



A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia
Protocol Number: AROAPOC3-2001

Original Protocol: 24 NOV 2020

Amendment 1, Version Date 19 JAN 2021

Amendment 2, Version Date 19 April 2021

Amendment 3, Version Date 01 November 2021

Amendment 4, Version Date 22 November 2022

Amendment 5, Version Date 26 January 2023

Product number: ARO-APOC3
Indication: Severe Hypertriglyceridemia (SHTG)
IND Number: 144947
EudraCT Number: 2021-000687-30
Sponsor: Arrowhead Pharmaceuticals, Inc.
177 East Colorado Boulevard, Suite 700
Pasadena, CA 91105
USA

Sponsor's Responsible Medical Monitor:

[REDACTED]
[REDACTED]
[REDACTED]
Arrowhead Pharmaceuticals, Inc.
177 East Colorado Boulevard, Suite 700
Pasadena, CA 91105
+1 (626) 304 3400

This study will be performed in compliance with the protocol, the principles of Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Confidentiality Statement: Information contained in this protocol should not be disclosed, other than to those directly involved in the execution or ethical review of the study, without written authorization from Arrowhead Pharmaceuticals, Inc. It is, however, permissible to provide information to a participant to obtain consent.

1. PROTOCOL SYNOPSIS

TITLE OF STUDY:

A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia

PROTOCOL NUMBER:

AROAPOC3-2001

PHASE OF DEVELOPMENT:

Phase 2b

STUDY SITES:

Approximately 80 centers globally

STUDY TREATMENTS:

There will be 2 study treatments; 1 active (Test Formulation) and 1 placebo (Reference Formulation).

Test Formulation:

The test formulation is active ARO-APOC3 Injection (also referred to as ARO-APOC3) administered subcutaneously (SC). The active pharmaceutical ingredient (API) contained in ARO-APOC3 is a synthetic, double-stranded, short interfering RNA (siRNA) duplex conjugated to an N-acetyl-galactosamine 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.

Doses and Number of Doses per Treatment:

Three dose levels of ARO-APOC3 will be compared to placebo in participants with severely high triglycerides (TG), or SHTG, who had mean fasting TG of ≥ 500 mg/dL (5.65 mmol/L) and ≤ 4000 mg/dL (45.2 mmol/L) at Screening. A total of approximately 216 participants will be enrolled in the study. All dose cohorts will enroll in parallel with 72 participants per dose cohort randomly assigned in a 3:1 ratio to receive AROAPOC3 or placebo. Each participant will receive SC injections on Day 1 and Week 12 for a total of 2 injections as follows:

- ARO-APOC3 **10 mg** (n=54) or volume-matched placebo (n=18) at Day 1 and Week 12;
- ARO-APOC3 **25 mg** (n=54) or volume-matched placebo (n=18) at Day 1 and Week 12; or
- ARO-APOC3 **50 mg** (n=54) or volume-matched placebo (n=18) at Day 1 and Week 12.

The duration of the study is approximately 54 weeks from Screening to the Week 48 End-of-Study (EOS) examination.

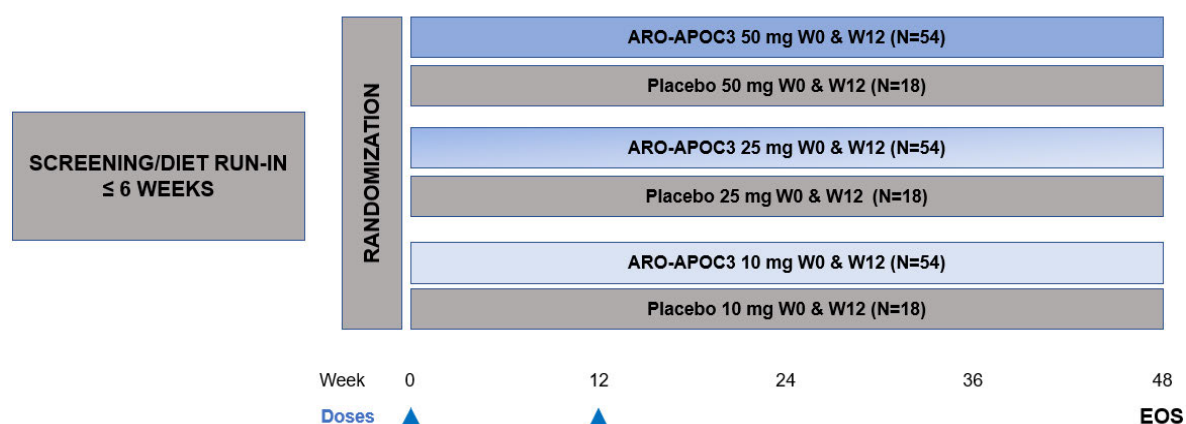
STUDY OBJECTIVE:

The primary objective of the study is to evaluate the safety and efficacy of ARO-APOC3 in adults with SHTG and to select a dosing regimen for later stage clinical studies in this patient population.

STUDY DESIGN:

This is a randomized, double-blind, placebo-controlled, Phase 2b clinical study. After informed consent participants will be assessed for eligibility. Participants who have met all the protocol eligibility criteria during Screening may be enrolled and randomly assigned to treatment in a double-blind fashion. Participants will be randomly assigned 3:1 to receive 1 of 3 ARO-APOC3 dosing regimens or matched placebo (see Study Schema). All dose cohorts will enroll in parallel. Enrolled participants will be counseled to remain on stable background medications and on the specified diet throughout the study, as recommended by the Investigator in accordance with local standard of care. The specifics of the diet will be at the discretion of the Investigator based on each individual's diagnosis and medical needs.

Study Schema



Abbreviations: EOS = end of study; W = week.

Blinding will be preserved to the extent possible; however, treatment unblinding may occur, at the Investigator's or Medical Monitor's discretion, where deemed necessary for treatment of an adverse event (AE) or for a safety-related decision or a decision to be made regarding study continuation in an individual participant.

Adverse Event Monitoring

Safety assessments will include:

AEs and serious AEs (SAEs), physical examinations, vital sign measurements (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECGs), clinical laboratory tests, concomitant medications/therapy, and reasons for treatment discontinuation. Safety assessments will be performed at specified time points and up to study completion.

The AE/SAE reporting period for an enrolled participant will begin when the participant provides informed consent. Treatment-emergent AEs (TEAEs) and SAEs are defined as those that occur following investigational product (IP) administration or are a pre-existing condition exacerbated by IP. The TEAE reporting period begins after the first dose and extends until the EOS visit is complete. All SAEs that occur during the reporting period, in addition to reporting via electronic case report forms (eCRFs), must also be reported to the Sponsor via the SAE report form immediately upon becoming aware of the event. 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 Investigator 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 IP, the Investigator will promptly notify the Sponsor. Laboratory or diagnostic assessment (eg, ECG) abnormalities will be reported as AEs if considered clinically significant (CS) by the Investigator. Laboratory or diagnostic assessment abnormalities not reported as AEs are not to be reported as CS in the study database.

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 IP dosing of that participant; or
- A need for apheresis or other emergent interventions indicated to lower TG; or
- Acute pancreatitis; or
- In participants with normal (per central laboratory reference range) aspartate aminotransaminase (AST) or alanine aminotransferase (ALT) on Day 1, treatment-emergent elevations $>3\times$ upper limit of normal (ULN) at least possibly related to IP per study Investigator, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to [Appendix 1](#) for specific guidelines regarding treatment discontinuation or interruption for participants with any of the below findings:
 - AST or ALT $>5\times$ ULN will lead to permanent discontinuation of IP dosing of that participant per [Appendix 1](#). The participant will remain on study follow-up visits until EOS as per the Schedule of Assessments (SOA) (refer to [Table 1](#)).
 - AST or ALT $>3\times$ ULN with a total bilirubin $>2\times$ ULN
 - AST or ALT $>3\times$ ULN with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia ($>5\%$)
 - AST or ALT $>3\times$ ULN with a treatment-emergent international normalized ratio (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 $>2\times$ baseline or ≥ 300 U/L (whichever occurs first) at least possibly related to IP per study Investigator, as specified below, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to [Appendix 1](#) for specific guidelines regarding treatment discontinuation or interruption for participants with any of the below findings:
 - AST or ALT $>3\times$ baseline or ≥ 300 U/L (whichever occurs first)

- AST or ALT $>2\times$ baseline or ≥ 300 U/L (whichever occurs first) with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia ($>5\%$)
- AST or ALT $>2\times$ baseline or ≥ 300 U/L with a total bilirubin $>2\times$ ULN
- AST or ALT $>2\times$ baseline or ≥ 300 U/L or 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 AST or ALT are provided in [Appendix 1](#).

Study Drug Discontinuation Criteria for Increased HbA1c

Regarding glycated hemoglobin (HbA1c) drug discontinuation criteria, participants should discontinue IP if they meet the following criteria (refer to [Appendix 3](#)):

- HbA1c measurement $>10\%$ (or >86 mmol/mol International Federation of Clinical Chemistry [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 IP due to HbA1c determinations will be followed for 6 months after their last dose per the Schedule of Assessments.

For any participant experiencing an acute pancreatitis, all TG levels will be provided by the central laboratory to the Investigator and Medical Monitor, and the participant will be unblinded to their assigned treatment allocation. If the participant was assigned to receive ARO-APOC3, their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor. If the participant was assigned to placebo, further dosing will be discontinued; however, the participant may continue to be followed for the remainder of the 48-week Treatment Period, after which, the subject may opt to receive ARO-APOC3 in the planned open-label extension study.

Sponsor or Investigator can discontinue any participant at any time.

DATA SAFETY COMMITTEE:

An independent Data Safety Committee (DSC) will review safety data after half of the total number of participants planned for enrollment have received at least 1 dose of IP. The DSC meetings may also occur on an ad hoc basis to review safety data and to make decisions related to the study if needed. Details of DSC structure, processes, and possible actions are provided in the DSC charter.

The DSC may recommend to the Sponsor to pause additional dosing in the study to allow 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

STUDY DURATION (PLANNED):

The duration of the study is approximately 54 weeks from Screening to the Week 48 EOS examination.

The Screening period will last up to approximately 6 weeks (Day -42 to Day -1). TG values assessed during the Screening period for eligibility and lipid parameters evaluated throughout the study will be collected from participants in a fasted state.

After Week 48, participants will be eligible and invited to consent and continue in an open-label extension study. All placebo participants who opt to continue will switch to active drug during the extension study.

STUDY POPULATION/NUMBER OF PARTICIPANTS PLANNED:

This study will be conducted in adults with SHTG (fasting TG ≥ 500 mg/dL, [5.65 mmol/L]). A total of approximately 216 participants will be enrolled in the study.

STUDY ELIGIBILITY:

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;
2. Based on medical history, prior evidence of fasting TG ≥ 500 mg/dL (5.65 mmol/L);
3. A mean fasting TG ≥ 500 mg/dL (5.65 mmol/L) and ≤ 4000 mg/dL (45.2 mmol/L) collected at two separate and consecutive visits at least 7 days apart and no more than 17 days apart during the Screening period;
4. If the participant has a medical history of clinical ASCVD or elevated 10-year ASCVD risk (eg, $\geq 7.5\%$ per American Heart Association/American College of Cardiology [ACC/AHA] risk calculator for subjects ≥ 40 years of age or Framingham risk score calculator for subjects under the age of 40) then the participant 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;
5. Able and willing to provide written informed consent prior to the performance of any study-specific procedures;

6. Willing to follow diet counseling and maintain a stable diet as per Investigator judgment based on local standard of care;
7. Participants of childbearing potential must agree to use highly-effective contraception, during the study and for at least 24 weeks following the last dose of IP. Males must not donate sperm during the study and for at least 24 weeks following the or last dose of IP;
8. Women of childbearing potential on hormonal contraceptives must be stable on the medication for >2 menstrual cycles prior to Day 1; and
9. Participants on any of the following medications must be on a stable regimen for the specified duration prior to collection of Screening Visit (S2) laboratory tests and for the duration of study participation:

Medication	Time on stable regimen prior to collection of Screening Visit (S2) laboratory tests
Lipid-lowering therapies (including statins)	≥4 weeks
Beta-blockers, thiazide diuretics	≥4 weeks
Fibrates	≥6 weeks
PCSK9 inhibitors	≥8 weeks
Retinoids	≥8 weeks
Atypical antipsychotics	≥12 weeks
Diabetes mellitus medications	≥12 weeks
Anticoagulation therapy	≥12 weeks
Thyroid hormone replacement therapy	≥12 weeks
Testosterone replacement therapy	≥16 weeks
Oral estrogens, tamoxifen, raloxifene	≥16 weeks
Immunosuppressants	≥24 weeks

NOTE: All laboratory tests used as inclusion criteria will be assessed by a central laboratory and may be repeated once 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.

Exclusion Criteria:

1. Current use or use within the last 365 days from Day 1 of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule;
2. Active pancreatitis within 12 weeks prior to Day 1;
3. Known genetically confirmed diagnosis of Familial Chylomicronemia Syndrome (FCS)

4. Any planned bariatric surgery or similar procedures to induce weight loss during the period starting at consent through end of the study;
5. History of major surgery within 12 weeks of Day 1 or planned major surgery during the study;
6. Planned coronary intervention (such as stent placement or heart bypass) during the study;
7. History of acute coronary syndrome event within 24 weeks of Day 1;
8. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%;
9. Uncontrolled hypertension (sitting blood pressure >160/100 mmHg at Screening); participant may be re-screened once hypertension is controlled;
10. History of hemorrhagic stroke within 24 weeks of Day 1;
11. History of bleeding diathesis or coagulopathy;
12. Current diagnosis of nephrotic syndrome;
13. Any of the following laboratory values at Screening:
 - a. Hepatic: ALT or AST >2× ULN at Screening;
 - b. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² (using the Modification of Diet in Renal Disease [MDRD] equation) at Screening;
 - c. HbA1c >9.0% (or >75 mmol/mol IFCC units) at Screening;
 - d. Spot urine protein/spot urine creatinine ratio >3 grams per day;
 - e. Clinically significant abnormality in PT, aPTT, or INR
14. 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 (stable doses of testosterone replacement therapy >16 weeks prior to Screening (visit S2) is permitted for a documented history of hypogonadism [low testosterone] as verified in subject health records)
 - b. Plasma apheresis within 4 weeks prior to Day 1 or planned during the study;
15. Blood donation of 50 to 499 mL within 4 weeks of Screening (visit S2) laboratory collection or of >499 mL within 8 weeks of Screening (visit S2) laboratory collection;
16. Known history of human immunodeficiency virus infection;
17. 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);
18. Clinical evidence of uncontrolled hypothyroidism or hyperthyroidism as per Investigator's judgment;
19. 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 Investigator's opinion, at risk of relapse for recent cancer;

20. Use of an investigational agent or device within 30 days or within 5 half-lives, based on plasma pharmacokinetics (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;
21. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week (1 unit = 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol); or
22. Any concomitant medical or psychiatric condition or social situation or any other situation that, in the Investigator's judgment, would make it difficult to comply with protocol requirements or put the participant at additional safety risk.

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

ENDPOINTS:

Primary Endpoint:

The primary endpoint of the study is:

- Percent change from baseline at Week 24 in fasting TG.

Secondary Endpoints:

The following are the secondary endpoints to be evaluated in this study:

- Percent change over time through Week 48 in fasting TG;
- Percent change from baseline at Week 24 and over time through Week 48 in apolipoprotein (Apo)C-III;
- Percent change from baseline at Week 24 and over time through Week 48 in fasting non-high-density lipoprotein-cholesterol (non-HDL-C);
- Percent change from baseline at Week 24 and over time through Week 48 in fasting HDL-C;
- Percent change from baseline at Week 24 and over time through Week 48 in fasting total apolipoprotein B (ApoB);
- Percent change from baseline at Week 24 and over time through Week 48 in fasting low-density lipoprotein-cholesterol (LDL-C) using ultracentrifugation;
- Change from baseline in plasma concentrations of ARO-APOC3 over time through Week 12; and
- The frequency and severity of AEs and SAEs over time through Week 48.

Exploratory Endpoints:

The following are the exploratory endpoints defined in this study:

- Change and/or percent change from baseline over time through Week 48 in TG and other fasting lipid parameters (total cholesterol, LDL-C measured using Martin-Hopkins methodology, LDL/HDL ratio, very-low-density lipoprotein-cholesterol [VLDL-C], ApoB-48, lipoprotein [LP][a], ApoB-100, ApoC-II, ApoA-I and ApoA-V [all values drawn after at least a 10-hour fast]);
- Change from baseline at Week 24 and overtime through Week 48 in fasting serum blood glucose, HbA1c, homeostatic model assessment for insulin resistance (HOMA-IR) and C-peptide;
- Change from baseline over time through Week 48 in high sensitivity C-reactive protein (hsCRP);
- Cumulative number of on-study occurrences of acute pancreatitis events over time through Week 48;
- Cumulative number of on-study hospitalizations for abdominal pain over time through Week 48;

Note: All AEs and SAEs reported by the Investigator during the study that are consistent with an event of acute pancreatitis as per 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) $\geq 3 \times$ ULN; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography.

- Proportion of participants requiring emergent apheresis over time through Week 48;
- Change and percent change from baseline to Week 24 in liver fat content using MRI-proton density fat fraction (PDFF); only in participants with a liver fat fraction of $\geq 8\%$ at Screening; and
- Emergence of and levels of anti-drug antibodies to ARO-APOC3 in those receiving ARO-APOC3 over time through Week 48.

DATA ANALYSIS / STATISTICAL METHODS:

Statistical Considerations:

The primary analysis of the primary endpoint will evaluate the difference in means between each ARO-APOC3 dose group and pooled placebo groups and will be conducted in all randomized participants who receive at least 1 dose of IP (Full Analysis Set [FAS]). Primary and all secondary efficacy endpoints, along with aggregate safety and tolerability data summaries, tabulated by treatment group, will be evaluated and reported after all randomized participants complete the Week 48 study visit.

Based on the previous Phase 1 study it is assumed that ARO-APOC3 dose groups will have 50% to 70% more reduction than placebo, with a standard deviation of 10% for ARO-APOC3 dose groups and 40% for placebo. With these assumptions, the study will have greater than 99% power to detect any active treatment dose cohort which is significantly different from placebo with 18 complete

participants per treatment group, using a two-sided test and 1.67% level of significance, adjusted for multiplicity. With the considerations of dropout and to observe more participants for clinical safety, a total of 216 participants will be randomly assigned to treatment in a 3:1 (active to placebo) ratio within each dose cohort (72 participants per dose cohort).

Randomization to placebo and active dose cohorts will be stratified based on:

- Mean level of TG at Screening (≥ 1000 mg/dL versus < 1000 mg/dL).

Prespecified subgroup analyses will be conducted for:

- Participants with a genotype consistent with FCS (including but not limited to homozygous, compound heterozygous, or double heterozygous loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase (LPL) activity including *LPL*, *APOC2*, *APOA5*, *GPIHBP1*, *LIPG*, *GPD1*, or *LMF1*);
- Participants with TG at baseline of 500 to 2000 mg/dL (5.65 to 22.6 mmol/L); and
- Participants with TG at baseline of > 2000 mg/dL (22.5 mmol/L).

Efficacy and Pharmacodynamic Analyses:

The primary analysis will be performed using a mixed model repeated measures (MMRM) approach and will evaluate the difference in means between each ARO-APOC3 dose group and pooled placebo groups in all randomized subjects who receive at least 1 dose of IP (FAS). The estimand of interest is the difference in means of percent change from baseline in fasting TG at Week 24 in adult SHTG population (as defined by the inclusion/exclusion criteria), regardless of treatment compliance or other intercurrent events post-baseline. When performing the primary analysis, the adjustment for multiplicity of testing several arms versus placebo will be carried out using Holm's step-down procedure.

All continuous secondary endpoints will be analyzed in a similar manner to the primary endpoint, unless otherwise noted. 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.

The final study report will be created following the completion of the study (Week 48).

Tolerability and Safety Data:

In general, safety analyses will be performed and the results summarized by dose cohort. Post-treatment safety assessments will be compared with measurements recorded at baseline. Treatment-emergent AEs will be summarized using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). The incidence and frequency of AEs, SAEs, related AEs, related SAEs, and AEs leading to discontinuation, will be summarized by dose cohort per SOC, PT, and severity. 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 and shift tables. 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 listings. Electrocardiogram parameters, changes from baseline, and qualitative assessments will be summarized. Pregnancy and follicle-stimulating hormone (FSH) test results will be listed separately by time point.

All safety and tolerability analyses will be performed using the Safety Analysis Population, defined as all enrolled participants who received at least 1 dose of IP.

Pharmacokinetics:

Plasma concentrations of ARO-APOC3 will be measured in all participants to evaluate trough and postdose levels throughout the study per the Schedule of Assessments (SOA). Serial PK sampling will be conducted in a subgroup of participants at specifically designated PK sites.

Full PK group: In each of the dose cohorts, 16 PK participants (12 active, 4 placebo, for 48 total participants for PK) will be enrolled at the designated PK sites. Plasma concentrations will be measured predose and serially postdose as per the SOA. Only samples collected from participants receiving active treatment will be included in the PK analysis.

Sparse Sample PK group: At the Day 1 and Week 12 visits, all other participants at all sites will provide a predose PK sample and PK sample postdose as per the SOA.

Immunogenicity (Anti-drug Antibodies):

Changes from assay negative to positive will be summarized by dose and number of doses administered. Descriptive statistics of immunogenicity parameters will include mean, standard deviation, minimum, and maximum.

Table 1: Schedule of Assessments

Assessment	Screening Period			Treatment Period													
	Day - 42 to Day - 21	Day - 35 to Day - 21	Day - 21 to Day - 1	Day 1 (Pre-dose) ¹	Day 2	Wk 4 ²	Wk 8 ²	Wk 12 ²	24 h post-dose	Wk 16 ²	Wk 20 ²	Wk 24 ²	2-7 Days Post Wk 24	Wk 28 ²	Wk 36 ²	Wk 48 ² EOS /ET	2-7 Days Post Week 48 EOS/ET
	S-1 ³	S-2 ³	S-3														
Informed Consent	X																
Dietary counseling to maintain diet	X	X	X	X		X	X	X		X	X	X		X	X	X	
Acute pancreatitis signs and symptoms counseling	X		X	X		X	X	X		X	X	X		X	X	X	
Eligibility Criteria	X	X	X	X													
Height and Weight ⁴	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	X		X	X	X	
Vital Signs (BP, temp, respiratory rate, heart rate)	X			X		X	X	X		X	X	X		X	X	X	
Concomitant Medications/Therapies	X	X	X	X		X	X	X		X	X	X		X	X	X	
Adverse Events (including pancreatitis, abdominal pain or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
HBV/HCV Serology Screen	X																

Assessment	Screening Period			Treatment Period													
	Day - 42 to Day - 21 S-1 ³	Day - 35 to Day - 21 S-2 ³	Day - 21 to Day - 1 S-3	Day 1 (Pre-dose) ¹	Day 2	Wk 4 ²	Wk 8 ²	Wk 12 ²	24 h post-dose	Wk 16 ²	Wk 20 ²	Wk 24 ²	2-7 Days Post Wk 24	Wk 28 ²	Wk 36 ²	Wk 48 ² EOS /ET	2-7 Days Post Week 48 EOS/ET
FSH (females not of childbearing potential)	X																
Clinical Laboratory Tests (predose on dosing days) ⁵	X			X		X	X	X		X	X	X		X	X	X	
Fasting Serum Triglyceride ⁶		X	X														
Fasting Lipid/Pharmacodynamic Parameters (predose on dosing days) ^{6,7}				X		X	X	X		X	X	X ⁸	X ⁸	X	X	X ⁸	X ⁸
Pregnancy test in females of childbearing potential (predose on dosing days)	X		X	X		X	X	X		X	X	X		X	X	X	
ECG ⁹		X		X				X				X			X	X	
MRI-PDF ¹⁰		X										X					
IP Administration				X				X									
Postdose Follow-up Contact ¹¹					X				X								
Optional Genotype (new sample or record from source documents, if available)				X													
Anti-drug antibodies (predose on dosing days)				X		X		X				X			X	X	

Assessment	Screening Period			Treatment Period													
	Day - 42 to Day - 21 S-1 ³	Day - 35 to Day - 21 S-2 ³	Day - 21 to Day - 1 S-3	Day 1 (Pre-dose) ¹	Day 2	Wk 4 ²	Wk 8 ²	Wk 12 ²	24 h post-dose	Wk 16 ²	Wk 20 ²	Wk 24 ²	2-7 Days Post Wk 24	Wk 28 ²	Wk 36 ²	Wk 48 ² EOS /ET	2-7 Days Post Week 48 EOS/ET
Full PK ¹²				X	X			X	X								
Sparse Sample PK ¹³				X				X									

Abbreviations: BP = blood pressure; COVID = coronavirus disease; ECG = electrocardiogram; EOS = End-of-Study; ET = Early Termination; FSH = follicle-stimulating hormone; h=hour; HBV = hepatitis B virus; HCV = hepatitis C virus; IP = investigational product; MRI-PDFF = magnetic resonance imaging – proton density fat fraction; PK = pharmacokinetic; temp = temperature; Wk = Week.

- Assessments completed on Day 1 and all other dosing days **are to be done predose** unless otherwise specified.
- The time window for visits conducted at Weeks 4, 8, 12, 16, 20, 24, 28, 36, and 48 is ± 5 days.
- S1 and S2 visit assessments may be conducted concurrently within the S2 visit timeframe (Day -35-Day -21) as long as the participant is in a fasted state for at least 10 hours and is on a stable diet and stable background therapy regimen as required per protocol [Section 8.1](#), [Section 8.4](#), and [Section 10.2](#).
- Height (cm) only at Screening Visit; Weight (kg) at all indicated visits.
- Blood and urine samples will be collected after obtaining informed consent. With prior consent, a separate sample will be collected and stored for future research at the following study visits: Day 1, Week 4, and Week 12. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, laboratory samples may be collected at an alternative location (eg, home health, local laboratory) using the central laboratory kit and shipped to central laboratory for analysis. If the central laboratory kit collection is not available, local laboratory safety testing may only be permitted in limited circumstances and only with prior Sponsor approval. Beginning on Day 1, clinical laboratory tests will be collected after confirming the participant has fasted (no food or drink other than water) for **at least 10 hours** prior to the blood draw, unless otherwise specified. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria ([Appendix 3](#)).
- Participant must be in a fasted state (no food or drink other than water) for at **least 10 hours** prior to collection and confirmed to be on a stable diet ([Section 10.2](#)) and on stable background medications ([Section 8.1](#) and [Section 8.4](#)).
- Beginning predose Day 1 and for the remainder of the study, fasting TG will be included as part of lipid/pharmacodynamic parameter laboratory collection.
- At Week 24 and Week 48, whole blood for pharmacodynamic analysis of **lipid parameters should be drawn on two separate occasions, separated by 2 – 7 days after a 10 hour fast** for calculation of primary and secondary endpoints.
- The ECGs are to be completed predose, then 30 min (± 10 minutes) and 2 hours (± 30 minutes) postdose. The ECG will be performed prior to any invasive procedures (eg, venipuncture).
- Selected sites (where MRI-PDFF is available) will perform MRI-PDFF assessments at Screening until up to 35 participants with baseline liver fat fraction $\geq 8\%$ have been enrolled in each of the 3 dosing cohorts after which, MRI-PDFF will no longer be included as an evaluation. If a participant terminates prior to the Week 24 visit, an unscheduled MRI-PDFF assessment should be performed.
- Site staff will contact the participant within 24 hours after dosing to document adverse events ([Section 10.4.3.7](#)).
- Whole blood for the plasma PK samples will be drawn in 16 participants (12 active and 4 placebo) enrolled in each of the 10, 25, and 50 mg dose cohorts at designated PK sites. PK time points are at predose, 0.25, 1, 3, 6, and 24 hours postdose. Recommended time window for PK samples through the 6-hour time point: ± 5 minutes.

Recommended time window for PK samples at the 24-hour time point: ± 60 minutes ([Section 10.5](#)). 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.

13. All other participants (Sparse PK participants) will have PK samples drawn predose and at least 15 minutes postdose on dosing days.

2. TABLE OF CONTENTS

1.	PROTOCOL SYNOPSIS	2
2.	TABLE OF CONTENTS	17
3.	STUDY INFORMATION AND SIGNATURE.....	22
4.	LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....	23
5.	BACKGROUND	27
5.1.	Overview of Severe Hypertriglyceridemia (SHTG).....	27
5.2.	Overview of ARO-APOC3 Development	29
5.2.1.	Mechanism of Action of ARO-APOC3 and Therapeutic Rationale	29
5.2.1.1.	siRNA Mechanism of Action	29
5.2.2.	Preclinical Studies	31
5.2.3.	Clinical Studies.....	31
5.3.	Risk Assessment for Participants.....	32
5.4.	Study Rationale.....	33
5.5.	Rationale for Dose and Schedule of Administration	33
5.6.	Benefit-Risk Assessment.....	34
6.	STUDY OBJECTIVES	36
7.	STUDY PLAN.....	36
7.1.	Overall Study Design and Plan.....	36
7.1.1.	Number of Study Sites	37
7.1.2.	Number of Participants	37
7.1.3.	Estimated Study Duration.....	37
7.2.	Discussion of Study Design, Including Choice of Control Group	38
8.	SUBJECT SELECTION.....	39
8.1.	Inclusion Criteria	39
8.2.	Exclusion Criteria	40
8.3.	Participant Withdrawal Criteria	42
8.3.1.	Data Safety Committee and Treatment Stopping Rules	42
8.3.2.	Study Drug Discontinuation Criteria for Increased HbA1c	44
8.4.	Restrictions and Concomitant Medications	45
8.5.	Lipid Monitoring	46

9.	INVESTIGATION PRODUCT	47
9.1.	Description, Identification, and Dosage	47
9.2.	Supply, Preparation, Storage, and Labeling of ARO-APOC3.....	47
9.3.	Study Drug Handling.....	48
9.4.	Allocation to Treatment.....	48
9.5.	Study Formulation Administration.....	49
9.6.	Accountability of Study Supplies	49
9.7.	Retention of Investigational Product Vials.....	50
9.8.	Blinding and Code-Break	50
10.	STUDY METHODS AND PROCEDURES	51
10.1.	Overview of Procedures	51
10.2.	Screening Diet Stabilization Period.....	52
10.3.	Selection and Screening.....	52
10.4.	On-Study Procedures/Assessments	53
10.4.1.	Efficacy Assessments	53
10.4.1.1.	Serum Triglycerides.....	53
10.4.1.2.	Other Lipid Parameters.....	53
10.4.1.3.	Glucose Metabolism	53
10.4.1.4.	Magnetic Resonance Imaging.....	53
10.4.1.5.	Blood Sampling for Pharmacodynamic Analysis.....	54
10.4.2.	Pharmacokinetic Assessments	54
10.4.2.1.	Sample Processing and Analysis for Pharmacokinetic Samples	54
10.4.3.	General and Safety Assessments	54
10.4.3.1.	Demographics and Medical History	55
10.4.3.2.	Physical Examination	55
10.4.3.3.	Vital Signs	55
10.4.3.4.	Electrocardiogram.....	56
10.4.3.5.	Clinical Laboratory Tests for Safety.....	56
10.4.3.6.	Early Termination Procedures	57
10.4.3.7.	Follow-Up Procedures	57
10.4.4.	Acute Pancreatitis Events	57

10.4.4.1.	Detecting and Reporting Pancreatic Events	57
10.4.4.2.	Hospitalization for Abdominal Pain	58
10.5.	Timing of Treatments and Procedures	59
10.6.	Pregnancy Testing and Contraception Requirements	59
11.	ADVERSE EVENTS	60
11.1.	Definitions	60
11.2.	Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events	61
11.3.	Timing, Frequency, and Method of Detecting Adverse Events	61
11.4.	Recording of Adverse Events	62
11.5.	Evaluating Adverse Events	62
11.5.1.	Severity of Adverse Events	62
11.5.2.	Injection Site Reactions	62
11.5.3.	Assessment of Causality	63
11.5.4.	Follow-up of Adverse Events	64
11.6.	Prompt Reporting of Serious Adverse Events	64
11.6.1.	Completion and Transmission of the Serious Adverse Event Reports	64
11.6.2.	Pregnancy Reporting	65
11.6.3.	SAE Reports to the IRB/EC	65
11.7.	Regulatory Requirements for Reporting of SAEs	65
11.8.	Poststudy Adverse Events	66
11.9.	Serious Adverse Events Related to Study Participation	66
12.	DATA ANALYSIS AND STATISTICAL CONSIDERATIONS	66
12.1.	Endpoints	66
12.1.1.	Primary Endpoint	66
12.1.2.	Secondary Endpoints	66
12.1.3.	Exploratory Endpoints	67
12.2.	Analysis Populations	68
12.3.	Sample Size Considerations	68
12.4.	Interim Analysis	68
12.5.	Stratification	68
12.6.	Analysis Methods	69

12.6.1.	Screening Data.....	69
12.6.2.	Efficacy and Pharmacodynamics Analysis.....	69
12.6.3.	Pharmacokinetics Analysis.....	70
12.6.4.	Safety/Tolerability Analysis	70
12.6.5.	Analysis of Immunogenicity (Anti-drug Antibodies) Data	70
12.7.	Data Recording and Quality Control	71
13.	STUDY APPROVAL AND CONDUCT	71
13.1.	Regulatory Approval	71
13.2.	Institutional Review Board (IRB)/Ethics Committee (EC) Approval	71
13.3.	Ethical Considerations	71
13.4.	Written Informed Consent	72
13.5.	Emergency Contact with Principal Investigator	72
13.6.	Notification of General Practitioner	72
13.7.	Clinical Laboratory Certification and Reference Ranges	72
13.8.	Protocol Deviations	73
13.9.	Termination of the Study	73
14.	STUDY ADMINISTRATION	74
14.1.	Study Monitoring.....	74
14.2.	Quality Assurance.....	75
14.3.	Records Retention.....	75
15.	INFORMATION DISCLOSURE AND INVENTIONS.....	76
15.1.	Ownership.....	76
15.2.	Confidentiality	76
15.3.	Data Protection	77
15.4.	Publication	77
16.	REFERENCES	78
APPENDIX 1. LIVER-RELATED STUDY MODIFICATION AND FOLLOWUP GUIDELINES.....		82
APPENDIX 2. LOCAL INJECTION SITE REACTIONS		84
APPENDIX 3. GLYCEMIC CONTROL-RELATED GUIDELINES		85

List of Tables

Table 1:	Schedule of Assessments	13
Table 2	Restricted Concomitant Medications.....	46
Table 3	Injection Number and Volume Per Dose Cohort.....	49
Table 4	Liver Related Study Modification and Follow-Up Guidelines for Participants	82
Table 5	Local Injection Site Reactions (LISRS)	84

List of Figures

Figure 1	siRNA Mechanism of Action	30
Figure 2	Study Schema	36

3. STUDY INFORMATION AND SIGNATURE

Protocol Title: A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia

Protocol Number: AROAPOC3-2001

Version: Amendment 5, Version Date 26 January 2023

INVESTIGATOR SIGNATURE:

I have read and understand the information in this protocol and agree to conduct the study according to the protocol (subject to any amendments) and in accordance with the principles of Good Clinical Practice. I have read and agree to comply with the Investigator obligations stated in this protocol. Any changes in procedure will only be made, if necessary, to protect the safety, rights, or welfare of participants. I agree to conduct in person or to supervise the study. I agree to ensure that all who assist me in the conduct of the study are aware of their obligations.

Signature

Date

Printed Name

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ASCVD	Atherosclerotic cardiovascular disease
AE	Adverse event
AHA/ACC	American Heart Association/American College of Cardiology
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ApoB	Apolipoprotein B
ApoB-48	Apolipoprotein B 48
ApoB-100	Apolipoprotein B 100
ApoA-I	Apolipoprotein A-I
ApoA-V or APOA5	Apolipoprotein A-V
ApoC-II or APOC2	Apolipoprotein C-II
ApoC-III or APOC3	Apolipoprotein C-III
AST	Aspartate aminotransferase
ARO	Arrowhead Pharmaceuticals, Inc
ARO-APOC3 Injection	Clinical drug product solution ready for SC injection
ARO-APOC3	Short name for ARO-APOC3 Injection
CECT	Contrast-enhanced computed tomography
COVID	Coronavirus disease
CTCAE	Common Terminology Criteria for Adverse Events
GalNAc	N-acetyl galactosamine
GCP	Good Clinical Practice
cGMP	Current Good Manufacturing Practice
CM	Chylomicronemia
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
CS	Clinically significant
DSC	Data Safety Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form

eGFR	Estimated glomerular filtration rate
EOS	End of study
ET	Early Termination
FAS	Full Analysis Set
FCS	Familial Chylomicronemia Syndrome
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GGT	Gamma-glutamyl transferase
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
hsCRP	high sensitivity C-reactive protein
HTG	Hypertriglyceridemia
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDL	Intermediate-density lipoprotein
IFCC	International Federation of Clinical Chemistry
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ISR	Injection site reaction
IWRS	Interactive Web Response System
LD	Lactate dehydrogenase
LDL-C	Low-density lipoprotein-cholesterol
LIPG	Endothelial lipase
LISR	Local injection site reaction
LMF1	Lipase maturation factor 1

Lp(a)	Lipoprotein (a)
LPL	Lipoprotein lipase
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCM	Multifactorial chylomicronemia
MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
mRNA	Messenger ribonucleic acid
NCEP	National Cholesterol Education Program
NHV	normal healthy volunteer
NOAEL	No adverse effect level
non-HDL-C	non-high-density lipoprotein-cholesterol
NYHA	New York Heart Association
OTC	Over-the-counter
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
Q12W	Once every 12 weeks
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SHTG	Severely high hypertriglyceridemia
siRNA	Short interfering RNA oligonucleotides
SOA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TG	Triglyceride(s)

TRL	Triglyceride-rich lipoprotein
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
VLDL-C	Very low-density lipoprotein-cholesterol

Definition of Terms

Investigational Product (IP) is defined as, “A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (from International Council for Harmonisation [ICH] of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

5. BACKGROUND

Severely high hypertriglyceridemia (SHTG) is a disorder characterized by marked elevations in triglyceride (TG) levels which can lead to acute pancreatitis, as well as an increased risk of cardiovascular disease and atherosclerosis (Hegele 2014, Scherer 2014). Acute pancreatitis typically causes severe upper abdominal pain and may result in emergency room visits, hospitalizations, and even deaths (Chatila 2019, Scherer, 2014). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III recommends TG-lowering therapy when TG are ≥ 500 mg/dL (≥ 5.65 mmol/L) to prevent acute pancreatitis (NCEP 2002, Pedersen 2016). This threshold was also used to define adult patients with SHTG indicated for TG-lowering medications such as VASCEPA® (icosapent ethyl), and EPANOVA® (omega-3-carboxylic acid) in the United States (US) and is the threshold used in the 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Blood Cholesterol (Grundy 2019). Lowering TG below 500 mg/dL (5.65 mmol/L) has been shown to be associated with significant clinical benefits (Christian 2012, Chen 2017, Murphy 2013). Compared with TG ≥ 500 mg/dL (≥ 5.65 mmol/L), TG < 500 mg/dL (< 5.65 mmol/L) was associated with a lower incidence of acute pancreatitis (0.47 versus 1.09 event per 100 person-years), cardiovascular events (4.93 versus 6.30 event per 100 person-years), and overall healthcare utilization and costs (Christian, 2012).

5.1. Overview of Severe Hypertriglyceridemia (SHTG)

The prevalence of SHTG in adults in the US is approximately 1.7%, based on the NHANES database (2001-2006) of individuals with TG levels between 500 and 2000 mg/dL (5.65 to 22.6 mmol/L) (Christian 2011, Laufs 2020). The prevalence of adults with TG levels > 885 mg/dL (> 10 mmol/L) or > 1000 mg/dL (> 11.3 mmol/L) are even lower (range 1:600 to 1:1000, or between 0.1% to 0.2%) (Laufs 2020, Brown 2018). SHTG can be caused by many factors, including a combination of genetics, diet, lifestyle choices (eg, excessive alcohol intake), and comorbid conditions, such as obesity, metabolic syndrome, hypothyroidism, and Type 2 diabetes mellitus (Laufs 2020, Yuan 2007). Genetic causes of SHTG are typically associated with high TG levels in excess of 885 mg/dL (10 mmol/L) and can have both monogenic (Familial Chylomicronemia Syndrome [FCS or hypertriglyceridemia Type 1]) and polygenic (Multifactorial Chylomicronemia [MCM or Type 5 hyperlipoproteinemia]) determinants (Paquette 2019). FCS is an autosomal recessive and rare condition with an estimated prevalence of 1 to 2 in a million that is caused by loss-of-function mutations in the gene encoding lipoprotein lipase (*LPL*) or, less frequently, by mutations in genes encoding other proteins necessary for LPL function (De La Torre 2000, Laufs 2020, Warden 2020). LPL activity is the primary mechanism by which plasma TG are hydrolyzed, with subsequent efficient removal of TG-rich lipoprotein (TRL) remnants by the hepatocyte. Patients with FCS routinely have TG levels > 2000 mg/dL (> 22.6 mmol/L), with some as high as 15000 mg/dL (169.5 mmol/L) (Gaudet 2014, Warden 2020). The other form of chylomicronemia, MCM, may include heterozygous variants in the 5 genes associated with FCS, as well as variants in other genes associated with regulating TG levels (Laufs 2020). MCM commonly involves increased polygenic risk on top of exacerbating factors such as a diet rich in fats and simple sugars,

obesity, and diabetes (Paquette 2019). The prevalence of MCM is estimated to be 1 in 600 to 1 in 1000 adults (Warden 2020, Brown 2018).

Acute pancreatitis, a known condition associated with SHTG, 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 deaths. The recurrence of acute pancreatitis can lead to chronic pancreatitis 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 (FDA 2018). 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 (Scherer 2014, Gelrud 2017). For example, the lifetime risk of acute pancreatitis is approximately 5% in patients with TG levels >1000 mg/dL (>11.3 mmol/L), which increases to approximately 10% to 20% in patients with TG levels >2000 mg/dL (22.6 mmol/L) (Scherer 2014; Sanchez 2021; Esparza 2019). Even within a lower threshold, the risk for acute pancreatitis was more than 5-fold higher for adults with TG levels ≥ 443 mg/dL (≥ 5.01 mmol/L) compared with individuals with TG levels in the normal range (<89 mg/dL or 1.01 mmol/L) (Pedersen 2016).

Conventional management of SHTG includes dietary restrictions of fat, lipid-lowering medications (eg, statins, omega-3-fatty acids), and other lifestyle changes (eg, smoking cessation, exercise, and weight reduction). In cases of acute pancreatitis due to SHTG, insulin infusions and apheresis may be used to rapidly reduced TG levels. Reduction and maintenance of TG levels to below 500 mg/dL (5.65 mmol/L) can effectively prevent recurrences of pancreatitis (NCEP 2002). However, this threshold level is difficult to achieve for many patients, despite dietary restrictions and the availability of lipid-lowering medications, including omega-3-fatty acids used to lower TG. Many available medications, including fibrates and omega-3-fatty acids, work through a LPL pathway. These treatments are not effective in patients with SHTG secondary to defective LPL pathways.

Apolipoprotein C3 (APOC3, ApoC-III), a component of TRLs, has been identified as a key regulator of serum TG levels and plays an important role in the pathogenesis of SHTG (Gaudet 2014, Khetarpal 2015, Saleheen 2017, Jorgensen 2014). Predominantly produced in hepatocytes, APOC3 inhibits hydrolysis of TG through inhibition of LPL (LPL dependent pathway) and delays clearance of lipoprotein remnants by hepatocyte receptor-mediated uptake (LPL-independent pathway), resulting in hypertriglyceridemia (TG and HDL Working Group 2014). Insights gained from studies in transgenic mice overexpressing APOC3 and in *Apoc3* knockout mice have shown that APOC3 delays very low-density lipoprotein (VLDL) hydrolysis *in vivo* and may delay the catabolism of TRL remnants by the liver and other tissues (Aalto-Setälä 1992, Aalto-Setälä 1996, Gerritsen 2005, Jong 2001, Khetarpal 2015). APOC3 knockout models in rabbits also exhibited significantly lower plasma levels of TG, VLDL, and intermediate-density lipoproteins (IDL) as well as greater TG clearance compared with wild-type animals. Both aortic and coronary atherosclerosis were significantly reduced in knockout rabbits compared with wild-type controls (Yan 2020). Loss-of-function mutations in *APOC3* in humans are associated with lower TG levels and decreased incidence of coronary artery disease.

Heterozygosity of “loss-of-function” mutations in *APOC3* caused a 46% reduction in circulating *APOC3* levels with associated reductions in TG of 39% (TG and HDL Working Group 2014). *APOC3* homozygous-deficient individuals demonstrate *APOC3* reductions of 88% and TG reductions of 59% compared to non-carriers (Saleheen 2017, Lek 2016). Individuals with *APOC3* deficiency do not demonstrate significant hepatic steatosis and appear phenotypically normal other than lower TG and higher high-density lipoprotein-cholesterol (HDL-C) (Jorgensen 2014).

5.2. 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) provided by the Sponsor, which should be reviewed prior to initiating the study.

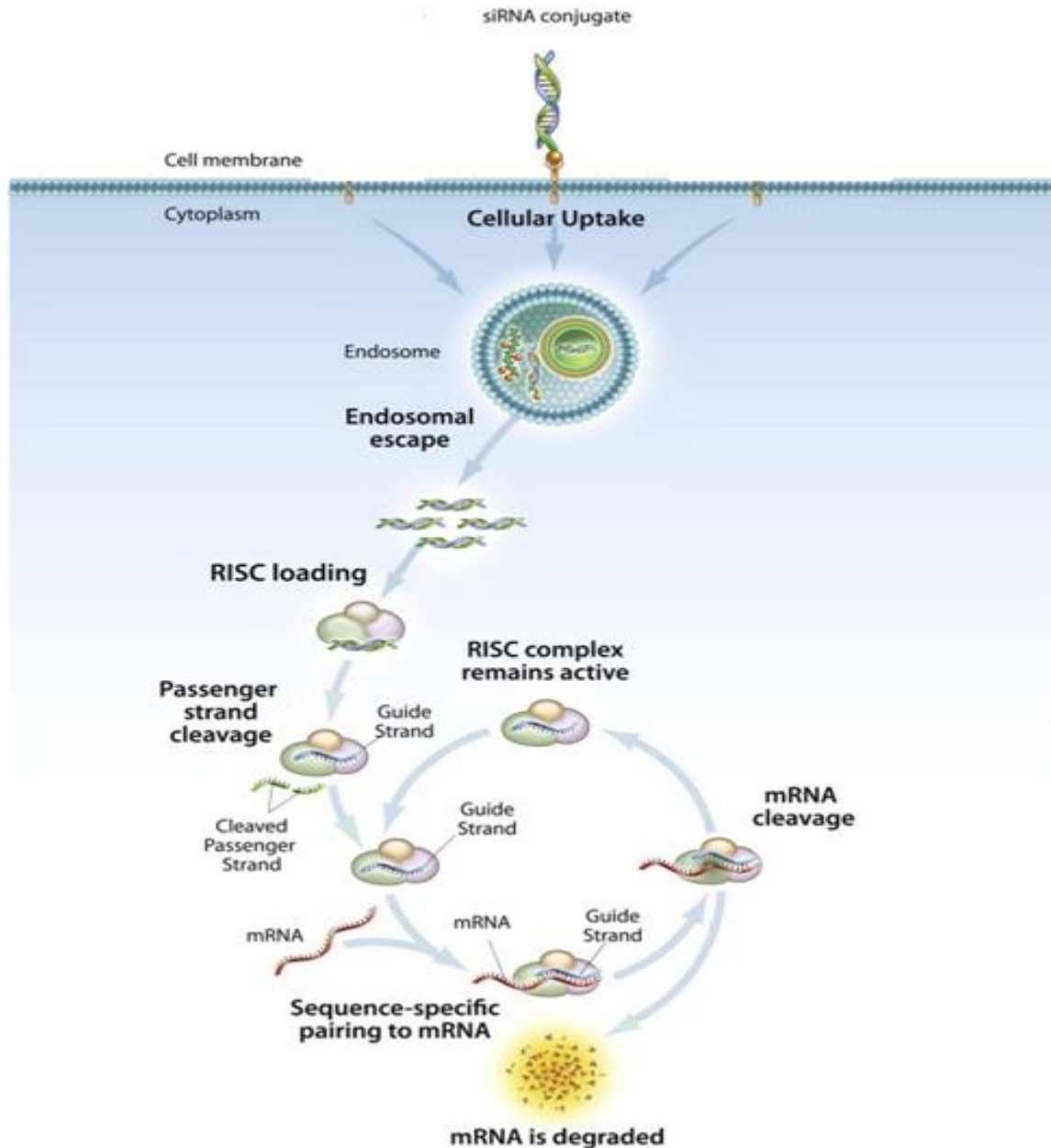
5.2.1. Mechanism of Action of ARO-APOC3 and Therapeutic Rationale

5.2.1.1. siRNA Mechanism of Action

ARO-APOC3 works through a mechanism of RNA interference (RNAi). RNAi-based therapeutics have the potential to silence the expression of any specific target gene. RNAi is a naturally occurring phenomenon by which short 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-acetyl galactosamine (GalNAc) targeting moiety, acting as a ligand for the highly expressed, hepatocyte-specific asialoglycoprotein receptor. Available non-clinical and clinical pharmacokinetics (PK) data show rapid absorption and clearance of all GalNAc conjugated triggers from the blood stream within 24 to 48 hours post-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, and subsequently, prolonged reduction of the expression of the corresponding protein. The persistence of pharmacologic activity significantly beyond the period of plasma exposure is due in part to this unique RNAi mechanism in which a small amount of guide strand can persist and be active within RISC in the cytoplasm of target cells for extended periods of time.

Figure 1 siRNA Mechanism of Action



Abbreviations: mRNA = messenger ribonucleic acid; RISC = RNA-induced silencing complex; siRNA = short interfering RNA oligonucleotides.

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 will remove the steric blockade of APOC3 at the hepatocyte, leading to enhanced clearance of TRLs from circulation by the liver.

5.2.2. 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. 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, shows 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-cholesterol [LDL-C]).
- Similar reductions in serum APOC3 were also observed after ADS-005 doses in a diet-induced dyslipidemic rhesus monkey model. ARO-APOC3 has been well tolerated in rats and in non-human primate toxicology studies.
- Results of non-Good Laboratory Practice (GLP) in vitro toxicology studies indicate there is minimal potential for induction of the innate immune system, no potential for complement activation, mitochondrial toxicity/cytotoxicity, or platelet aggregation in whole blood associated with ADS-005 exposure at concentrations up to 250 µg/mL, which far exceeds the blood concentrations anticipated at the doses to be used clinically.
- ADS-005 was shown to be non-genotoxic 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 GalNAc-siRNA drugs.

5.2.3. Clinical Studies

The Sponsor is investigating ARO-APOC3, which contains the API ADS-005, as a potential therapeutic candidate for the treatment of SHTG. 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 ApoB, and increases in high-density lipoprotein-cholesterol (HDL-C). Results from the Phase 1 study provided information for the design of the current Phase 2 study, AROAPOC3-2001. Detailed Phase 1 results are provided in the IB.

5.3. Risk Assessment for Participants

- **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 2 highly-effective forms of contraception during the study or agree to abstinence (acceptable only if this method is in alignment with the normal lifestyle of the participant).
- **Liver Function:** ARO-APOC3 targets the liver. siRNA literature has described alanine aminotransferase (ALT) changes associated with off-target effects of the siRNA seed region on microRNAs in the hepatocyte (Janas 2018). The siRNA sequence 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. In the AROAPOC31001 study, transient mild to moderate elevations in ALT were occasionally seen (See IB for details) without accompanying elevation in international normalized ratio (INR) or total bilirubin. To mitigate this risk, the proposed study protocol has built in stopping rules for ALT and aspartate aminotransferase (AST) elevation. Blood samples will be drawn as specified in the Schedule of Assessments (SOA) (Table 1) to evaluate liver injury and liver function. The Data Safety Committee (DSC) will review all available safety data including laboratory data periodically.
- **Injection Site Adverse Events (AEs):** Other SC-administered, modified siRNA drug candidates evaluated in clinical studies have been associated with mild to moderate injection site reactions (ISRs) (eg pain, erythema). Generally mild injection site AEs have been reported in the AROAPOC1001 study. In this study, steps will be taken to minimize ISRs such as rotating injection sites and allowing the ARO-APOC3 solution to come to room temperature prior to injection.
- **Glycemic Control:** An administrative analysis of the 2 ongoing Phase 2 studies has indicated increases in serum glycated hemoglobin (HbA1c) in the ARO-APOC3 treatment group versus the placebo group. The increased HbA1c values were observed in a small group of subjects who had preexisting diabetes at baseline and 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 the diabetes status and adjust diabetes treatment according to clinical practice and diabetes care guidance.

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 protocol pre-established level a number of study drug discontinuation criteria have been established ([Appendix 3](#)).

Routine monitoring of HbA1c and fasting glucose concentrations will be assessed as part of the clinical laboratory panels to monitor glycemic control, as specified in the SOA ([Table 1](#)).

5.4. Study Rationale

Interim results from the Phase 1, first in human 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 Week 12. Aside from mild and transient ISRs and transient, self-limited ALT elevations, single and repeat doses of ARO-APOC3 were well tolerated in healthy volunteers and the safety profile based on Phase 1 warrants additional later stage clinical evaluation.

Based on these results, this current study will be conducted in adults with SHTG, defined as patients whose mean fasting triglyceride level is ≥ 500 mg/dL (5.65 mmol/L) and ≤ 4000 mg/dL (45.2 mmol/L) at Screening. The design is intended to evaluate the effects of 3 different dosing levels of ARO-APOC3 (10, 25, or 50 mg) with 2 doses administered per dose level on Day 1 and Week 12, against volume-matched placebo in lowering TG levels on top of lipid-lowering medications and dietary modifications. Plasma concentrations of ARO-APOC3 will also be measured over time to evaluate the PK profile. Administration of doses on Day 1 and Week 12 with extended follow-up through Week 48 will allow complete assessment of effect duration. This study is expected to inform on dose level and dose interval selection for later stage clinical development.

5.5. Rationale for Dose and Schedule of Administration

In the Phase 1 study evaluating ARO-APOC3 in healthy volunteers, single doses of 10, 25, or 50 mg consistently reduced serum APOC3 and TG levels through Week 16 with a gradual rise in these PD parameters occurring in several healthy volunteers after Week 16 and an increase from nadir levels occurring after approximately Week 8 in the 50 mg cohorts. A clearer dose response is seen with HDL-C with dose-dependent HDL-C increases demonstrated with increasing doses. While limited data are available for patients with HTG, ARO-APOC3 50 mg administered on Days 1 and 29 maintains APOC3 reduction through Week 12.

The 10, 25, 50, and 100 mg dose levels were assessed in the Phase 1 study (AROAPOC31001), and based on safety and efficacy analyses from that study the dose levels of 10, 25, and 50 mg were selected for use in this Phase 2 study based on their durable PD activity and overall safety/tolerability profile. The 10, 25, and 50 mg single doses of ARO-APOC3 demonstrate PD

activity lasting beyond Week 12. The proposed study design is intended to evaluate the duration of effect after doses of 10, 25, or 50 mg administered on Day 1 and Week 12 with follow-up through Week 48. This design will inform on optimal dose and duration based on time for TG, APOC3 levels, and other lipid parameters to return to baseline after the second dose. The results of this study will inform on dose level and intervals to be used in later stage clinical studies.

The planned dose levels of 10, 25, and 50 mg are approximately 1/2100th, 1/840th, and 1/420th, respectively, 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 for the top proposed dose of 50 mg in this study of approximately 20-fold based on the rat NOAEL and 250-fold based on the monkey NOAEL. It should be additionally noted that the dose frequency in this proposed study is only once every 12 weeks (Q12W), 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 planned clinical doses and animal toxicology study NOAELs.

5.6. Benefit-Risk Assessment

ARO-APOC3 has been shown to have a favorable benefit-risk profile to date that warrants further clinical investigation and longer exposure periods. As of the October 08, 2020 (for non-safety) and October 15, 2020 (for safety) cutoff dates, interim PD data from the Phase 1 study AROAPOC31001 showed that administration of ARO-APOC3 at doses ranging from 10 to 100 mg resulted in significant and durable reduction of serum APOC3 when compared with placebo in healthy volunteers as well as in patients with HTG and CM.

Silencing of APOC3 led to reductions in the levels of serum TG and other lipid parameters. Results using single doses of ARO-APOC3 in normal healthy volunteers (NHVs) demonstrate dose-dependent reductions in serum APOC3 of up to -94% when compared to baseline. As would be predicted, knockdown of APOC3 resulted in decreased fasting serum TG (up to -66%) and non-HDL-C (up to -31%) as well as increased serum HDL-C levels (up to +74%) with a dose response generally correlating with APOC3 serum level reductions in participants receiving the active drug. Results for repeat doses of AROAPOC3 in NHVs demonstrated consistent reductions of APOC3 (up to -94%), TGs (up to -75%), and non-HDL-C (up to -34%), and increases in HDL-C levels (up to +75%). These responses were overall sustained through Week 16, which is 12 weeks after the last dose.

Results for repeat doses of ARO-APOC3 in patients with HTG and/or CM demonstrated similar or even larger effects of ARO-APOC3 at similar doses studied in NHVs. Reductions of serum APOC3 (up to -98%), TGs (up to -88%), non-HDL-C (up to -58%), and increases in HDL-C levels (up to +122%) were observed. The effects of ARO-APOC3 treatment on these and other key lipid parameters were sustained over the 16 weeks of study duration.

ARO-APOC3 has been generally well tolerated and has demonstrated favorable safety and tolerability. There have been no deaths in the study or study discontinuation due to AEs. Three (3) serious AEs (SAEs) involving 3 subjects have been reported, all of which were deemed not related to study drug, and the subjects completed the study. There is no clear pattern of an

increased frequency or intensity of AEs with increasing dose level. The combined placebo treatment-emergent AEs (TEAEs) reported were comparable to those seen in the ARO-APOC3 treatment group. The majority of the reported TEAEs were not related to study treatment, and there were no subjects that discontinued from the study due to TEAEs. The most frequently reported AEs that were drug-related were the ISRs, which were all mild in intensity. The AEs at the injection site are anticipated based on similar findings reported in other clinical studies of SC-administered siRNA therapeutics. Overall, there were no clinically significant (CS) adverse laboratory trends observed. There were no CS adverse electrocardiogram (ECG), vital sign, or physical examination findings during the mentioned study period.

The Sponsor conducted an administrative analysis of the ongoing Phase 2 studies (AROAPOC3-2001 and AROAPOC3-2002). This analysis identified substantially decreased mean serum APOC3 levels and median triglyceride levels in subjects receiving ARO-APOC3.

In the course of the review an apparent increase in the level of HbA1c was observed when comparing subjects in the placebo group and those receiving ARO-APOC3. 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. A meaningful improvement in lipids and lipoprotein metabolism, particularly a decrease in triglycerides, may minimize the risk of pancreatitis and coronary artery disease, which is the goal of therapy in these patient populations.

This observation does not impose an immediate health risk because worsening of diabetes 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 acceptable in this patient population.

6. STUDY OBJECTIVES

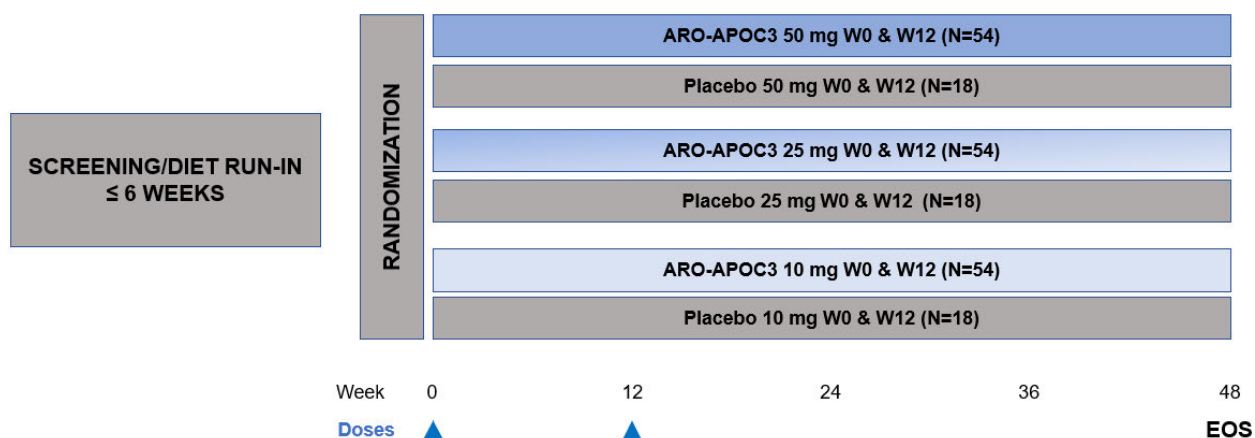
The primary objective of the study is to evaluate the safety and efficacy of ARO-APOC3 in adults with SHTG and to select a dosing regimen for later stage clinical studies in this patient population.

7. STUDY PLAN

7.1. Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, Phase 2b clinical study. Participants who have signed an Ethics Committee (EC)/Institutional Review Board (IRB) approved informed consent form may initiate screening during which eligibility assessments will be completed. Participants must maintain a stable diet and stable lipid-lowering therapy, diabetes mellitus therapies, and other background medications, as applicable (see [Sections 8.1, 8.4, and 10.2](#)), throughout the Screening period and for the duration of the 48-week Treatment Period. Enrolled participants will remain on a specified diet throughout the study, as recommended by the Investigator, in accordance with local standard of care. Dietary counseling will continue to be performed throughout the study as per the SOA ([Table 1](#)). Participants who have met all the protocol eligibility criteria during screening may be randomized into the study in a double-blind fashion. All dose cohorts will enroll in parallel with participants randomly assigned to treatment in a 3:1 ratio to receive ARO-APOC3 (10, 25, or 50 mg) or placebo. Each participant will receive a total of 2 SC injections on Day 1 and Week 12.

Figure 2 Study Schema



Abbreviations: EOS = end of study; W = week.

Blinding will be preserved to the extent possible (or unless otherwise specified); however, treatment unblinding may occur at the Investigator's or Medical Monitor's discretion where deemed necessary for treatment of an AE or for a decision to be made regarding study continuation in an individual participant.

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 specified time points and up to study completion.

The AE/SAE reporting period for an enrolled participant will begin when the participant provides informed consent. Treatment-emergent AEs (TEAEs) and SAEs are defined as AEs that occur following investigational product (IP) administration or a pre-existing condition exacerbated following IP administration. The TEAE-reporting period begins after the first dose and extends until the End-of-Study (EOS) visit is complete. All SAEs that occur during the reporting period, in addition to reporting via electronic case report forms (eCRFs), must also be reported to the Sponsor via the SAE report form within 24 hours of 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 Investigator 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 IP, the Investigator will promptly notify the Sponsor. Laboratory or diagnostic assessment (eg, ECG) abnormalities will be reported as AEs if considered CS by the Investigator. Laboratory or diagnostic assessment abnormalities not reported as AEs are not to be reported as CS in the study database.

7.1.1. Number of Study Sites

Approximately 80 centers globally.

7.1.2. Number of Participants

Approximately 216 participants.

7.1.3. Estimated Study Duration

The duration of the study is approximately 54 weeks from Screening to the Week 48 EOS examination. The treatment duration of the study will be approximately 48 weeks from Day 1 to the Week 48 EOS examination. The overall study duration from first participant enrolled to last participant last visit is expected to be approximately 2 years.

The Screening period will last up to approximately 6 weeks (Day -42 through Day -1) consisting of dietary stabilization and other required eligibility assessments. Laboratory values assessed to determine TG eligibility during the Screening period and all other lipid parameters throughout the study will be collected from participants in a fasted state.

At Week 48, participants will be eligible and invited to consent and continue in an open-label extension study. All placebo participants will switch to active drug during the extension study.

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

The primary objective of the study is to select 1 dose and dose interval for later stage clinical studies based on evaluation of the safety and efficacy of 3 doses of ARO-APOC3 in participants with SHTG.

Participants confirmed to be on a stable diet and on stable background medications, as applicable (see [Sections 8.1, 8.4, and 10.2](#)), will complete all eligibility assessments within 6 weeks (Day -42 to Day -1) prior randomization on Day 1 in accordance with the SOA ([Table 1](#)). The Treatment Period will begin on Day 1 and will continue for 48 weeks. 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 because it would have been impractical to maintain blinding with an active control. All participants in active and placebo groups on lipid-lowering therapies will be required to remain on a stable regimen during the study. In response to diabetes evaluations, adjustments to treatment medication are allowed at the discretion of the Principal Investigator (refer to see [Section 8.1](#) and [Section 8.4](#)). Compared with the potent effect of ARO-APOC3 in lowering TG levels, other first-line therapies have modest effects on TGs. For example, patients with SHTG receiving omega-3 fatty acid only had 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 effect is expected when ARO-APOC3 is used on top of optimal lipid-lowering therapy. In this Phase 2 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 (see [Sections 8.1 and 8.4 \[Table 2\]](#)) prior the Screening laboratory assessments and will agree to stay on this baseline regimen during the Treatment Period. Randomization will be stratified by mean level of TG at Screening (≥ 1000 mg/dL versus < 1000 mg/dL).

The duration of the treatment is intended to ensure adequate exposure to ARO-APOC3 to evaluate the safety and efficacy for its long-term use and to facilitate selection of a lowest effective dose to maximally lower TG. The primary analysis will be at Week 24. Additional analysis at various timepoints from Week 24 over time through Week 48 will assess the durability of the treatment effect, additional efficacy outcomes, and long-term safety.

8. SUBJECT SELECTION

The proposed participant population is adults with SHTG, defined as mean fasting TG level ≥ 500 mg/dL (≥ 5.65 mmol/L) and ≤ 4000 mg/dL (45.2 mmol/L) at Screening ([Esparza 2019](#)). The NCEP Adult Treatment Panel III recommends TG-lowering therapy when TG are ≥ 500 mg/dL (≥ 5.65 mmol/L) to prevent acute pancreatitis ([NCEP 2002](#), [Pedersen 2016](#)). This threshold was also used to define adult patients with SHTG indicated for TG-lowering medications such as VASCEPA[®] (icosapent ethyl), and EPANOVA[®] (omega-3-carboxylic acid) in the US, and is the threshold used in the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol ([Grundy 2019](#)). Lowering TG below 500 mg/dL (5.65 mmol/L) has been shown to be associated with significant clinical benefits ([Christian 2012](#), [Chen 2017](#), [Murphy 2013](#)). Compared with TG ≥ 500 mg/dL (≥ 5.65 mmol/L), TG < 500 mg/dL (< 5.65 mmol/L) was associated with a lower incidence of acute pancreatitis (0.47 versus 1.09 events per 100 person-years), cardiovascular events (4.93 versus 6.30 events per 100 person-years), and overall healthcare utilization and costs ([Christian 2012](#)). To ensure that appropriate participants are selected, the inclusion and exclusion criteria are provided in [Section 8.1](#) and [Section 8.2](#).

Information about the study population size is provided in [Section 7.1.2](#).

8.1. 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;
2. Based on medical history, prior evidence of fasting TG ≥ 500 mg/dL (5.65 mmol/L);
3. A mean fasting TG ≥ 500 mg/dL (5.65 mmol/L) and ≤ 4000 mg/dL (45.2 mmol/L) collected at two separate and consecutive visits at least 7 days apart and no more than 17 days apart during the Screening period;
4. If the participant has a medical history of clinical ASCVD or elevated 10-year ASCVD risk (eg, $\geq 7.5\%$ per American Heart Association/American College of Cardiology [ACC/AHA] risk calculator for subjects ≥ 40 years of age or Framingham risk score calculator for subjects under the age of 40) then participant 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;
5. Able and willing to provide written informed consent prior to the performance of any study-specific procedures;
6. Willing to follow diet counseling and maintain a stable diet as per Investigator judgment based local standard of care;
7. Participants of childbearing potential must agree to use highly effective contraception as described in [Section 10.6](#), during the study and for at least 24 weeks following the last dose of IP. Males must agree to not donate sperm during the study and for at least 24 weeks following the last dose of IP.

8. Women of childbearing potential on hormonal contraceptives must be stable on the medication for ≥ 2 menstrual cycles prior to Day 1; and
9. Participants on any of the following medications must be on a stable regimen for the specified duration prior to collection of Screening Visit (S2) laboratory tests and for the duration of study participation.

Medication	Time on stable regimen prior to collection of Screening Visit (S2) laboratory tests
Lipid-lowering therapies (including statins)	≥ 4 weeks
Beta-blockers, thiazide diuretics	≥ 4 weeks
Fibrates	≥ 6 weeks
PCSK9 inhibitors	≥ 8 weeks
Retinoids	≥ 8 weeks
Atypical antipsychotics	≥ 12 weeks
Diabetes mellitus medications	≥ 12 weeks
Anticoagulation therapy	≥ 12 weeks
Thyroid hormone replacement therapy	≥ 12 weeks
Testosterone replacement therapy	≥ 16 weeks
Oral estrogens, tamoxifen, raloxifene	≥ 16 weeks
Immunosuppressants	≥ 24 weeks

NOTE: All laboratory tests used as inclusion criteria will be assessed by a central laboratory and may be repeated once 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 (see [Table 1](#)).

8.2. Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Current use, or use within the last 365 days from Day 1, of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule;
2. Active pancreatitis within 12 weeks prior to Day 1;
3. Known genetically-confirmed diagnosis of FCS
4. Any planned bariatric surgery or similar procedures to induce weight loss during the period starting at consent through EOS;
5. History of major surgery within 12 weeks of Day 1 or planned major surgery during the study;
6. Planned coronary intervention (such as stent placement or heart bypass) during the study;

7. History of acute coronary syndrome event within 24 weeks of Day 1;
8. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%;
9. Uncontrolled hypertension (sitting blood pressure >160/100 mmHg at Screening), participant may be rescreened once hypertension is controlled;
10. History of hemorrhagic stroke within 24 weeks of Day 1;
11. History of bleeding diathesis or coagulopathy;
12. Current diagnosis of nephrotic syndrome;
13. Any of the following laboratory values at Screening:
 - a. Hepatic: ALT or AST >2× upper limit of normal (ULN) at Screening
 - b. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² (using the Modification of Diet in Renal Disease [MDRD equation]) at Screening
 - c. HbA1c >9.0% (or >75 mmol/mol International Federation of Clinical Chemistry [IFCC] units) at Screening;
 - d. Spot urine protein/spot urine creatinine ratio >3 grams per day;
 - e. Clinically significant abnormality in PT, aPTT, or INR;
14. Use of any of the following:
 - a. Systemic corticosteroids or anabolic steroids within 4 weeks prior to Day 1 or planned use during the study (stable doses of testosterone replacement therapy ≥16 weeks prior to Screening [visit S2] is permitted for a documented history of hypogonadism [low testosterone] as verified in subject health records)
 - b. Plasma apheresis within 4 weeks prior to Day 1 or planned during the study;
15. Blood donation of 50 to 499 mL within 4 weeks of Screening (visit S2) laboratory collection or of >499 mL within 8 weeks of Screening (visit S2) laboratory collection;
16. Known history of human immunodeficiency virus infection;
17. 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);
18. Clinical evidence of uncontrolled hypothyroidism or hyperthyroidism as per Investigator's judgment;
19. History of malignancy within the last 2 years prior to the date of consent 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 Investigator's opinion, at risk of relapse for recent cancer;
20. 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;

21. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week (1 unit = 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol);
22. Any concomitant medical or psychiatric condition or social situation or any other situation that, in the Investigator's judgment, would make it difficult to comply with protocol requirements or put the participant at additional safety risk.

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

8.3. 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 Investigator, 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 which may interfere with study measurements;
- intolerable/unacceptable adverse experiences;
- major violation of or deviation from study protocol procedures;
- noncompliance of participant with protocol;
- participant unwilling to proceed and/or consent is withdrawn; or
- withdrawal from the study if, in the Investigator'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, along with any AEs and any necessary medical treatment.

If a participant is withdrawn from the study due to significant AE or SAE, the Investigator, or medically trained designee, will evaluate the urgency of the event. If the situation warrants, the Investigator, or medically trained designee, will take appropriate diagnostic and therapeutic measures. If the situation is not an immediate emergency, the Investigator, 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.

8.3.1. Data Safety Committee and Treatment Stopping Rules

An independent DSC will be assembled to review safety data after half of the total number of participants planned for enrollment have received at least 1 dose of IP. 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 modifying, stopping, or continuing the study as planned. Blinded data will be reviewed initially and if there are any concerns or unblinded review is warranted based on blinded review, the DSC may review unblinded data in a closed session.

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

Sponsor or Investigator can discontinue any participant at any time.

A decision to modify the study or pause/suspend dosing in an individual participant, 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 IP dosing of that participant; or
- A need for apheresis or other emergent interventions indicated to lower TG; or
- Acute pancreatitis; or
- In participants with normal (per central laboratory reference range) aspartate aminotransaminase (AST) or alanine aminotransferase (ALT) on Day 1, treatment-emergent elevations $>3\times$ upper limit of normal (ULN) at least possibly related to IP per study Investigator, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 1 for specific guidelines regarding treatment discontinuation or interruption for participants with any of the below findings:
 - AST or ALT $>5\times$ ULN will lead to permanent discontinuation of IP dosing of that participant per [Appendix 1](#). The participant will remain on study follow-up visits until EOS as per the Schedule of Assessments (SOA) (refer to [Table 1](#)).
 - AST or ALT $>3\times$ ULN with a total bilirubin $>2\times$ ULN
 - AST or ALT $>3\times$ ULN with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia ($>5\%$)
 - AST or ALT $>3\times$ ULN with a treatment-emergent international normalized ratio (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 or ≥300 U/L (whichever occurs first) at least possibly related to IP per study Investigator, as specified below, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 1 for specific guidelines regarding treatment discontinuation or interruption for participants with any of the below findings:

- AST or ALT >3× baseline or ≥300 U/L (whichever occurs first)
- AST or ALT >2× baseline or ≥300 U/L (whichever occurs first) with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
- AST or ALT >2×baseline or ≥300 U/L with a total bilirubin >2× ULN
- AST or ALT >2× baseline or ≥300 U/L or 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 AST or ALT are provided in [Appendix 1](#).

For any participant experiencing an acute pancreatitis, all TG levels will be provided by the central laboratory to the Investigator and Medical Monitor, and the participant will be unblinded to their assigned treatment allocation. If the participant was assigned to receive ARO-APOC3, their next dose should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor. If the participant was assigned to placebo, further dosing will be discontinued; however the participant may continue to be followed for the remainder of the 48-week Treatment Period, after which, the subject may opt to receive ARO-APOC3 in the planned open-label extension study.

8.3.2. Study Drug Discontinuation Criteria for Increased HbA1c

Regarding HbA1c drug discontinuation criteria participants should discontinue IP 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 IP due to HbA1c elevations will be followed for 6 months after their last dose per the Schedule of Assessments.

8.4. Restrictions and Concomitant Medications

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 IP administration or blood draw unless otherwise specified.
2. **Recreational Drugs & 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, more than 14 units per week [1 unit = 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.
3. **Concomitant Medications:** Use of optimal statin therapy, nicotinic acid/niacin, omega-3 fatty acids (prescription or OTC), fibrates, or other lipid management regimens, is acceptable if the participant has been on a stable regimen for the minimum period specified in [Table 2](#) (below) prior to the S2 Screening Visit and if the participant is willing to maintain a constant dosing regimen during the Treatment Period. Adjustments to medications regimens during the study, including lipid-lowering and diabetes mellitus therapies, are only allowed if, at the discretion of the Investigator, this is 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 Investigator 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.
4. **Local 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 Investigator and will be blinded after Day 1. After Day 1, Investigators should not perform local non-protocol testing of these analytes during a participant's study participation from first dose administration of IP until after the participant's EOS visit.

Table 2 Restricted Concomitant Medications

Restricted Background Medications	Time on stable regimen prior to collection of Screening Visit (S2) laboratory tests and throughout study duration
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
Anticoagulation therapy	≥12 weeks
Thyroid hormone replacement therapy	≥12 weeks
Testosterone replacement therapy	≥16 weeks
Oral estrogens, tamoxifen, raloxifene	≥16 weeks
Immunosuppressants	≥24 weeks

8.5. Lipid Monitoring

Following the Week 24 visit, in cases where a participant with a baseline LDL-C ≥ 130 mg/dL (≥ 3.37 mmol/L) experiences an increase from baseline $\geq 25\%$ on two consecutive visits, LDL-C values for this subject will be unblinded for the remainder of the study, and the central laboratory will notify the Investigator and Medical Monitor for medical follow-up. Appropriate medical follow-up will include dietary and medication compliance counseling, which may also include modification to the participant's lipid-lowering regimen to lower LDL-C according to country-specific guidelines (eg, initiate statin therapy or increase the statin dose for patients who are already on treatment).

Following the Week 24 visit, 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) on two consecutive visits, LDL-C values for this subject will be unblinded for the remainder of the study, and the central laboratory will notify the Investigator and Medical Monitor for appropriate medical follow-up. Appropriate medical follow-up will include dietary and medication compliance counseling, which may also include modification to the participant's lipid-lowering regimen to lower LDL-C according to country-specific guidelines (eg, initiate statin therapy or increase the statin dose for patients who are already on treatment).

In cases where any participant with a history of acute pancreatitis in the 24 months prior to Study Day 1 has a TG > 2000 mg/dL (22.6 mmol/L) at any post-baseline visit, the central laboratory will

notify the Investigator and Medical Monitor. A fasting TG repeat test will be requested. If the retest confirms TG >2000 mg/dL (>22.6 mmol/L), the Investigator and Medical Monitor will be informed so that appropriate medical follow-up can be initiated. Appropriate medical follow-up will include dietary and medication compliance counseling, which may also include modification to the participant's lipid lowering regimen.

9. INVESTIGATION PRODUCT

9.1. Description, Identification, and Dosage

The Sponsor is responsible for the supply of ARO-APOC3 together with detailed instructions (in the Pharmacy Manual) describing preparation of ARO-APOC3. The placebo (normal saline 0.9%) will be supplied by the clinical site or may be provided by the Sponsor upon request.

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.

Placebo will be 0.9% normal saline administered SC.

Doses administered per Dose Level:

Each dose of either active drug (ARO-APOC3) or placebo (normal saline 0.9%), will be administered by SC injection by the Investigator or appropriately trained and qualified clinical staff designated by the Investigator. Injections will be made into the SC tissue at an appropriate site (eg, abdomen, thigh, upper arm, etc) using a 25 to 30 Gauge, ½ inch needle. The abdomen is the preferred site. Injection site is to be varied (no multiple injections into the same exact site; alternating various locations on the abdomen are acceptable). Injection site location is to be recorded in the eCRF. Prior to dose administration, the IP vial must be allowed sufficient time to come to room temperature. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections. Injection volume per site should not exceed approximately 0.25 mL.

There will be no dose escalation or dose reduction (ie, the same IP dose will be administered to each participant within dose cohort).

9.2. Supply, Preparation, Storage, and Labeling of ARO-APOC3

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).

Strength	200 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°C to 8°C

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 IP vials will be labeled per current Good Manufacturing Practice (cGMP)/Good Clinical Practice (GCP).

Investigational product supplies will be stored at clinical sites securely under the appropriate conditions.

9.3. Study Drug Handling

The Sponsor will provide the Investigator with a sufficient quantity of clinical drug supplies. The Investigator must ensure that deliveries of IP 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 Investigator to ensure that the integrity of packaged study product not be jeopardized prior to dispensing.

Only participants enrolled in the study may receive IP in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer IP. The IP must be stored in a secure area with access limited to the Investigator and authorized staff and under the physical conditions that are consistent with the IP-specific requirements.

An authorized and trained staff member at each clinical study site will dispense the IP per predefined drug dispensing requirements. The dispensing will be verified by a second member of site staff.

ARO-APOC3 will be supplied by the Sponsor and labeled with the drug name, batch number, expiration date (as applicable), and storage conditions. The IP will be dispensed by clinical study site staff members on the day of dosing and recorded in the drug accountability records. A Pharmacy Manual will be prepared to define the procedures for dispensing.

9.4. Allocation to Treatment

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 3:1 to either active (ARO-APOC3) treatment in 1 of 3 dose groups (10, 25, or 50 mg) or to placebo treatment. Treatments will be administered per the randomized sequence generated by an Interactive Web

Response System (IWRS). The allocation of active treatment or placebo will be performed using a block randomization algorithm.

9.5. Study Formulation Administration

Appropriately trained employees of the clinical site will administer the IP. Each dose will be administered as a single SC injection. The site of injection will be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs.

Table 3 Injection Number and Volume Per Dose Cohort

ARO-APOC3 Dose¹	Concentration	Total Injection Volume	Number of Injections per Planned Dose	Total Number of Study Injections
10 mg	200 mg/mL	0.05 mL	Single	2
25 mg	200 mg/mL	0.13 mL	Single	2
50 mg	200 mg/mL	0.25 mL	Single	2

¹ Placebo injections of normal saline will be volume matched.

9.6. Accountability of Study Supplies

All material supplied is for use only in this clinical study and should not be used for any other purpose. The Investigator is responsible for the IP accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain IP accountability records throughout the course of the study. This person will document the amount of IP received from the Sponsor and the amount administered to participants. A non-blinded Clinical Research Associate (CRA) will perform initial and ongoing IP kit and placebo accountability. The non-blinded 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 non-blinded CRA during IP and placebo reconciliation.

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

- the identification of the participant to whom the drug was dispensed; and
- the date(s) and quantity of the drug dispensed to the participant.

The date and time of dose preparation and dispensation will be maintained to support administration of IP. 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 IP as assigned by the IWRS. Investigational product administration will be documented and recorded on the eCRFs. The inventory must be available

for inspection by the non-blinded monitor during the study. Drug supplies will either be collected at the end of the study by the study monitor or returned by the Investigator or designee to the Sponsor, or the designated Sponsor-approved depot.

9.7. Retention of Investigational Product Vials

For this study, used and partially used drug vials will be retained for an adequate period to allow accountability. No additional IP samples will be retained.

9.8. Blinding and Code-Break

Treatment assignment (active versus 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 (refer to [Table 3](#)). In order 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.

Blinding of IP/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 Investigator or documented designated treating physician, or the Medical Monitor can unblind the treatment assignment. 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 electronic data capture system. The study monitor should be informed promptly.

The randomization schedules will be maintained under controlled access. The personnel involved in the dispensing of IP will be accountable for ensuring compliance to randomization schedules. The non-blinded CRA will verify correct randomization.

If the Investigator 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 IWRS system. Medical emergency unblinding in IWRS is only accessible to the designated, unblinded Pharmacist, Investigator, and Sub-Investigator. The Medical Monitor should be informed promptly.

If a participant requires emergency unblinding (with or without a discussion between the Investigator and the Medical Monitor preceding the unblinding), the Investigator 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.

10. STUDY METHODS AND PROCEDURES

10.1. Overview of Procedures

The SOA is provided in [Table 1](#). Potential participants will visit the site to provide informed consent prior to the start of any screening assessments. Initial eligibility assessments will begin up to 6 weeks prior to randomization, beginning with the first Screening Visit (S1).

At the Investigator's discretion and if permitted by local requirements, the first and second Screening visit (S1 and S2) assessments may be conducted concurrently within the S2 visit window (Day -35 to Day -21) as long as the participant meets stable diet, stable background medications, and fasting requirements as outlined in [Sections 8.1, 8.4, and 10.2](#).

The total duration between the initial Screening Visit (S1) and randomization on Day 1 may take up to 6 weeks. Dietary counseling will be reinforced at intervals throughout the study (for details, see [Section 10.2](#)).

Participants who successfully pass the Screening requirements will be enrolled into the study. All dose cohorts will enroll in parallel with participants randomized 3:1 to receive ARO-APOC3 or placebo. Each participant will receive SC injection on Day 1 and Week 12, for a total of 2 injections as follows:

- ARO-APOC3 **10 mg** (n=54) or volume-matched placebo (n=18) at Day 1 and Week 12;
- ARO-APOC3 **25 mg** (n=54) or volume-matched placebo (n=18) at Day 1 and Week 12; or
- ARO-APOC3 **50 mg** (n=54) or volume-matched placebo (n=18) at Day 1 and Week 12.

Each participant will present to the clinical facility on Day 1 (baseline). On arrival at the clinical facility, the Investigator or designee will meet with the participants 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 Investigator's discretion for safety reasons.

All Screening Visits, Day 1, and Week 12 study visits must be conducted at the clinical study site. At the discretion of the Investigator and with prior Sponsor approval, utilization of home health care services to conduct other study assessment visits is permissible when COVID pandemic restrictions or other logistical disruptions occur in order to avoid missed study visits. Utilization of home health services to conduct study assessments is contingent upon compliance with local laws and regulations and the capability of the Investigator to adequately monitor participant safety. In cases where home health care services are to be utilized, this approach, and any specific risks associated with it, must be clearly outlined in the EC/IRB approved informed consent form.

All participants will have a predose and postdose PK sample collected at Day 1 and Week 12 as specified in the SOA ([Table 1](#)). In a subset of participants undergoing full PK (12 active, 4 placebo in each dose cohort), PK will be measured predose and serially postdose on Day 1 and Week 12 as per the SOA ([Table 1](#)). Pharmacokinetic time points on Day 1 and Week 12 are at predose, 0.25, 1, 3, 6, and 24 hours postdose. Time window for PK sample through the 6-hour timepoint is ± 5 minutes. Time window for PK sample at the 24-hour time point is ± 60 minutes. 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.

Parameters to be assessed and the timing of assessments are provided in the SOA in [Table 1](#). 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, chemistry analysis, and urinalysis. Blood samples will also be collected for PK and immunogenicity analysis. Participants will have fasted for at least 10 hours predose.

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

10.2. Screening Diet Stabilization Period

Confirmation of ≥ 2 weeks diet stabilization will precede qualifying TG laboratory assessments at Screening. Enrolled participants will be counseled to remain on the specified diet throughout the study, as recommended by the Investigator in accordance with local standard of care. For example, in the US, Investigators may refer to the guidelines established by the AHA/ACC ([Van Horn 2016](#)). The specifics of the diet will be at the discretion of the Investigator 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 as per the SOA ([Table 1](#)).

This diet may vary at the Investigator's discretion and certain populations may require more strict dietary regimens.

10.3. Selection and Screening

Prior to commencement of any screening procedures, the Investigator 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 provide a copy of the IRB/EC-approved informed consent form 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 Investigator or designee, who will also sign and date the informed consent form.

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 Investigator, and a copy of the original will be given to the participant.

Informed consent will be performed per the Principles of the ICH 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 Investigator 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 1) will be performed. Timing will abide by fasting restrictions outlined in Section 8.4.

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

10.4. On-Study Procedures/Assessments

10.4.1. Efficacy Assessments

10.4.1.1. Serum Triglycerides

In order to determine the average (arithmetic mean) TG level during Screening, two fasting serum TG levels will be collected separately and consecutively at least 7 days but no more than 17 days apart in accordance with the SOA (Table 1).

Fasting TG levels will be assessed by a central laboratory using a standard method. Beginning on Day 1, predose fasting TG will be collected as part of the lipid parameter panel in accordance with the SOA (Table 1).

10.4.1.2. Other Lipid Parameters

Lipid parameters (TG, 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 be collected on Day 1 prior to dosing, after at least a 10-hour fast, and measured by a central laboratory. LDL-C will be measured using an ultracentrifugation methodology preferentially as well as Martin-Hopkins methodology (which will be used as back-up).

10.4.1.3. Glucose Metabolism

Serum samples will be collected 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, homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide will be measured as per the SOA and assessed by a central laboratory.

10.4.1.4. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) using magnetic resonance imaging-proton density fat fraction (MRI-PDFF) for the evaluation of percentage liver fat will be conducted at Screening, after completion of the S2 visit, and at Week 24, as outlined in the SOA (Table 1) and in

accordance with procedural standards detailed in the Imaging Acquisition Manual. Selected sites (where MRI-PDFF is available) will perform MRI-PDFF assessments at screening until up to 35 participants with baseline liver fat fraction $\geq 8\%$ have been enrolled in each of the 3 dosing cohorts, after which MRI-PDFF will no longer be included as an evaluation. The MRI protocol used should be consistent across all individual participant visits (same MRI imaging technique/protocol will be used predose and at Week 24 on a participant-by-participant basis). Please refer to the Imaging Acquisition Manual for further instructions.

10.4.1.5. Blood Sampling for Pharmacodynamic Analysis

Fasting blood samples 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. During Weeks 24 and 48, two fasting PD blood samples will be collected, each separated by at least 2 days and no more than 7 days. Blood samples will be collected at time points outlined in the SOA ([Table 1](#)).

The actual sample times (times samples 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.

10.4.2. Pharmacokinetic Assessments

Plasma samples for analysis of circulating ARO-APOC3 will be obtained in a subset of participants at time points following IP administration as outlined in the SOA ([Table 1](#)). Blood samples will be collected from participants through an indwelling cannula or through repeated venipuncture. For postdose samples that require next-day collection (nonfasting permitted), 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. Sparse sampling PK blood draws and analysis will also be conducted on all participants not included in the specified PK group as per the SOA.

10.4.2.1. Sample Processing and Analysis for Pharmacokinetic Samples

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.

10.4.3. General and Safety Assessments

General assessments include optional genotype, medical history, and demographics. Safety will be evaluated by the incidence, frequency, and severity of AEs and SAEs, including ISRs.

The safety of ARO-APOC3 will also be evaluated by the collection of the following measurements performed at time points specified in the SOA ([Table 1](#)) as well as CS changes from baseline to scheduled time points:

- Monitoring of AEs/SAEs
- Physical examinations
- Vital signs
- ECG measurements
- Clinical laboratory assessments (hematology, chemistry, HbA1c, coagulation, amylase, lipase, urinalysis)
- Concomitant medications/therapy
- Reasons for treatment discontinuation due to toxicity.

The AE/SAE reporting period for an enrolled participant will begin when the participant provides informed consent. Treatment-emergent AEs/SAEs will be those defined as following IP administration. All AEs/SAEs that occur during the AE reporting period specified in the protocol must be reported to the Sponsor, regardless of the relationship of the AE to IP. Any known untoward event that occurs beyond the AE reporting period that the Investigator considers an SAE and possibly related to IP will be reported to the Sponsor.

10.4.3.1. Demographics and 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.

Optionally, participants will be invited to consent for pharmacogenetic analyses. Participants who consent will have blood sample drawn for these analyses.

10.4.3.2. Physical Examination

A complete physical examination will be performed at Screening and as per SOA ([Table 1](#)). At Screening, height (centimeters, without shoes) and weight (kilograms, without shoes). At all other time points outlined in the SOA, a symptom-directed physical examination will be performed if indicated.

10.4.3.3. Vital Signs

Systolic/diastolic blood pressure (mm Hg), temperature (degrees Celsius [°C]), heart rate (beats/minute), and respiratory rate (breaths/minute) will be obtained at time points outlined in the SOA ([Table 1](#)) after the participant is sitting for at least 3 minutes. Vital signs will be obtained prior to venipuncture and other invasive procedures.

10.4.3.4. Electrocardiogram

A single 12-lead ECG measurement will be obtained at time points outlined in the SOA (Table 1) after the participant is semisupine for at least 3 minutes. Any abnormal and CS ECGs, as per the Investigator's medical judgment, will be repeated in triplicate, with each measurement approximately 1 minute apart. ECGs will be performed prior to venipuncture and any other invasive procedures.

10.4.3.5. Clinical Laboratory Tests for Safety

Blood and urine clinical laboratory samples for safety will be collected at the site and shipped to the central laboratory for analysis. In the event of major 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, 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. In accordance with the SOA (Table 1), 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 draw is allowed per assessment to establish eligibility. The results will be assessed by the Investigator or medically qualified designee before study enrollment. Any abnormality in laboratory values (that are confirmed on repeat) deemed CS by the Investigator or 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.

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

Biochemistry: 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-glutamyl transferase (GGT), alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LD), C-reactive protein, thyroid-stimulating hormone (TSH) and free T4.

Hematology: Hemoglobin, red blood cell (RBC) count, hematocrit, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Coagulation: Partial thromboplastin time (PTT), prothrombin time with INR and fibrinogen.

Urinalysis: Leukocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose.

Microscopic urinalysis will be performed if indicated: white blood cells, red blood cells, epithelial cells, bacteria.

Spot urine protein and spot urine creatinine: will be performed at screening only in order to determine the spot urine protein/spot urine creatinine ratio.

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

Follicle-stimulating hormone (FSH): Postmenopausal status at screening will be supported based on FSH level consistent with postmenopausal state.

Immunogenicity: Participants will be assessed for anti-drug antibodies.

The Day 1 value will be used as each participant's baseline value for data analysis purposes or as otherwise specified. If Day 1 or as otherwise specified values are erroneous or not available and repeat blood draw is not possible, the Screening value may be used as baseline.

10.4.3.6. 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 subject's study participation. The reason for Early Termination will be documented in source documents and eCRF. Procedures as outlined in the SOA ([Table 1](#)) will be completed. Participants who discontinue ARO-APOC3 due to SAE will be encouraged to remain available for follow-up for medical monitoring until resolution.

10.4.3.7. Follow-Up Procedures

Contact will be made with each participant and documented to verify the following:

- AEs occurring over the 24 hours following doses at Day 1 and at Week 12

10.4.4. Acute Pancreatitis Events

All treatment-emergent AEs and SAEs reported by the Investigator through Week 48/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) $\geq 3 \times \text{ULN}$
3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT), MRI, or transabdominal ultrasonography

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

10.4.4.1. Detecting and Reporting Pancreatic Events

During each study visit, the Investigator 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 Investigator 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.

Adverse events terms that could signal a potential case of pancreatitis are listed below according to the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (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 Investigator will follow each subject and provide further information on the participant's condition as deemed appropriate.

The Investigator will follow all pancreatitis or possible pancreatic AEs until resolution until the condition stabilizes, or until the event is otherwise explained. Once resolved, the Investigator or medically qualified designee will update the appropriate AE eCRF page and SAE report form (if the event is serious). The Investigator 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 Investigator.

10.4.4.2. Hospitalization for Abdominal Pain

All SAEs resulting in hospitalizations for abdominal pain will also be recorded as described in [Section 10.4.4.](#)

10.5. Timing of Treatments and Procedures

Actual times of procedures for each participant will vary depending on scheduling and will be recorded in the eCRF.

In the event of multiple procedures scheduled at the same time, non-invasive procedures (ie, vital signs, ECGs, AE assessment) will be conducted prior to invasive procedures (ie, blood sample collection). Timing of activities may be adjusted slightly to accommodate all procedures.

The following windows are allowed for study assessments/visits:

Predose	Any time during the study visit, and before first dose
Plasma PK¹ up to 6-hour sampling timepoint	±5 minutes
Plasma PK¹ 24-hour sampling timepoint	±60 minutes
Day 1	Not Applicable
Post-baseline visits	±5 days

Abbreviation: PK = pharmacokinetic.

¹ Only for Full PK Group assessments.

10.6. Pregnancy Testing and Contraception Requirements

Female participants of childbearing potential will have urine pregnancy tests at Screening (visits S1 and S3), Day 1 (baseline), and at subsequent study visits prior to dosing throughout the study, as indicated in [Table 1](#). Females 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 FSH consistent with postmenopausal state based on laboratory reference ranges.

If a subject's 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 between Day 1 and Week 12 will not receive the second administration of IP 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 one of the following highly effective contraception methods during the study and for at least 24 weeks following the last dose of IP:

- 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;
- Surgical sterilization as a single form of birth control: ie, tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy, or equivalently effective surgical form of birth control;

- True sexual abstinence for the duration of the study and for at least 24 weeks following the last dose of IP is acceptable only when in line with the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not considered “true” abstinence and are not acceptable methods of contraception.

11. ADVERSE EVENTS

The Investigator 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. AEs will be recorded from time of signed consent through to EOS; only AEs that occur postdose will be considered treatment-emergent. The Investigator and clinical facility staff are responsible for detection, recording, and reporting of pregnancy and appropriate follow-up. Information regarding any reported pregnancy should be collected for at least 1 year after birth or longer if it is decided that additional follow-up is required, or until the end of the pregnancy.

11.1. Definitions

An **Adverse Event (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 International Council for Harmonisation [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 IP, or when a pre-existing medical condition increases in severity or frequency after IP administration.

AEs will not include:

- A medical or surgical 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); or
- An overdose of either the IP or a concurrent medication without any resulting signs or symptoms.

A **Serious Adverse Event (SAE)** is an AE that:

- Results in death;

- Is 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 inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is a medically important event or reaction.

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.

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

Abnormal assessments (eg, ECGs and vital signs) that are judged by the Investigator as CS or result in clinical sequelae should be recorded as AEs. Laboratory abnormalities should be reported by the Investigator as AEs if the abnormality is considered CS or result in clinical sequelae. Laboratory abnormalities not reported as AEs are not to be reported as CS in the study database.

Clinically significant abnormal laboratory findings or other CS 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 Investigator 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 CS.

11.3. 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.

At each visit/assessment in the period defined above, AEs will be evaluated by the Investigator, or medically qualified designee, and recorded in the medical notes and eCRF.

11.4. Recording of Adverse Events

When an AE occurs, it is the responsibility of the Investigator or medically qualified designee to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator or medically qualified designee will then record the AE on the AE case report form (CRF). Additional reporting requirements for an AE meeting serious criteria are discussed in [Section 11.5](#).

The Investigator 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 Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the appropriate AE eCRF pages.

11.5. Evaluating Adverse Events

11.5.1. Severity of Adverse Events

The Investigator or medically qualified designee will assess the severity for each AE reported during the study. The assessment will be based on the Investigator's, or medically qualified designee's, clinical judgment. The severity of all AEs will be graded using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions:

- **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 a SAE. Severity is a category utilized for rating the intensity 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 11.1](#).

11.5.2. Injection Site Reactions

For purposes of data analysis, a local injection site reaction (LISR) is defined as an adverse reaction (usually immunologic) developing at the site of injection and lasting at least 48 hours

which must be based on the specified Medical Dictionary for Regulatory Activities (MedDRA) PT as provided in [Appendix 2](#). For data analysis purposes, AEs at the injection site with reported terms of bruising or hematoma will not be considered LISRs. Injection site reactions are graded based on CTCAE.

Grade 1: Tenderness with or without associated symptoms (eg, warmth, erythema, itching).

Grade 2: Pain; lipodystrophy; edema; phlebitis.

Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Results in death.

11.5.3. Assessment of Causality

The Investigator or medically qualified designee is obligated to assess the relationship between IP and the occurrence of each AE. The Investigator 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 IP will be considered and investigated. The Investigator or medically qualified designee will also consult the IB in the determination of his/her assessment.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial SAE report. However, it is very important that the Investigator or medically qualified designee always assess causality for every event prior to transmission of the SAE report form. The Investigator 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 Investigator or medically qualified designee will provide the assessment of causality utilizing 3 possible categories: Not Related, Possibly Related, and 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 IP, 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 IP, unlikely to be attributed to concurrent disease or other drugs or chemicals. Also, an event that follows a known or expected response pattern to the IP, or that is confirmed by stopping or reducing the dosage of the IP and that could not reasonably be explained by known characteristics of the participant’s clinical state.

11.5.4. Follow-up of Adverse Events

After the initial AE, the Investigator 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 Investigator 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 Investigator 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 Investigator.

11.6. Prompt Reporting of Serious Adverse Events

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

11.6.1. Completion and Transmission of the Serious Adverse Event Reports

Once an Investigator 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 Investigator or medically qualified designee. If the Investigator 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 Investigator or medically qualified designee will always provide an assessment of causality at the time of the initial report as described in [Section 11.5.3](#). However, as new information becomes available, causality may be modified.

Electronic transmission of the SAE report form is the preferred methods to transmit this information to the designated Pharmacovigilance CRO. 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 Investigator 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 Investigator may be of immediate or potential concern for the participant's health or well-being will be reported to the Sponsor emergency contact listed below.

Sponsor Emergency Contact

[REDACTED]

[REDACTED] *

*Regional contact information will be provided in the site manual.

Sponsor Medical Monitor Contact

[REDACTED]

Telephone: [REDACTED]

11.6.2. 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 within 24 hours of initially becoming aware of the pregnancy by the Investigator.

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

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

11.6.3. SAE Reports to the IRB/EC

The Investigator, 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 EC.

11.7. Regulatory Requirements for Reporting of SAEs

The Investigator or medically qualified designee will promptly report all SAEs in accordance with the procedures detailed in [Section 11.6.1](#). Prompt notification of SAEs by the Investigator 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, Investigators, and IRBs/ECs in accordance with the Sponsor's procedures and local regulatory requirements.

11.8. Poststudy Adverse Events

A poststudy AE is defined as any event that occurs outside of the AE detection period defined in [Section 11.3](#).

Investigators are not obligated to actively seek AEs in former study participants. However, if the Investigator 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 IP, the Investigator will promptly notify the Sponsor.

11.9. 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 (see [Section 11.7](#)).

12. DATA ANALYSIS AND STATISTICAL 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 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 (SD), minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percent. Data will be analyzed by treatment groups of ARO-APOC3 10, 25, and 50 mg, and placebo.

Additional details of all planned analyses for this study will be provided in the Statistical Analysis Plan.

12.1. Endpoints

12.1.1. Primary Endpoint

The primary endpoint in this study is:

- Percent change from baseline at Week 24 in fasting TG.

12.1.2. Secondary Endpoints

The following secondary endpoints will be evaluated:

- Percent change over time through Week 48 in fasting TG;
- Percent change from baseline at Week 24 and over time through Week 48 in ApoC-III;

- Percent change from baseline at Week 24 and over time through Week 48 in fasting non-HDL-C;
- Percent change from baseline at Week 24 and over time through Week 48 in fasting HDL-C;
- Percent change from baseline at Week 24 and over time through Week 48 in fasting total ApoB;
- Percent change from baseline at Week 24 and over time through Week 48 in fasting LDL-C using ultracentrifugation;
- Change in plasma concentrations of ARO-APOC3 over time through Week 12; and
- The frequency and severity of AEs and SAEs over time through Week 48.

12.1.3. Exploratory Endpoints

The following exploratory endpoints are defined in this study:

- Change and/or percent change from baseline over time through Week 48 in TG and other fasting lipid parameters (total cholesterol, LDL-C measured using Martin-Hopkins methodology, LDL/HDL ratio, VLDL-C, ApoB-48, Lp(a), ApoB-100, ApoC-II, ApoA-I and ApoA-V [all values drawn after at least 10-hour fast]);
- Change from baseline to Week 24 and overtime through Week 48 in fasting serum blood glucose, HbA1c, HOMA-IR and C-peptide;
- Change from baseline over time through Week 48 in high sensitivity C-reactive protein (hsCRP);
- Cumulative number of on-study occurrences of acute pancreatitis events over time through Week 48;
- Cumulative number of on-study hospitalizations for abdominal pain over time through Week 48;
- Note: All AEs and SAEs reported by the Investigator during the study that are consistent with an event of acute pancreatitis, as per 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) $\geq 3 \times$ ULN; and (3) characteristic findings of acute pancreatitis on CECT, MRI, or transabdominal ultrasonography.
- Proportion of participants requiring emergent apheresis over time through Week 48;
- Change and percent change from baseline to Week 24 in liver fat content using MRI-PDF (only in participants with a liver fat fraction of $\geq 8\%$ at Screening); and
- Emergence of and levels of anti-drug antibodies to ARO-APOC3 in those receiving ARO-APOC3 over time through Week 48.

12.2. Analysis Populations

The following study populations are defined in this study:

- **Full Analysis Set (FAS):** All randomized participants who receive at least 1 dose of IP. All efficacy analyses will be performed using FAS. Participants will be analyzed according to the treatment assigned at randomization.
- **Safety Analysis Set:** All participants who receive at least 1 dose of IP. All safety and tolerability analyses will be performed using this set. Participants will be analyzed according to the treatment they actually received.
- **PK Analysis Set:** All FAS participants who have sufficient plasma concentration data to facilitate determination of PK parameters.

12.3. Sample Size Considerations

From previous Phase 1 study, the PD data of patients with SHTG showed fasting TG reduction of 57.7% (SD=18.2%) for ARO-APOC3 10 mg dose group, 73.6% (SD=9.6%) for 25 mg dose group, and 80.1% (SD=7.0%) for 50 mg dose group, while 0.4% reduction in placebo group with SD as 41.7%. Therefore, it's reasonable to assume ARO-APOC3 dose groups will have 50% to 70% more reduction than placebo, with SD of 10% for ARO-APOC3 dose groups and 40% for placebo.

With these assumptions, the study will have greater than 99% power to detect any active treatment dose cohort which is significantly different from placebo with 18 complete participants per treatment group, using a two-sided test and 1.67% level of significance, adjusted for multiplicity. With the considerations of dropout and to observe more participants for clinical safety, 72 participants per active treatment group or placebo is designed. A total of 216 participants will be randomly assigned to treatment in a 3:1 (active to placebo) ratio within each dose cohort (72 participants per dose cohort).

12.4. Interim Analysis

An interim analysis is planned for this study after all participants have completed the Week 24 visit. The interim analysis will be conducted by an unblinded independent biostatistician and reviewed by the unblinded individual(s) from sponsor or their designee. Safety data and select PD data, will be reviewed in aggregate, comparing the treatment groups: ARO-APOC3 (10, 25, or 50 mg) to pooled placebo. Following receipt of the interim analysis data, recipients will not be involved in further planning or conduct of the study so as to maintain the study blind. The primary endpoint will be evaluated and, therefore, no adjustment to the alpha level for the final analysis is necessary.

12.5. Stratification

Randomization to placebo and active groups will be stratified based on:

- Mean level of TG at Screening (≥ 1000 mg/dL versus < 1000 mg/dL).

Prespecified subgroup analyses will be conducted for:

- Participants with a genotype consistent with FCS (including but not limited to homozygous, compound heterozygous, or double heterozygous loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including *LPL*, *APOC2*, *APOA5*, *GPIHBP1*, *LIPG*, *GPD1*, or *LMF1*);
- Participants with TG at baseline of 500 to 2000 mg/dL (5.65 to 22.6 mmol/L); and
- Participants with TG at baseline of >2000 mg/dL (>22.6 mmol/L).

12.6. Analysis Methods

12.6.1. Screening Data

Demographics will be tabulated by participant and summarized by for each dose level and for pooled placebo. Eligibility assessments at baseline, including medical/surgical history data and physical examination data (including height and weight), will be listed for each participant.

Medical history will be summarized and listed by participant. Medical history will be coded using 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. Preferred terms will be summarized and listed, and verbatim terms will be listed by participant.

12.6.2. Efficacy and Pharmacodynamics Analysis

The primary objective of this study is to evaluate the effect of ARO-APOC3 on fasting TG levels in adults with SHTG. The primary endpoint is the percent change from baseline at Week 24 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 who receive at least 1 dose of IP (FAS). The estimand of interest is the difference in means of percent change from baseline in fasting TG at Week 24 in adult SHTG population (as defined by the inclusion/exclusion criteria), regardless of treatment compliance or other intercurrent events post-baseline.

For endpoint analysis based on Week 24 data, the laboratory value will be the arithmetic mean of two fasting TG values, separated by at least 2 days and no more than 7 days, taken during Week 24. If only one value is available during Week 24, 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 two fasting TG values collected during the Screening period.

The primary analysis will be performed using a mixed model repeated measures (MMRM) approach with treatment, study visit, stratification factor, and baseline TG level included as model terms. The model will also include treatment by visit and treatment by baseline interaction terms. The primary estimate of interest will be the difference in means between each active treatment dose group and pooled placebo group, evaluated at Week 24. When performing the primary analysis, the adjustment for multiplicity of testing several arms versus placebo will be

carried out using Holm's step-down procedure. Normality and other statistical assumptions will be assessed.

All continuous secondary endpoints will be analyzed in a similar manner to the primary endpoint, unless otherwise noted. The frequency and severity of AEs and SAEs over time through Week 48 will be summarized with descriptive statistics.

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. For lipid related, lipoprotein and serum pharmacodynamic assessments, baseline is defined as the predose value on Day 1.

The final study report will be created following the completion of the study (Week 48).

12.6.3. Pharmacokinetics Analysis

Plasma concentrations of ARO-APOC3 will be measured in all participants to evaluate trough and postdose levels through the study (see the SOA in [Table 1](#)). Serial PK sampling will be conducted in a subset of participants at specifically designated PK sites.

Full PK group: In each of the dose cohorts, 16 PK participants (12 active, 4 placebo for a total of 48 participants for PK) will be enrolled at the designated PK sites. Plasma concentrations will be measured predose and serially postdose as per the SOA. Only samples collected from participants receiving active treatment will be included in the PK analysis.

Sparse Sample PK group: All other participants at all sites will provide a predose PK sample and one additional sample at ≥ 15 minutes postdose at Day 1 and Week 12 as per the SOA.

12.6.4. Safety/Tolerability Analysis

In general, safety analyses will be performed and the results summarized by treatment groups. Post-treatment safety assessments will be compared with measurements recorded at baseline. Treatment-emergent AEs will be summarized using the latest version of MedDRA by System Organ Class (SOC) and PT. The incidence of AEs, SAEs, related AEs, related SAEs, and AEs leading to discontinuation, will be summarized by treatment group and by dose level per SOC, PT, and severity. 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 and shift tables. 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 listings. ECG parameters, changes from baseline, and qualitative assessments will be summarized. Pregnancy and FSH test results will be listed separately by time point.

12.6.5. Analysis of Immunogenicity (Anti-drug Antibodies) Data

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

Shankar et al ([Shankar 2014](#)). The effect of ADA formation status on ARO-APOC3 PK, PD, and safety (AE) will be analyzed.

12.7. Data Recording and Quality Control

Source documents must be maintained for each participant in the study, consisting of all demographic and medical information, including clinical laboratory data, etc. A copy of the signed informed consent form must be retained. All information on the eCRFs must be traceable to these source documents in the participant's file.

Data recorded in all participants' eCRFs will be subjected to a quality control review.

13. STUDY APPROVAL AND CONDUCT

The following conditions will be met:

13.1. Regulatory Approval

The requirements for the conduct of clinical studies in accordance with local applicable regulations will be met before commencement of this study.

13.2. Institutional Review Board (IRB)/Ethics Committee (EC) Approval

Prior to initiation of the study, written IRB/EC approval of the Protocol and Informed Consent Forms, based on the principles of ICH GCP, will be received. A copy of the signed and dated letter of approval will be provided to the clinical site and the Sponsor prior to study commencement. Any written information and/or advertisements to be used for participant recruitment will be approved by the IRB/EC prior to use. A list of the IRB/EC voting members, their titles or occupations, FWA 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/EC, following written agreement from the Sponsor.

13.3. Ethical Considerations

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 GCP and the applicable regulatory requirement(s). The protocol will be submitted for approval to the IRB/EC, and written approval obtained before participants are enrolled. The composition of the IRB/EC will also be provided to the Sponsor. If approval is suspended or terminated by the IRB/EC, the Investigator will notify the Sponsor immediately.

Where applicable, the clinical site and the Sponsor agree to abide by the local compensation guidelines for injury resulting from participating in a company-sponsored research project. Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability and is subject to the proposed recipient signing a full and complete release of the company from all claims, damages and costs.

13.4. 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 washout of excluded medications.

It is the responsibility of the Investigator 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 Investigator or medically qualified designee must also explain to the participants 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 Investigator or by the Sponsor.

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 Investigator 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. 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 informed consent form to retain.

13.5. Emergency Contact with Principal Investigator

Suitable arrangements will be made for participants to contact the Investigator or medically trained designee in the event of an emergency.

13.6. Notification of General Practitioner

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

13.7. Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the Investigator 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 major logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site and central laboratory kit collection is not available, local laboratory safety testing with associated local lab reference ranges may only be permitted in limited circumstances and only with prior Sponsor approval.

13.8. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. The Investigator 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, Investigator, 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; and
- Procedural deviations such as incorrect storage of IP, failure to update the informed consent form when new risks become known, failure to obtain IRB/EC approvals for the protocol, and informed consent form 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/EC/competent regulatory authority per local regulatory requirements.

The Investigator 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.

13.9. Termination of the Study

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 trial participants;
- Continuation of the clinical trial no longer serves a scientific purpose

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

14. STUDY ADMINISTRATION

14.1. Study Monitoring

The Sponsor 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 the Sponsor's procedures, the Sponsor 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 and remote monitoring visits. The extent, nature and frequency of monitoring visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity and enrollment rate.

During special circumstances (eg, COVID-19 restrictions) the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, remote monitoring may be implemented to adhere to study specifications.

During these site visits, the study monitor will:

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

This will be done to verify that the:

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

The Investigator 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 Investigator or site staff as appropriate:

- Return of all study data to the Sponsor;
- Data queries;

- Accountability, reconciliation and arrangements for unused IP(s);
- Inventory and final disposition (eg, destruction, shipping to repository, etc); and
- Review of site study records for completeness.

14.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor 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 Investigator and clinical site agree to notify Sponsor as soon as possible following awareness of an impending regulatory inspection. The Investigator 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.

14.3. Records Retention

Following closure of the study, the Investigator 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 Investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The Sponsor will inform the Investigator 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 the Sponsor's 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/EC approval, letter of constitution of the IRB/EC and copies of any other correspondence relevant to the study with the IRB/EC or regulatory authorities;
- The IRB/EC-approved informed consent form;
- Current curriculum vitae (signed and dated) of the Principal Investigator and co-workers with major responsibilities in the study;

- Site Signature and Delegation of Responsibility Log;
- Food and Drug Administration (FDA) Form 1572 (where applicable);
- Financial Disclosure Form(s);
- Blank CRF/eCRF;
- Signed participant informed consent forms;
- Laboratory reference ranges (signed and dated);
- The completed Clinical Trial Notification Application Form (where applicable); and
- Clinical raw data including the Source Data Forms, all clinical laboratory report forms, participant CRFs, drug accountability forms, and dispensing records, etc.

15. INFORMATION DISCLOSURE AND INVENTIONS

15.1. Ownership

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

15.2. Confidentiality

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

16. REFERENCES

Aalto-Setälä 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;90:1889-900.

Aalto-Setälä K, Weinstock PH, Bisgaier CL, Wu L, Smith JD, and Breslow JL. Further Characterization of the Metabolic Properties of Triglyceride-Rich Lipoproteins from Human and Mouse ApoC-III Transgenic Mice. *J Lipid Res*. 1996;37:1802-11.

Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of Acute Pancreatitis--2012: Revision of the Atlanta Classification and Definitions by International Consensus. *Gut*. 2013;62:102-11.

Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, and 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;108:682-90.

Brown WV, Gaudet D, Goldberg I, and Hegele R. Roundtable on Etiology of Familial Chylomicronemia Syndrome. *J Clin Lipidol*. 2018;12:5-11.

Chatila A, Bilal TM, and Guturu P. Evaluation and Management of Acute Pancreatitis. *World J Clin Cases* 2019;7:1006-20.

Chen WJ, Sun XF, Zhang RX, Xu MJ, Dou TH, Zhang XB, et al. Hypertriglyceridemic Acute Pancreatitis in Emergency Department: Typical Clinical Features and Genetic Variants. *J Dig Dis* 2017;18:359-68.

Christian JB, Arondekar B, Buysman EK, Johnson SL, Seeger JD, and Jacobson TA. Clinical and Economic Benefits Observed When Follow-up Triglyceride Levels Are Less Than 500 mg/dL in Patients with Severe Hypertriglyceridemia. *J Clin Lipidol*. 2012;6:450-61.

Christian JB, Bourgeois N, Snipes R, and Lowe KA. Prevalence of Severe (500 to 2,000 mg/dL) Hypertriglyceridemia in United States Adults. *Am J Cardiol*. 2011;107:891-7.

De La Torre A, Hamilton L, and Wilson DP. A Clinical Approach to Aggressive Treatment of Children with Severe Hypertriglyceridemia. In *Endotext*, edited by K. R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, K. Dungan, A. Grossman, et al. South Dartmouth (MA), 2000.

Esparza MI, Li X, Adams Huet B, Vasandani D, Vora A, Das SR, et al. Very severe hypertriglyceridemia in a large US county health care system: associated conditions and management. *J Endocr Soc*. 2019 May 20;3(8):1595-1607.

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

Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, and Mello CC. Potent and Specific Genetic Interference by Double-Stranded RNA in *Caenorhabditis Elegans*. *Nature*. 1998;391:806-11.

Gaudet D, Brisson D, Tremblay K, Alexander VJ, Singleton W, Hughes SG, et al. Targeting Apoc3 in the Familial Chylomicronemia Syndrome. *N Engl J Med*. 2014;371:2200-6.

Gelrud A, Williams KR, Hsieh A, Gwosdow AR, Gilstrap A, and Brown A. The Burden of Familial Chylomicronemia Syndrome from the Patients' Perspective. *Expert Rev Cardiovasc Ther*. 2017;15:879-87.

Gerritsen G., Rensen PC, Kypreos KE, ZannisVI, Havekes LM, and Willems van Dijk K. ApoC-III Deficiency Prevents Hyperlipidemia Induced by ApoE Overexpression. *J Lipid Res*. 2005;46:1466-73.

Grundy SM, Stone, NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285-e350.

Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Aversa M, et al. The Polygenic Nature of Hypertriglyceridaemia: Implications for Definition, Diagnosis, and Management. *Lancet Diabetes Endocrinol*. 2014;2:655-66.

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;46:735-45.

Jong MC, Rensen PC, Dahlmans VE, van der Boom H, van Berkel TJ, and Havekes LM. Apolipoprotein C-III Deficiency Accelerates Triglyceride Hydrolysis by Lipoprotein Lipase in Wild-Type and ApoE Knockout Mice. *J Lipid Res*. 2001;42:1578-85.

Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, and Tybjaerg-Hansen A. Loss-of-Function Mutations in ApoC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*, 2014;371:32-41.

Khetarpal SA, and Rader DJ. Triglyceride-Rich Lipoproteins and Coronary Artery Disease Risk: New Insights from Human Genetics. *Arterioscler Thromb Vasc Biol*. 2015;35:e3-9.

Laufs U, Parhofer KG, Ginsberg HN, and Hegele RA. Clinical Review on Triglycerides. *Eur Heart J*. 2020;41:99-109c.

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;536:285-91.

Murphy MJ, Sheng X, MacDonald TM, and Wei L. Hypertriglyceridemia and Acute Pancreatitis. *JAMA Intern Med.* 2013;173:162-4.

NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106:3143-421.

Paquette M, Bernard S, Hegele RA, and Baass A. Chylomicronemia: Differences between Familial Chylomicronemia Syndrome and Multifactorial Chylomicronemia. *Atherosclerosis.* 2019;283:137-42.

Pedersen SB, Langsted A, and Nordestgaard BG. Nonfasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis. *JAMA Intern Med.* 2016;176:1834-42.

Regev A, Palmer M, Avigan MI, 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;49:702-13

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;341:410-8.

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;544:235-9.

Sanchez RJ, Ge W, Wei W, Ponda M, Rosenson R. The association of triglyceride levels with the incidence of initial and recurrent acute pancreatitis. *Lipids in Health and Disease* 2021, 20:72.

Scherer J, Singh VP, Pitchumoni CS, and Yadav D. Issues in Hypertriglyceridemic Pancreatitis: An Update. *J Clin Gastroenterol.* 2014;48:195-203.

Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, Quarmby V, Richards S, Schneider CK, Subramanyam M, Swanson S, Verthelyi D, Yim S; American Association of Pharmaceutical Scientists. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. *AAPS J.* 2014 Jul;16(4):658-73. doi: 10.1208/s12248-014-9599-2. Epub 2014 Apr 24. PMID: 24764037; PMCID: PMC4070270.

TG and HDL Working Group, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitzel NO, et al. Loss-of-Function Mutations in ApoC3, Triglycerides, and Coronary Disease. *N Engl J Med.* 2014;371:22-31.

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:e505-e29.

Warden BA, Minnier J, Duell PB, Fazio S, and Shapiro MD. Chylomicronemia Syndrome: Familial or Not? *J Clin Lipidol*. 2020;2:201-6.

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):2095-2107.

Yuan G, Al-Shali KZ, and Hegele RA. Hypertriglyceridemia: Its Etiology, Effects and Treatment. *CMAJ*. 2007;176:1113-20.

APPENDIX 1. LIVER-RELATED STUDY MODIFICATION AND FOLLOWUP GUIDELINES

Table 4 Liver Related Study Modification and Follow-Up Guidelines for Participants

Treatment-Emergent AST or ALT	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
Normal baseline: AST or ALT $>3\times$ ULN Elevated baseline: AST or ALT $>2\times$ baseline or ≥ 300 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome or hemolysis- no change in baseline TBL	None	Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies ¹ Follow-up for symptoms.
Normal baseline: AST or ALT $>5\times$ ULN Elevated baseline: AST or ALT $>3\times$ baseline or ≥ 300 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome or hemolysis- no change in baseline TBL	None	Discontinue IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies ¹ Refer to guidelines for close observation below. Follow-up for symptoms.
Normal baseline: AST or ALT $>3\times$ ULN Elevated baseline: AST or ALT $>2\times$ baseline or ≥ 300 U/L (whichever occurs first)	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 IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. ¹ IP can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred. Refer to guidelines for close observation below. Follow-up for symptoms.
Normal baseline: AST or ALT $>3\times$ ULN Elevated baseline: AST or ALT $>2\times$ baseline or ≥ 300 U/L (whichever occurs first)	TBL $>2\times$ ULN or increased INR to >1.5 In participants with Gilbert's syndrome or hemolysis-	None	Interrupt IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. ¹

	doubling of direct bilirubin if baseline >0.5 mg/dL		Initiate close observation and workup for competing etiologies. ¹ IP can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred.
--	---	--	--

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

Source: Regev A, Palmer M, Avigan MI, 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;49:702-13.

¹Acute and chronic viral hepatitis (hepatitis A - E), cholelithiasis, alcohol, other drugs both prescribed and over-the-counter herbs and supplements.

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, 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 ALT, AST, alkaline phosphatase, total bilirubin, and INR.

Evaluate participants two or three 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 site Investigator.

APPENDIX 2. LOCAL INJECTION SITE REACTIONS

Table 5 Local Injection Site Reactions (LISRS)

The following MedDRA Preferred Terms determined by the Sponsor's pharmacovigilance personnel represent the local injection site reaction:

Injection site discomfort	Injection site abscess
Injection site discoloration	Injection site abscess sterile
Injection site erythema	Injection site atrophy
Injection site irritation	Injection site calcification
Injection site inflammation	Injection site cellulitis
Injection site induration	Injection site dermatitis
Injection site pain	Injection site erosion
Injection site edema	Injection site fibrosis
Injection site pruritus	Injection site indentation
Injection site rash	Injection site necrosis
Injection site urticaria	Injection site nodule
Injection site reaction	Injection site ulcer
Injection site swelling	

LISRs will only include events that start on the day of injection and persist for at least 48 hours post injection (ie, event onset date on the day of injection and resolution date not on the day of injection or the day after the injection) will be included. Events with onset date on the day of injection and missing resolution date will also be included in the summary.

The following calculation will be utilized to determine the percentage of injections leading to local injection site reactions:

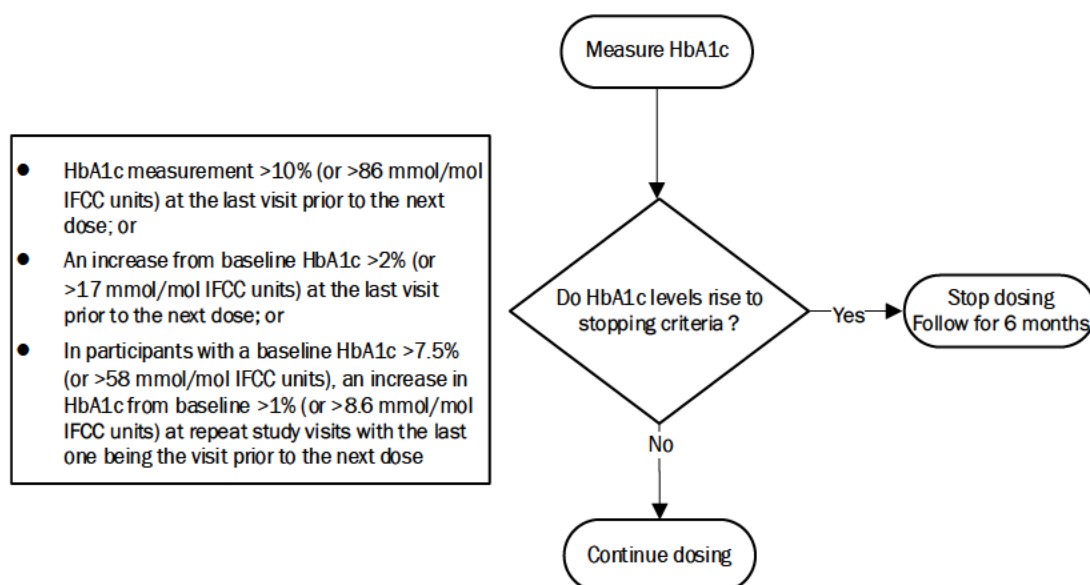
$(A/B)*$, where A = number of injections with a local injection site reactions, and B = total number of injections.

APPENDIX 3. Glycemic Control-Related Guidelines

HbA1c Investigational Product Discontinuation Criteria

Participants should discontinue IP 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 IP due to the above criteria will be followed for 6 months after their last dose per the Schedule of Assessments.

Signature Page for VV-CLIN-000114 v7.0

Approval	 2023 00:43:39 GMT+0000
----------	--

Approval	 2023 00:47:20 GMT+0000
----------	--

Approval	 2023 17:05:41 GMT+0000
----------	---

Signature Page for VV-CLIN-000114 v7.0