkins), Lp (a), LDL/HDL Ratio, Apo C-III, Total Apo B, Chylomicrons by Preparative Ultracentrifugation, Triglycerides, Direct LDL, LDL-C by Preparative Ultracentrifugation.

[f] For the purposes of assessing subject eligibility criteria, site should consider the fasting TG value at the most recent Open Label Extension visit.

[g] Serial postmeal laboratory assessments will be evaluated at each of the following time points (1 hour, 2 hours, 5 hours, and 8 hours postmeal). The following parameters will be evaluated: glucose, insulin, C-peptide, lipid parameters (Total Cholesterol, Triglycerides, Calculated non-HDL-C, HDL-C, Calculated VLDLC, Calculated LDL-C (Friedewald & Hopkins), Lp (a), LDL/HDL Ratio, Apo C-III, Total Apo B, Chylomicrons by Preparative Ultracentrifugation, Triglycerides, Direct LDL, LDL-C by Preparative Ultracentrifugation), Free Fatty Acids, Lipoprotein Particles, Proinflammatory Panel (IL-1b, IL-6, TNFa)

Signature Page for VV-CLIN-000096 v10.0
AROAPOC3-3001 Clinical Study Protocol Amendment 8

Approval Task	[redacted]-2024 17:50:17 GMT+0000
Approval Task	[redacted]v-2024 17:58:36 GMT+0000
Approval Task	[redacted]-2024 20:11:39 GMT+0000
Approval Task	[redacted]-2024 00:46:00 GMT+0000

Signature Page for VV-CLIN-000096 v10.0