
# ARO-APOC3
# PROTOCOL AROAPOC3-2002
# PROTOCOL DATED 26-JAN-2023

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|---|---|
| **Amendment 3** | **Version Date: 26-Jan-2023** |
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| **Amendment 1** | **Version Date: 17-May-2022** |
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# A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2B STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ARO-APOC3 IN ADULTS WITH MIXED DYSLIPIDEMIA

**Product number:** ARO-APOC3

**Study Phase** 2b

**Indication:** Mixed Dyslipidemia

**IND Number:** 144947

**EudraCT Number:** 2021-000688-57

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# 1. SYNOPSIS

**Title of Study:** A Double-blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia

**Protocol Number: AROAPOC3-2002**

**Phase of Development:** 2b

**Study Sites:** Approximately 35 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 ribonucleic acid (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 evaluated against placebo in participants with elevated triglycerides (TG) ≥150 mg/dL or 1.69 mmol/L and ≤499 mg/dL or 5.64 mmol/L; and non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL (≥2.59 mmol/L) or low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL (1.8 mmol/L) at Screening. A total of approximately 320 participants will be enrolled in the study. All dose cohorts will enroll in parallel with approximately 80 participants per dose cohort, randomly assigned in a 3:1 ratio to receive ARO-APOC3 or placebo. In the 10, 25, and 50 mg cohorts, each participant will receive SC injection on Day 1 and Week 12 for a total of 2 injections. In 1 additional 50 mg cohort, each participant will receive SC injection on Day 1 and Week 24 for a total of 2 injections, as follows:

- ARO-APOC3 **10 mg** (n=60) or volume-matched placebo (n=20) at Day 1 and Week 12
- ARO-APOC3 **25 mg** (n=60) or volume-matched placebo (n=20) at Day 1 and Week 12
- ARO-APOC3 **50 mg** (n=60) or volume-matched placebo (n=20) at Day 1 and Week 12
- ARO-APOC3 **50 mg** (n=60) or volume-matched placebo (n=20) at Day 1 and Week 24

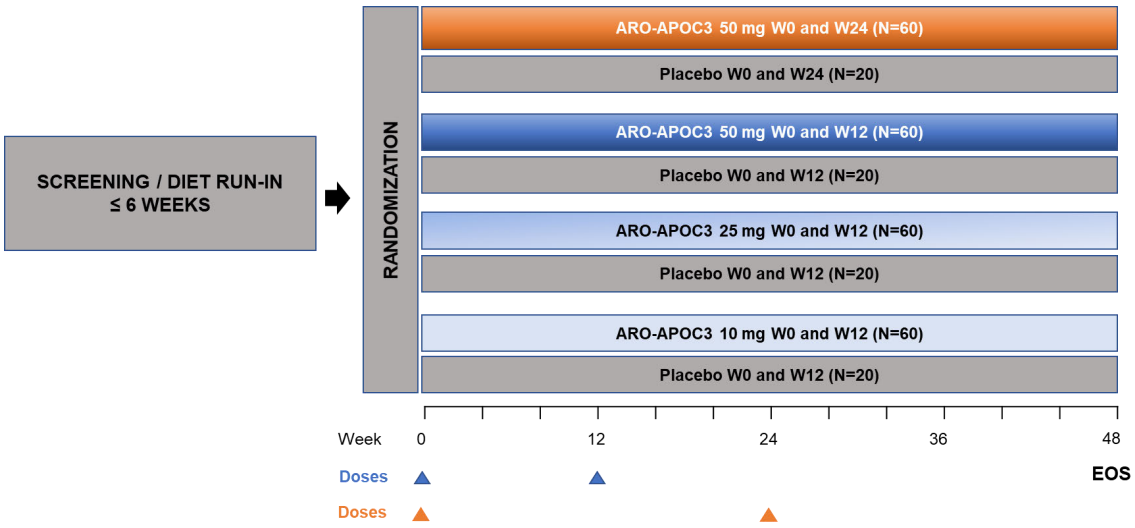
The duration of the study is approximately 54 weeks from Screening to the Week 48 End-of-Study examination.

**Study Objective:** The primary objective of the study is to evaluate the safety and efficacy of ARO-APOC3 in adults with mixed dyslipidemia (MD) and to select a dose and 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 and at least 2 weeks on a stable diet, at least 4 weeks on a stable optimal statin regimen (+ or – ezetimibe) and confirmation of stable background medications, the participant will be assessed for eligibility. All subjects are required to maintain a stable regimen of optimal statin therapy during screening and throughout the treatment period. 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 4 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 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; N=number of participants; W0=Week 0; W12=Week 12; W24=Week 24.

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 a pre-existing condition exacerbated by IP. The TEAE reporting period begins after the first dose and extends until the End-of-Study 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 being notified 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 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.
- A need for apheresis or other emergent interventions indicated to lower TG
- In participants with normal (per central laboratory reference range) aspartate aminotransaminase (AST) and alanine aminotransferase (ALT) on Day 1, treatment-emergent elevations >3× the 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× ULN
  - AST or ALT >3× ULN with a total bilirubin >2× ULN
  - AST or ALT >3× ULN with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
  - AST or ALT >3× 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.
- 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.

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) study 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.

The 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.

**Study Duration Planned:** The duration of the study is approximately 54 weeks from Screening to the Week 48 End-of-Study examination.

The Screening period will last up to approximately 6 weeks (Day -42 to Day -1). All eligibility criteria assessments and laboratory value reviews must be completed prior to Day 1. Study visits at which lipid values are assessed during the Screening period for eligibility and 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 mixed dyslipidemia (fasting LDL-C ≥70 mg/dL [1.8 mmol/L] OR fasting non-HDL-C ≥100 mg/dL [2.59 mmol/L], after at least 4 weeks of stable optimal statin therapy (unless statin intolerant), AND mean fasting TG ≥150 mg/dL [≥1.69 mmol/L] but ≤499 mg/dL [5.64 mmol/L] at Screening. A total of approximately 320 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 TG ≥150 mg/dL or 1.69 mmol/L and ≤499 mg/dL or 5.64 mmol/L;
3. A mean fasting TG level of ≥150 mg/dL (≥1.69 mmol/L) and ≤499 mg/dL (5.64 mmol/L) collected at two separate and consecutive visits and at least 7 days apart and no more than 17 days apart during the Screening period;
4. Fasting levels at Screening of non-HDL-C ≥100 mg/dL (2.59 mmol/L), OR LDL-C ≥70 mg/dL (1.8 mmol/L) after at least 2 weeks of stable diet and 4 weeks on stable optimal statin therapy (unless documented as statin intolerant as defined in Section 8.4);
5. Able and willing to provide written informed consent prior to the performance of any study-specific procedures;

6. Willing to follow diet counseling as per Investigator judgment based on local standard of care; and
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 agree to not donate sperm during the study and for at least 24 weeks following the last dose of IP. Females must agree to not donate eggs 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;
9. Participants taking 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:**

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

1. Current use or use within 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. Any planned bariatric surgery or similar procedures to induce weight loss during the period starting at consent through the end of the study;
4. History of major surgery within 12 weeks of Day 1 or planned major surgery during the study
5. Planned coronary intervention (such as stent placement or heart bypass) during the study;
6. History of acute coronary syndrome event within 24 weeks of Day 1
7. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%;
8. Uncontrolled hypertension (sitting blood pressure >160/100 mmHg at Screening); participant may be re-screened once hypertension is controlled;
9. History of hemorrhagic stroke within 24 weeks of Day 1;
10. History of bleeding diathesis or coagulopathy;
11. Current diagnosis of nephrotic syndrome;
12. 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 $m^2$ (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;
13. 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);
14. Blood donation of 50 to 499 mL within 4 weeks of Screening (Visit S2) or of >499 mL within 8 weeks of Screening (Visit S2) laboratory collection;
15. Known history of human immunodeficiency virus infection.
16. 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);
17. Clinical evidence of uncontrolled hypothyroidism or hyperthyroidism, as per Investigator's judgment;
18. 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;
19. 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;
20. 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);
21. 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 from baseline at each scheduled assessment 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-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;
- Subject incidence of TEAEs

**Exploratory Endpoints:**

The following are the exploratory endpoints defined in this study:

- Change from baseline over time through Week 48 in other fasting lipid parameters (total cholesterol, 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 8-hour fast]);
- Change from baseline to Week 24 and over time 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);
- Incidence of anti-drug antibodies to ARO-APOC3;
- Plasma PK of ARO-APOC3

**Data Analysis/Statistical Methods:**

**Sample Size 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 efficacy analysis, along with aggregate safety, and tolerability data summaries, tabulated by treatment group, will be evaluated upon completion of the study (Week 48).

With a total of 320 participants, where 80 will be randomly assigned to treatment in a 3:1 (60 active to 20 placebo) ratio within each dosing cohort, the study will have 99% power to detect at least 1 active dose cohort which is significantly different from placebo, and at least 91% power to detect all dose cohorts which are significantly different from placebo using a two-sided test, with family-wise

5% level of significance, adjusted for multiplicity. These estimates are based on the expected 30%, 45%, 60%, and 70% reduction from baseline in fasting TG in the 4 active dose groups and no change in fasting TG in the pooled placebo dose group. The standard deviation (SD) is assumed to be 50% for all treatment groups.

**Efficacy, Pharmacodynamics, and Safety Analysis:**

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 the pooled placebo group 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 adults with mixed dyslipidemia regardless of treatment compliance or other intercurrent events postbaseline (treatment policy strategy). 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. Safety evaluations will include tabulation of incidence of TEAEs in all participants who receive at least one dose of IP.

Following the completion of the study (Week 48), a final study report is planned.

**Pharmacokinetics:**

A population PK analysis of ARO-APOC3 plasma concentration data will be performed using nonlinear mixed effect methods and appropriate software. If there is sufficient diversity in demographics and other baseline characteristics in the study population, an attempt will be made to evaluate these baseline characteristics as potential covariates on ARO-APOC3 population PK.

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 a total of 64 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: All other participants at all sites will provide a predose PK sample and 1 additional sample postdose during their study visit, 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, SD, minimum, and maximum.

**Table 1: Schedule of Assessments**

| Assessment | Screening Period | | | Treatment Period | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -42 to Day -21 S-1[1] | Day -35 to Day -21 S-2[1] | Day -21 to Day -1 S-3 | Day 1 (Pre-dose)[2] | Day 2 | Wk 4[3] | Wk 8[3] | Wk 12[3] | 24 h post-dose | Wk 16[3] | Wk 20[3] | Wk 24[3] | 24 h post-dose | Wk 28[3] | Wk 36[3] | Wk 48 EOS or Early Term |
| Informed Consent | X | | | | | | | | | | | | | | | |
| Dietary counseling to maintain diet | X | 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 |
| ECG[5] | | 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 |
| Pregnancy test in females of childbearing potential (predose on dosing days) | X | | X | X | | X | X | X | | X | X | X | | X | X | X |
| FSH (females not of childbearing potential to confirm postmenopausal status) | X | | | | | | | | | | | | | | | |
| HBV/HCV Serology Screen | X | | | | | | | | | | | | | | | |

| Assessment | Screening Period | | | Treatment Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -42 to Day -21 S-1[1] | Day -35 to Day -21 S-2[1] | Day -21 to Day -1 S-3 | Day 1 (Pre-dose)[2] | Day 2 | Wk 4[3] | Wk 8[3] | Wk 12[3] | 24 h post-dose | Wk 16[3] | Wk 20[3] | Wk 24[3] | 24 h post-dose | Wk 28[3] | Wk 36[3] | Wk 48 EOS or Early Term |
| Clinical Laboratory Tests (predose on dosing days)[6] | X | | | X | | X | X | X | | X | X | X | | X | X | X |
| Serum Triglycerides[7,8] | | X[9] | X[9] | | | | | | | | | | | | | |
| LDL-C and non-HDL-C[7,8] | | X | | | | | | | | | | | | | | |
| Lipid Parameters (predose on dosing days)[7,8] | | | | X | | X | X | X | | X | X | X[10,11] | | X | X | X[10] |
| Optional Genotype (new sample or record from source documents, if available) | | | | X | | | | | | | | | | | | |
| Anti-drug antibodies (predose on dosing days) | | | | X | | X | | X[12] | | X | | X[12] | | X[13] | X[13] | X |
| IP Administration | | | | X | | | | X[14] | | | | X[13] | | | | |
| Postdose Follow-up | | | | | X | | | | X[14] | | | | X[13] | | | |
| Full PK[15] | | | | X | X | | | X[14] | X[14] | | | X[13] | X[13] | | | |
| Sparse Sample PK[16] | | | | X | | | | X[14] | | | | X[13] | | | | |
| Concomitant Medications/Therapies | X | X | X | X | | X | X | X | | X | X | X | | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X | X[14] | X | X | X | X[13] | X | X | X |

Abbreviations: ADA=antidrug antibodies; BP=blood pressure; COVID=coronavirus disease; ECG=electrocardiogram; EOS=End-of-Study; FSH= follicle-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HDL-C=high-density lipoprotein cholesterol; IP=investigational product; LDL-C=low-density lipoprotein cholesterol; non-HDL-C=non-high-density lipoprotein cholesterol; PK=pharmacokinetic; temp=temperature; TG=triglycerides; Wk=Week.

1. S1 assessments may be performed within the timeframe of the S2 visit as long as the participant is in a fasted stated 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.

2. Assessments completed on Day 1 and all other dosing days are to be done predose unless otherwise specified.
3. The time window for visits conducted at Weeks 4, 8, 12, 16, 20, 24, 28, 36, and 48 is ±5 days.
4. Height (cm) at Screening visit only; weight (kg) at all indicated visits.
5. The ECGs are to be completed predose, then 30 min (±10 min), and 2 hours (±30 min) postdose. ECG will be performed prior to any invasive procedures (eg, venipuncture).
6. Blood and urine samples will be collected only 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 the central laboratory for analysis. If the central laboratory collection kit 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).
7. 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).
8. Beginning predose Day 1, fasting TG, LDL-C and non-HDL-C will be included as part of lipid/pharmacodynamic parameter collection.
9. S2 and S3 visits must be separated by a minimum of 7 days and no more than 17 days.
10. Whole blood for pharmacodynamic analysis of lipid parameters should be drawn **on 2 separate occasions, separated by 2 to 7 days, after a 10-hour fast** for calculation of primary and secondary endpoints.
11. **The Week 24 dosing cohort must have one fasting lipid sample collected at least 2 days and no more than 7 days prior to the Week 24 Visit and a second fasting lipid sample collected (predose) at the Week 24 Visit.**
12. ADA sample will be drawn for all participants. For those who are being dosed at this visit, the ADA sample will be drawn before IP administration.
13. Only for participants in the W24 dosing regimen group.
14. Only for participants in the W12 dosing regimen group.
15. 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.
16. All other participants (Sparse PK participants) will have PK samples drawn predose and after at least 15 minutes postdose on dosing days.

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# 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 Mixed Dyslipidemia

**Protocol Number**: AROAPOC3-2002

**Version:** Amendment 2, Dated 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 DEFINITIONS OF TERMS

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

**Table 2: Abbreviations**

| Abbreviation | Definition |
|---|---|
| ACS | Acute coronary syndrome |
| AE | Adverse event |
| AHA/ACC | American Heart Association / American College of Cardiology |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| API | Active Pharmaceutical Ingredient |
| Apo(B) | 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 |
| ARO | Arrowhead Pharmaceuticals, Inc |
| ARO-APOC3 Injection | Clinical drug product solution ready for SC injection |
| ARO-APOC3 | Short name for ARO-APOC3 Injection |
| ASCVD | Atherosclerotic cardiovascular disease |
| AST | Aspartate aminotransferase |
| BMI | Body mass index |
| CECT | Contrast-enhanced computed tomography |
| cGMP | current Good Manufacturing Practice |
| CM | Chylomicronemia |
| COVID | Corona virus disease |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CS | Clinically significant |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DSC | Data Safety Committee |

| Abbreviation | Definition |
|---|---|
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated glomerular filtration rate |
| EOS | End-of-Study |
| FAS | Full Analysis Set |
| FCS | Familial Chylomicronemia Syndrome |
| FDA | Food and Drug Administration |
| FSH | Follicle-Stimulating Hormone |
| GCP | Good Clinical Practice |
| 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 |
| HMG-CoA | 3-hydroxy-3-methyl-glutaryl-coenzyme A |
| 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 |

| Abbreviation | Definition |
|---|---|
| LD | Lactate dehydrogenase |
| LDL-C | Low-density lipoprotein cholesterol |
| LISR | Local injection site reaction |
| LPL | Lipoprotein lipase |
| MCH | Mean cell hemoglobin |
| MCHC | Mean cell hemoglobin concentration |
| MCV | Mean cell volume |
| MD | Mixed dyslipidemia |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed model repeated measures |
| mRNA | Messenger ribonucleic acid |
| NAG | N-acetyl galactosamine |
| 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 |
| OLE | Open-label extension |
| OTC | Over-the-Counter |
| PCSK9 | Proprotein convertase subtilisin kexin type-9 |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PT | Preferred Term |
| QT | QT interval - a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle |
| RISC | RNA-induced silencing complex |
| RNA | Ribonucleic acid |
| RNAi | RNA interference |
| SAE | Serious adverse event |
| SC | Subcutaneous(ly) |
| SD | Standard deviation |

| Abbreviation | Definition |
|---|---|
| SHTG | Severe 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 |
| W0 | Week 0 |
| W12 | Week 12 |
| W24 | Week 24 |

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 study, 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 of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

# 5. BACKGROUND

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality worldwide and is associated with substantial morbidity and healthcare costs (Barquera 2015). Elevated concentrations of low-density lipoprotein cholesterol (LDL-C) is an established risk factor for ASCVD and a primary target for prevention of major adverse cardiovascular events. However, even in the setting of adequate LDL-C control with approved LDL-C reducing therapeutics, considerable residual cardiovascular disease risk remains (Hussain 2020) due to hypertriglyceridemia (HTG), ie, elevated triglycerides (TG) and TG-rich lipoprotein levels (TRLs) (Lawler 2017; Chapman 2011; Jorgensen 2013; Nordestgaard 2016).

## 5.1. Overview of Mixed Dyslipidemia

Dyslipidemia is a major risk factor for ASCVD (Kersten 2017). While current standard of care including a low-fat and low-cholesterol diet, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), ezetimibe, niacin, and proprotein convertase subtilisin kexin type-9 (PCSK9) inhibitors is effective at lowering LDL-C, a large unmet medical need for lipid-lowering and risk-modifying therapies with novel mechanisms of action persists. Despite statin use, and even when achieving LDL-C of less than 50 mg/dL, there remains a residual risk of developing ASCVD (Giugliano 2017). Such residual risk is derived from additional independent risk factors other than LDL-C, including elevated TG, lipoprotein(a) (Lp[a]), highly atherogenic remnant particles and lipoproteins such as apolipoprotein (Apo) C-III. Novel therapeutics designed to target the factors contributing to residual risk which could be used in combination with standard of care are needed.

In the United States (US), 21% (42.0 M) of adults have mixed dyslipidemia, defined as the presence of high LDL-C combined with at least one other lipid abnormality (ie, high LDL-C with either low high-density lipoprotein-cholesterol [HDL-C] and/or high TG). Nearly 6% (11.6 M) of US adults have all 3 lipid abnormalities (Toth 2012).

There are several studies that strongly suggest a causal relationship between excess TG and ASCVD. First, both ApoB100 and ApoB48, lipoproteins associated with very low-density lipoprotein cholesterol (VLDL) and chylomicrons, respectively, have been extracted from atherosclerotic plaque in preclinical models (Proctor 2003). Further, TRLs and their remnants have been shown to penetrate the arterial wall and are then directly taken up by macrophages without the need for oxidative modification (Tada 2018a; Chung 1989). Clinical data have also shown that TG are significantly associated with risk of ASCVD even in patients with familial hypercholesterolemia mainly caused by LDL receptor dysfunction (Tada 2018b). Evidence from a large prospective study of over 4,000 patients hospitalized for acute coronary syndrome (ACS) (PROVE-IT TIMI 22 study), indicate that the risk of death, myocardial infarction or recurrent ACS event at 2 years follow-up, was reduced by 2.3% for every 10% reduction from baseline in TG (after adjusting for high LDL-C and low HDL-C) that occurred during the first month of statin therapy (Miller 2008). These results are also supported by genetic studies in which there were robust associations between rare genetic variations associated with TGs and ASCVD risk in targeted and exome wide analyses (Khera 2017; Liu 2017). Genetic variants that lowered TGs were consistently associated with reduced ASCVD (Tada 2019).

Metabolic syndrome is recognized as a multiplex risk factor for both ASCVD and type 2 diabetes mellitus. Available evidence from meta-analyses suggests that metabolic syndrome is independently associated with ASCVD risk, essentially doubling the risk (Jacobson 2015).

Although LDL-C has traditionally been the primary target of therapy in previous lipid guidelines and in the practice of clinical lipidology, the National Lipid Association Expert Panel's consensus view is that non-high-density lipoprotein cholesterol (non-HDL-C) is a better primary target for modification than LDL-C. Non-HDL-C comprises the cholesterol carried by all potentially atherogenic particles, including low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), VLDL, and VLDL remnants, chylomicron particles and chylomicron remnants, and Lp (a). Epidemiologic studies have shown that non-HDL-C is a stronger predictor of ASCVD morbidity and mortality than LDL-C (Jacobson 2015).

A metanalysis demonstrated that among statin-treated patients, on-treatment levels of LDL-C, non-HDL-C, and ApoB were each associated with risk of future major cardiovascular events, but the strength of this association was greater for non-HDL-C than for LDL-C and ApoB (Boekholdt 2012).

A more recent meta-regression analysis examined the association between the magnitude of non-HDL-C, LDL-C, and TG lowering and the reduction in major vascular events across studies of fibrates, niacin, and marine omega-3 fatty acids, as well as statins as an established reference. In randomized controlled studies, TG lowering was associated with a lower risk of major vascular events, but to a lesser extent per absolute amount of reduction than with LDL. Additionally, reduction in non-HDL-C, a measure of atherogenic LDL and VLDL particles, was strongly associated with a lower risk of major vascular events regardless of the lipid-lowering drug class (Marston 2019).

Statins remain the first-line pharmacologic treatment for reducing ASCVD risk in patients with hyperlipidemia. Despite statin therapy, many patients have persistently high TG and TRLs. While diet and lifestyle changes can lower TGs, compliance with dietary restrictions is difficult to maintain long-term. Available therapies to treat HTG include fibric acid derivatives, niacin, prescription omega-3-acid ethyl esters, and ethyl eicosapentaenoic acid. Triglycerides reductions achieved with these medications are often variable, ranging from 20% to 40%, and are sometimes accompanied by increasing LDL-C. Consequently, additional treatment options are needed for patients at risk of ASCVD.

Apolipoprotein C3 (ApoC3, ApoC-III), a component of triglyceride-rich lipoproteins (TRLs), has been identified as a key regulator of serum TG levels (Gaudet 2014; Khetarpal 2015; Saleheen 2017; Jorgensen 2014). Predominantly produced in hepatocytes, ApoC3 inhibits hydrolysis of TG through inhibition of lipoprotein lipase (LPL) (LPL-dependent pathway) and delays clearance of lipoprotein remnants by hepatocyte receptor-mediated uptake (LPL-independent pathway), resulting in HTG (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 VLDL hydrolysis in vivo and may delay the catabolism of TRL remnants by the liver and other tissues (Aalto-Setala 1992; Aalto-Setala 1996; Gerritsen 2005; Jong 2001; Khetarpal 2015). Apolipoprotein C3 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 with noncarriers (Saleheen 2017; Lek 2016). Individuals with *APOC3* deficiency do not demonstrate significant hepatic steatosis and appear phenotypically normal other than lower TGs and higher 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.

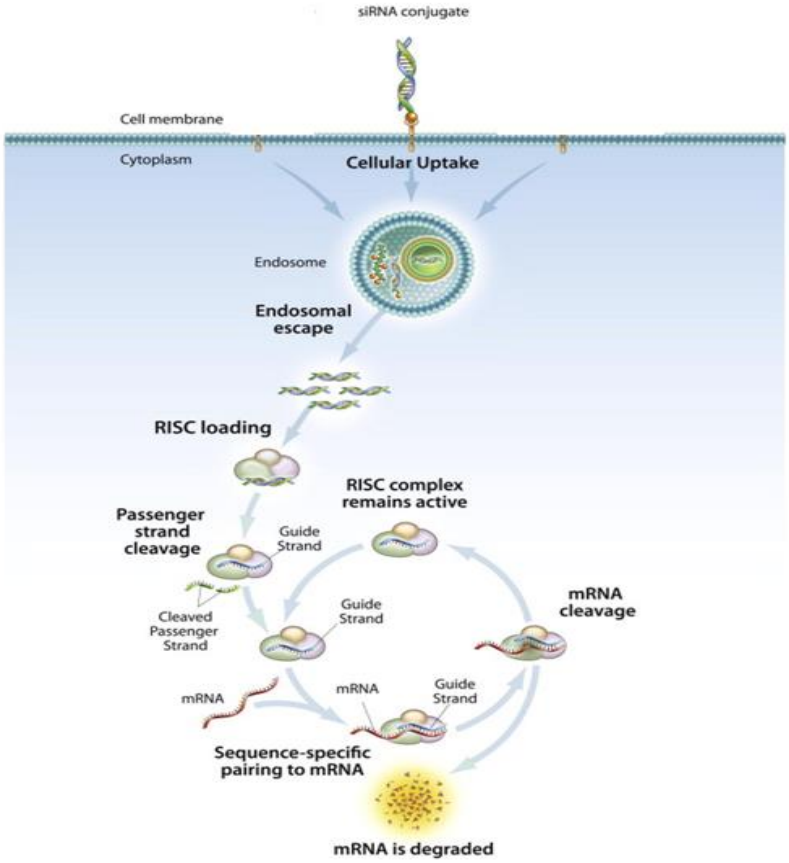
### 5.2.1. Mechanism of Action of ARO-APOC3 and Therapeutic Rationale

#### 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 (NAG) targeting moiety, acting as a ligand for the highly expressed, hepatocyte-specific asialoglycoprotein receptor. Available nonclinical and clinical pharmacokinetics (PK) data show rapid absorption and clearance of all NAG conjugated triggers from the blood stream within 24 to 48 hours post-subcutaneous (SC) administration.

ARO-APOC3 is a synthetic, double-stranded, hepatocyte-targeted RNAi trigger designed to specifically silence mRNA transcripts from the *APOC3* gene using an RNA interference (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 messenger RNA 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 enhance 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 HTG. Findings of potential clinical significance and relevance to this protocol are summarized below. Additional details regarding preclinical pharmacology, pharmacokinetics, 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 LDL-C).

- Similar reductions in serum ApoC3 were also observed after ADS-005 doses in a dyslipidemic rhesus monkey model induced by diet. ADS-005 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 NAG-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 mixed dyslipidemia (MD).

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. Final results from Study AROAPOC31001 showed that in healthy volunteers, treatment with ARO-APOC3 reduces hepatic production of ApoC3 via RNAi, leading to reductions in serum TG and non-HDL-C, and increases in HDL-C. All doses of 10, 25, 50, and 100 mg demonstrated durable PD activity lasting beyond 12 weeks after the last dose. Similarly, data from participants with HTG or chylomicronemia (CM) also demonstrated substantial reductions in serum ApoC3, TG, and non-HDL-C levels and increases in HDL-C with repeat doses (Day 1 and Day 29) of ARO-APOC3. Additional information regarding results of Study AROAPOC31001 can be found in the IB. Aside from mild and transient injection-site reactions (ISRs), and transient and self-limited alanine aminotransferase (ALT) elevations, single and repeat doses of ARO-APOC3 were well tolerated in healthy volunteers and patients with HTG or CM, and the safety profile based on this Phase 1 data warrants additional later-stage clinical evaluation.

Results from the Phase 1 study informed the design of Phase 2 studies AROAPOC3-2001 in participants with severe hypertriglyceridemia (SHTG) and AROAPOC3-2002 in participants with mixed dyslipidemia.

## 5.3. Risk Assessments of 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 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 (refer to the 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 aminotransaminase (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 (eg, pain, erythema). Generally mild injection site AEs have been reported in the AROAPOC31001 study. In this study, steps will be taken to minimize injection site reactions such as rotating injection sites and allowing the ARO-APOC3 solution to come to room temperature prior to injection.
- **Glycemic Control:** An administrative analysis in 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

Results from the Phase 1, First-in-Human study AROAPOC31001 showed that in healthy volunteers, treatment with ARO-APOC3 reduces hepatic production of ApoC3 via RNAi, leading to reductions in serum TG and non-HDL-C, and increases in HDL-C. Doses of 10, 25, and 50 mg demonstrated durable PD activity lasting beyond 12 weeks following the last dose. Data for patients with HTG or CM also demonstrated substantial reductions in serum ApoC3, TG, and non-HDL-C levels and increases in HDL-C with repeat doses (Day 1 and Day 29) of ARO-APOC3. Aside from mild and transient injection-site reactions and transient, self-limited ALT elevations, single and repeat doses of ARO-APOC3 were well tolerated in healthy volunteers and patients with HTG or CM, and the safety profile based on this Phase 1 data warrants additional later stage clinical evaluation.

Based on these results, the current study will be conducted in adults with MD, defined as patients whose fasting TG level is ≥150 mg/dL or 1.69 mmol/L and ≤499 mg/dL or 5.64 mmol/L and fasting non-HDL-C ≥100 mg/dL (≥2.59 mmol/L) or fasting LDL-C ≥70 mg/dL (1.8 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) versus volume-matched placebo with each participant receiving SC injections on Day 1 and Week 12 for a total of 2 injections. In one additional cohort, each participant will receive SC injection of ARO-APOC3 (50 mg) or volume-matched placebo on Day 1 and Week 24 for a total of 2 injections. In addition, this study will evaluate whether doses of 10, 25, or 50 mg of ARO-APOC3 improves other lipid parameters (eg, LDL-C, non-HDL-C). Plasma concentrations of ARO-APOC3 will also be measured over time to evaluate the PK profile. Administration of doses on Day 1, Week 12, and Week 24 (Week 24 dose only in one of the 50 mg dosing groups - see study schema) 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, 50, or 100 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 was seen with HDL-C, with dose-dependent HDL-C increases demonstrated with increasing doses. While limited data were available for patients with HTG, ARO-APOC3 50 mg administered on Days 1 and 29 maintained 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 demonstrated PD activity lasting at least 12 weeks after the last dose. 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, or doses of 50 mg administered on Day 1 and Week 24, with follow up through Week 48. Although the primary endpoint is at Week 24, analyses for dose selection will include assessments up to and including Week 48 to account for participants in the Week 24 dosing cohort who will receive 2 doses of ARO-APOC3. This design will inform on optimal dose and

duration based on time for TG, ApoC3 levels, and other lipid parameters, including non-HDL-C, 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 on Day 1 and Week 12 or Week 24, 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. Final 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) demonstrated 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 -69%) 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 ARO-APOC3 in NHVs demonstrated consistent reductions of ApoC3 (up to -94%), TGs (up to -74%), and non-HDL-C (up to -39%), 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 equivalent doses studied in NHVs. Reductions of serum ApoC3 (up to -98%), TGs (up to -90%), non-HDL-C (up to -55%), and increases in HDL-C levels (up to +128%) 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 a favorable safety profile. 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 ISRs, which were all mild in intensity. The injection site AEs are

anticipated based on similar findings reported in other clinical studies of SC-administered siRNA therapeutics. While abnormalities in liver function tests were noted during this study, these alterations were transient, self-limited, and returned to baseline level by the end of the study without any intervention (such as cessation of study drug or changes to study participation). 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 analysis also revealed an apparent increase in the level of HbA1c 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 improve the metabolic lipids and lipoprotein profile with the goal of reduce cardiovascular atherosclerotic 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), 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 mixed dyslipidemia (MD) and to select a dose and dosing regimen for later stage clinical studies in this patient population.

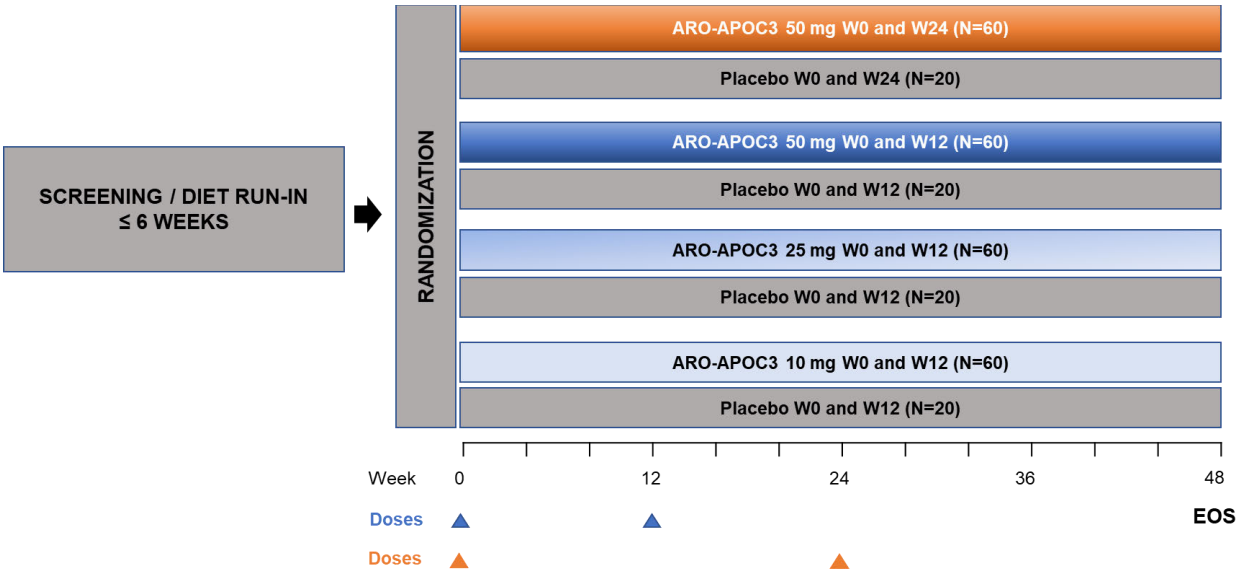
# 7. STUDY PLAN

## 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 (+ or – ezetimibe), as well as diabetes mellitus therapies and other background medications, as applicable (see Section 8.1, Section 8.4, and Section 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. In one additional 50 mg cohort, each participant will receive SC injection on Day 1 and Week 24 for a total of 2 injections.

**Figure 2: Study Schema**




Abbreviations: EOS=end of study; N=number of participants; W0=Week 0; W12=Week 12; W24=Week 24.

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 and SAEs are defined as those that occur following investigational product (IP) administration or a preexisting condition exacerbated following IP administration. 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 being notified 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 patient 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

abnormalities will be reported as AEs if considered CS by the Investigator. Laboratory abnormalities not reported as AEs are not to be reported as CS in the study database.

### 7.1.1. Number of Study Sites

Approximately 35 centers globally.

### 7.1.2. Number of Participants

Approximately 320 participants.

### 7.1.3. Estimated Study Duration

The duration of the study is approximately 54 weeks from Screening to the Week 48 End-of-Study (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. Study visits at which lipid values are assessed during the Screening period for eligibility and 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

Participants confirmed to be on a stable diet and on stable background medications, as applicable (see Section 8.1, Section 8.4, and Section 10.2), will complete all remaining eligibility assessments prior to 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 PI (refer to Section 8.1). 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 Section 8.1 and Section 8.4 [Table 3]) prior to the Screening laboratory assessments and will agree to stay on this baseline regimen during the Treatment Period.

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 elevated fasting TGs ≥150 mg/dL or 1.69 mmol/L and ≤499 mg/dL or 5.64 mmol/L and fasting non-HDL-C ≥100 mg/dL (≥2.59 mmol/L) or fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at Screening. The lower limit of 150 mg/dL was selected considering the variability in fasting TG levels and in line with National Cholesterol Education Program (NCEP) Adult Treatment Panel III definition of HTG (NCEP 2002). A maximum TG level of 499 mg/dL was selected to minimize the occurrence of acute pancreatitis associated with severely elevated TGs.

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 TG ≥150 mg/dL or 1.69 mmol/L and ≤499 mg/dL or 5.64 mmol/L;
3. A mean fasting TG level of ≥150 mg/dL (≥1.69 mmol/L) and ≤499 mg/dL (5.64 mmol/L) collected at two separate and consecutive visits and at least 7 days apart and no more than 17 days apart during the Screening period;
4. Fasting levels at Screening of non-HDL-C ≥100 mg/dL (2.59 mmol/L), OR LDL-C ≥70 mg/dL (1.8 mmol/L) after at least 2 weeks of stable diet and 4 weeks on stable optimal statin therapy (unless documented as statin intolerant per Section 8.4);
5. Able and willing to provide written informed consent prior to the performance of any study specific procedures;
6. Willing to follow diet counseling as per the Investigator judgment based on local standard of care; and
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. Females must agree to not donate eggs 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;
9. Participants taking any of the following medications (Table 3) 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.

**Table 3: Restricted Concomitant Medications**

| 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 (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 last 365 days of any hepatocyte targeted siRNA or antisense oligonucleotide molecule;
2. Active pancreatitis within 12 weeks prior to Day 1
3. Any planned bariatric surgery or similar procedures to induce weight loss during the period starting at consent through the end of the study;

4. History of major surgery within 12 weeks of Day 1 or planned major surgery during the study;
5. Planned coronary intervention (such as stent placement or heart bypass) during the study;
6. History of acute coronary syndrome event within 24 weeks of Day 1;
7. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%;
8. Uncontrolled hypertension (sitting blood pressure >160/100 mmHg at Screening); participant may be re-screened once hypertension is controlled;
9. History of hemorrhagic stroke within 24 weeks of Day 1;
10. History of bleeding diathesis or coagulopathy;
11. Current diagnosis of nephrotic syndrome;
12. 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 $m^2$ (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;
13. 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);
14. Blood donation of 50 to 499 mL within 4 weeks of Screening (Visit S2) or of >499 mL within 8 weeks of Screening (Visit S2) laboratory collection;
15. Known history of human immunodeficiency virus infection;
16. 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);
17. Clinical evidence of uncontrolled hypothyroidism or hyperthyroidism, as per Investigator's judgment;
18. 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;
19. 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;

20. 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);
21. 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 Sponsor's 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 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

A decision to 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.
- A need for apheresis or other emergent interventions indicated to lower TG.
- In participants with normal (per central laboratory reference range) AST and ALT on Day 1, treatment-emergent elevations >3× ULN at least possibly related to 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× ULN
  - AST or ALT >3× ULN with a total bilirubin >2× ULN
  - AST or ALT >3× ULN with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
  - AST or ALT >3× ULN with a treatment-emergent INR >1.5 (must be confirmed on repeat) and which is not explained by another plausible cause.
- 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.

Treatment modification guidelines for participants with elevated AST or ALT are provided in Appendix 1.

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

### 8.3.2. Study Drug Discontinuation Criteria for Increased HbA1c

Regarding HbA1c study 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 SOA.

## 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 study treatment administration or blood draw unless otherwise specified.
2. ***Recreational Drugs and 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***: A stable optimal statin regimen for at least 4 weeks prior to Screening (S2 visit) laboratory assessments and throughout the study is required of all participants. In cases where a participant is taking lower than the recommended statin dose (as defined by local standard of care) the reason will be clearly documented in the eCRF by the Investigator. Participants not receiving a statin must have documented evidence of statin intolerance to at least two different statins, one at the lowest starting daily dose and another at any daily dose.

   Participants taking any of the concomitant medications specified in Table 3 must be on a stable regimen for the minimum duration specified below prior to collection of Screening (Visit S2) laboratory blood tests and for the duration of the study through Week 48/EOS visit in accordance with the SOA (Table 1). In cases where any concomitant medication

specified in Table 3 is initiated after Day 1, continued participation in the study must be approved by the Sponsor's Medical Monitor. Adjustments to background medication specified in Table 3 during the study, are only allowed if, at the discretion of the Investigator, this is needed to provide adequate supportive care. In response to diabetes evaluations, adjustments to treatment medication are allowed at the discretion of the PI (refer to see Section 8.1 and Section 8.4). 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.

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.

## 8.5. Lipid Monitoring

Beginning with 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 >25% at two consecutive timepoints, LDL-C values for this participant 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 participants who are already on treatment).

Beginning with 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) at two consecutive timepoints, LDL-C values for this participant 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 has TG >2000 mg/dL (>22.6 mmol/L) at any postbaseline 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.

### 8.5.1. Informed Consent

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

It is the responsibility of the Principal Investigator (PI) (or medically qualified designee) to obtain a written informed consent from everyone participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The PI (or medically qualified designee) must also explain to the 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 PI or by Arrowhead Pharmaceuticals, Inc.

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

All eligible participants will have the study explained by the PI or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomforts, risks and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. 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 volunteer will be given a copy of the signed Informed Consent Form to retain.

# 9. INVESTIGATIONAL PRODUCT

## 9.1. Description, Identification, and Dosage

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

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 25-30 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 is acceptable). Injection site location is to be recorded in the eCRF. Prior to dose administration, the ARO-APOC3 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 (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 ºC to 8 ºC |

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. Individual doses will be dispensed by clinical study site staff members on the morning 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. Within each of the 4 dose cohorts (10, 25, or 2 cohorts at 50 mg), participants will be randomly assigned in a 3:1 ratio to either active (ARO-APOC3) treatment 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 4: Injection Number and Volume Per Dose Cohort**

| ARO-APOC3 Dose[a] | Concentration | Total Injection Volume | No. of Injections per Planned Dose | Total No. of Study Injections |
|---|---|---|---|---|
| 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 |

[a] 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 nonblinded Clinical Research Associate (CRA) will perform initial and ongoing IP kit and placebo accountability. The nonblinded CRA will protect the integrity of the assignment blind and will not participate in data review for study participants. Used vials of ARO-APOC3/placebo will be retained sequestered

per participant (where allowable by local policy) and made available to the nonblinded CRA during 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 release will be maintained to support administration of IP. The authorized pharmacist or qualified staff will be unblinded to treatment group (ie, active or placebo). The pharmacy will dispense the study medication and the study center will administer the IP only to participants included in this study following the procedures set out in the study protocol. 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 nonblinded 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 (Table 4). 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 and start the Screening period. Initial eligibility assessments will begin at the first Screening visit (S1) up to 42 days prior to Day 1. At the investigator's discretion and if the participant meets the requirements for a stable diet and stable background therapy regimen and is in a fasted state, the S1 visit assessments may occur within the timeframe of the S2 visit (Day -35 to Day -21). The third Screening visit (S3) must occur at least 7 days but no more than 17 days after the second Screening (S2) visit.

Participants who successfully pass the requirements during the Screening period will be enrolled into the study. All dose cohorts will enroll in parallel with participants randomized 3:1 to receive ARO-APOC3 or placebo. In the 10, 25, and 50 mg cohorts, each participant will receive SC injection on Day 1 and Week 12 for a total of 2 injections. In one additional 50 mg cohort, each participant will receive SC injection on Day 1 and Week 24 for a total of 2 injections, as follows:

- ARO-APOC3 **10 mg** (n=60) or volume-matched placebo (n=20) at Day 1 and Week 12;
- ARO-APOC3 **25 mg** (n=60) or volume-matched placebo (n=20) at Day 1 and Week 12;
- ARO-APOC3 **50 mg** (n=60) or volume-matched placebo (n=20) at Day 1 and Week 12; and
- ARO-APOC3 **50 mg** (n=60 or volume-matched placebo (n=20) at Day 1 and Week 24.
- All participant Screening visits and dosing visits (Day 1 and Week 12/Week 24) 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 pandemic restrictions or other logistical disruptions occur in order to avoid missed visits. Utilization of home health services is contingent upon compliance with local laws and regulations; 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.

Some participants enrolling into this study may have baseline elevations in transaminases. See Appendix 1 for treatment modification guidelines in participants with baseline/predose elevated ALT.

All participants will have a pre-and postdose PK sample collected at Day 1 and Week 12, and also Week 24 for the cohort dosed on Week 24. In a subset of participants undergoing full PK (12 active, 4 placebo in each dose cohort), plasma concentrations for PK will be measured predose and serially postdose on Day 1 and Week 12, and also Week 24 for the cohort dosed on Week 24, as per the SOA (Table 1). Pharmacokinetic time points are at predose, 0.25, 1, 3, 6, and 24 hours postdose. Recommended time window for PK sample through the 6-hour timepoint: ±5 minutes. Recommended time window for PK sample at the 24-hour time point: ±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 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, AEs 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 8 hours predose.

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

## 10.2. Screening Diet Stabilization

Confirmation of ≥2 weeks diet stabilization will precede lipid parameter laboratory assessments collected at Screening visit (S2 and S3). 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 ICH GCP. 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 and Other Lipid Parameters

Fasting serum TG, LDL-C, and non-HDL-C, will be collected at the Screening visit S2 after a 10-hour fast in order to evaluate lipid parameters. In order to determine the average (arithmetic mean) TG level during Screening, a second fasting serum TG will be collected at the S3 visit, at least 7 days but no more than 17 days after the S2 Screening visit, refer to the SOA (Table 1). Fasting serum TG will be measured as per the SOA (Table 1) and assessed by a central laboratory standard method. LDL-C will be measured as per the SOA and assessed by a central laboratory using an ultracentrifugation methodology preferentially as well as Martin-Hopkins methodology (which data will be used as backup). During Screening, either ultracentrifugation methodology or Martin-Hopkins methodology may be used to determine eligibility. In the event of logistical disruptions (eg, corona virus disease [COVID]-related) where a participant does not have direct access to the site, laboratory samples may be collected at alternative location (eg, home health, local laboratory) using the central laboratory kit and shipped to central laboratory for analysis.

Fasting TG and other lipid metabolism 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, ANGPTL3) will be collected on Day 1 prior to dosing after a 10-hour fast.

#### 10.4.1.2. Glucose Metabolism

Beginning on Day 1 and for the remainder of the treatment period, glucose metabolism analytes will be collected after at least 10 hours of fasting and predose on dosing days. 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.

#### 10.4.1.3. Blood Sampling for Pharmacodynamic Analysis

Blood samples will be collected from participants through an indwelling cannula or through venipuncture. The actual blood collection time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections, for the actual time of sample collection will be incorporated at the time of data analysis. Blood samples will be collected at time points outlined in the SOA (Table 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 a fresh vein puncture. 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. 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 injection site reactions.

The safety of ARO-APOC3 will also be evaluated by the collection of the following measurements performed at time points specified in the SOA 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 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 exam 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 (mmHg), temperature (°C), heart rate (beats/min), respiratory rate (breaths/min) will be obtained at time points outlined in the SOA (Table 1) after the participant is sitting for at least 3 minutes. Vitals 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 semi-supine 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 samples will be collected at the site and shipped to the central laboratory for analysis. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, 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 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 lab 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. Clinical laboratory tests will be performed on participants' blood and urine at specified time-points listed in the SOA (Table 1). 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 glutamyltransferase (GGT), alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LD), TG, C-reactive protein, thyroid stimulating hormone, and free T4.

***Hematology***: (differential of percent and absolute) hemoglobin, red blood cell count (RBC), 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***: leucocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketone, 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. If necessary, participants will be counseled by the Investigator, or medically trained designee, concerning the blood tests for HBsAg, hepatitis C 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 participant'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

Follow-up 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
- AEs occurring over the 24 hours following doses at Week 24 (for the Week 24 dosing group only)

## 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 PK[a] up to 6-hour sampling time point | ± 5 minutes |
| Plasma PK[a] 24-hour sampling time point | ± 60 minutes |
| Day 1 | Not Applicable |
| Postbaseline visits | ± 5 days |

[a] Only for Full PK assessments.

## 10.6. Pregnancy Testing and Contraception Requirements

Female participants of childbearing potential will have urine pregnancy tests at the Screening and Day 1 (baseline) visits, prior to dosing throughout the study, and at the completion of 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 participant'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 their second scheduled dose 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 highly effective methods of contraception during the study and for 24 weeks following the last dose of IP.

- Using twice the normal protection of birth control by using a condom AND 1 other form of either birth control pill (The Pill), depot or injectable birth control, intrauterine device, birth control patch (eg, Ortho Evra), vaginal contraceptive ring, (eg, NuvaRing®), contraceptive implant (eg, Nexplanon).
- 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 informed consent through to end of study; 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 up to 1 year after birth or until the end of the pregnancy.

## 11.1. Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or diagnostic test), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether related to this product or not. (refer to 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 preexisting 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 preexisting 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.

An 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 (does not include hospitalization for elective procedures for pre-existing conditions that did not worsen from baseline);
- 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, physical exam 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 preexisting 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 or reported by the participant, it is the responsibility of the Investigator or medically qualified designee to assess the AE and review all available 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 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 participant'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) Preferred Term (PT) is 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); or

- 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 AEs

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 SAEs

Any AEs meeting serious criteria MUST be reported immediately to the designated Pharmacovigilance Contract Research Organization (CRO), and the IRB/EC, as required in accordance with local/institutional requirements.

### 11.6.1. Completion and Transmission of the SAE 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 upon being notified of the event. 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, 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*** |
|---|
| **IQVIA Biotech Medical Monitoring**<br>[redacted]<br><br>**Sponsor Medical Monitor Contact**<br>[redacted]<br>[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 AEs unless accompanied by an adverse medical condition in mother or infant. However, pregnancy data will be collected at the initial notification, birth/termination of pregnancy, and for up to 1 year after the birth.

Any SAE that occurs during pregnancy (eg, 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 regulatory requirements related to the reporting of SAEs to the IRB/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/EC in accordance with the Sponsor's procedures and local regulatory requirements.

## 11.8. Poststudy AEs

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. SAEs Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly (Section 11.6.1).

# 12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

**General Considerations**

Statistical analyses and descriptive summaries will be presented for primary, secondary and exploratory endpoints using appropriate methods. A detailed Statistical Analysis Plan (SAP) will be prepared and finalized prior to submission of the initial protocol to regulatory authorities and prior to study initiation. Any proposed amendments to the SAP will only occur prior to database lock. Descriptive statistics will be presented for all analyses unless otherwise specified. For continuous variables, data will be presented as number (n), mean, median, standard deviation (SD), minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percent. Data will be summarized by treatment group: ARO-APOC3 10 mg, 25 mg, 50 mg (Day 1 and Week 12) and 50 mg (Day 1 and Week 24), and pooled placebo.

## 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 from baseline at each scheduled assessment 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;
- Subject incidence of TEAEs

### 12.1.3. Exploratory Endpoints

The following exploratory endpoints are defined in this study:

- Change from baseline over time through Week 48 in other fasting lipid parameters (total cholesterol, LDL/HDL ratio, VLDL-C, ApoB-48, LP(a), ApoB-100, ApoC-II, ApoA-I and ApoA-V [all values drawn after at least 8-hour fast]).
- Change from baseline to Week 24 and over time 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);
- Incidence of anti-drug antibodies to ARO-APOC3;
- Plasma PK of ARO-APOC3

## 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

With a total of 320 participants randomly assigned to treatment in a 3:1 (60 active to 20 placebo) ratio within each dose cohort, the study will have 99% power to detect at least 1 active treatment group which is significantly different from placebo, and at least 91% power to detect all treatment groups which are significantly different from placebo using a two-sided test, with family-wise 5% level of significance, adjusted for multiplicity. These estimates are based on the

expected 30%, 45%, 60%, and 70% reduction from baseline in fasting TG in the 4 active treatment dose arms and no change in fasting TG in the pooled placebo group. The SD is assumed to be 50% in all treatment groups (Ballantyne 2012).

## 12.4. Interim Analysis

An interim analysis is planned for this study after all participants 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 mg, 25 mg, 50 mg (Day 1 and Week 12) or 50 mg (Day 1 and Week 24) 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

None.

## 12.6. Analysis Methods

### 12.6.1. Demographic and Baseline Characteristics

Demographics, medical/surgical history data, and physical examination data (including height and weight), will be summarized by treatment group.

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.

Listings of each participant may be provided.

### 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 mixed dyslipidemia. 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 adults with mixed dyslipidemia, regardless of treatment compliance or other intercurrent events postbaseline (treatment policy strategy).

For endpoint analysis based on Week 24 data, the laboratory value will be the arithmetic mean of 2 fasting TG values, separated by at least 2 days and no more than 7 days. If only 1 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 the Day 1 predose assessment and 2 fasting TG values collected during the Screening period.

The primary analysis will be performed using a linear mixed model repeated measures (MMRM) approach with treatment, study visit, baseline TG level, and interaction of treatment by visit

included as model terms. The primary estimate of interest will be the difference in means between each active treatment group and pooled placebo group, evaluated at Week 24. To preserve the family-wise error rate at 0.05, Holm's step-down multiplicity adjustment procedure will be used. The corresponding 95% confidence interval will be reported as well as the *P* value from each ARO-APOC3 dose regimen vs pooled placebo group, evaluated for family-wise significance at the 5% level. 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. Safety evaluations will include tabulation of incidence of TEAEs in all participants who receive at least one dose of IP.

For the analysis of exploratory endpoints, descriptive summaries will be provided, as applicable, and any inferential statistics (ie, *P* values) will only be considered exploratory. For lipid-related lipoprotein and serum PD assessments, baseline is defined as the predose value on Day 1.

Following the completion of the study (Week 48), a final study report is planned.

### 12.6.3. Pharmacokinetics Analysis

A population PK analysis of ARO-APOC3 plasma concentration data will be performed using nonlinear mixed effect methods and appropriate software (eg, Phoenix NLME or NONMEM). If there is sufficient diversity in demographics and other baseline characteristics in the study population, an attempt will be made to evaluate these baseline characteristics (eg, age, weight, sex, race, renal and hepatic function) as potential covariates on ARO-APOC3 population PK. The PK data collected in this study may be combined with those from Study ARO-APOC31001 in an attempt to develop an integrated population PK model.

### 12.6.4. Safety Analysis

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

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

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

# 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/Ethics Committee 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 wash-out 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 participant'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 laboratory 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 study 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.

## 13.10. 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.

# 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 Sponsor 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 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]

## 15.2. Confidentiality

[redacted]

## 15.3. Data Protection

The Sponsor complies with data minimization principles and will collect and process the minimum amount of personal data necessary for purposes of the study. The Sponsor has implemented information security policies and procedures designed to prevent unauthorized persons from gaining access to personal data collected and processed in the context of the study ("Clinical Data") and to ensure that persons authorized to access Clinical Data gain access only in accordance with their access rights. The Sponsor also maintains policies and procedures for detecting, monitoring, and responding to data security incidents and, as appropriate, for reporting data security incidents to regulators and/or individuals. The Sponsor carries out periodic risk assessments/reviews and, as appropriate, updates its information security policies and procedures.

Clinical Data received by the Sponsor is pseudonymized/key-coded, and the key is retained by the study site. Where third party processors are engaged to process Clinical Data, due diligence is carried out to ensure such third parties are capable of maintaining appropriate security measures to protect Clinical Data. For transfers of Clinical Data to countries outside of the European Economic Area and United Kingdom, consistent with the requirements of the General Data Protection Regulation ("GDPR"), the Sponsor will ensure that appropriate safeguards are in

place such as “standard contractual clauses” or such transfers will be made in reliance on an Article 49 GDPR derogation.

## 15.4. Publication

[redacted]

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# APPENDIX 1. LIVER-RELATED STUDY MONITORING AND STOPPING GUIDELINES FOR PARTICIPANTS

**Table 5: Liver-Related Study Monitoring and Stopping Guidelines for Participants**

| Treatment-Emergent ALT | Treatment-Emergent Total Bilirubin (TBL) | Liver Symptoms | Action |
|---|---|---|---|
| Normal baseline: AST or ALT >3× ULN<br>Elevated baseline: AST or ALT >2× baseline or ≥300 U/L<br>(whichever occurs first) | Normal<br>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. [a] Follow-up for symptoms. |
| Normal baseline: AST or ALT >5× ULN<br>Elevated baseline: AST or ALT >3× baseline or ≥300 U/L<br>(whichever occurs first) | Normal<br>Participants with Gilbert's syndrome or hemolysis – no change in baseline TBL | None | Discontinue IP.<br>Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [a] Refer to guidelines for close observation below. Follow-up for symptoms. |
| Normal baseline: AST or ALT >3× ULN<br>Elevated baseline: AST or ALT >2× baseline or ≥300 U/L<br>(whichever occurs first) | Normal<br>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 reaction (eg rash, >5% eosinophilia) | Interrupt IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [a]<br>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× ULN<br>Elevated baseline: AST or ALT>2× baseline or ≥300 U/L<br>(whichever occurs first) | TBL >2×ULN or increased INR to >1.5<br>Participants with Gilbert's syndrome or hemolysis– doubling of direct bilirubin if baseline >0.5 mg/dL | None | Interrupt IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [a]<br>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 |

| Treatment-Emergent ALT | Treatment-Emergent Total Bilirubin (TBL) | Liver Symptoms | Action |
|---|---|---|---|
| | | | for close observation below. Follow-up for symptoms. |

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; IP=investigational product; TBL=total bilirubin; ULN=upper limit of normal.
[a] Competing etiologies include acute and chronic viral hepatitis (hepatitis A-E), cholelithiasis, alcohol, other drugs both prescribed and over-the-counter herbs and supplements.
Source: Adapted from Regev 2019 (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: 702-713).

**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, ALP, total bilirubin, and INR

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

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

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

# APPENDIX 2. LOCAL INJECTION SITE REACTIONS

**Table 6: Local Injection Site Reactions (LISRS)**

The following MedDRA PTs 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 | |

Local injection-site reactions (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:

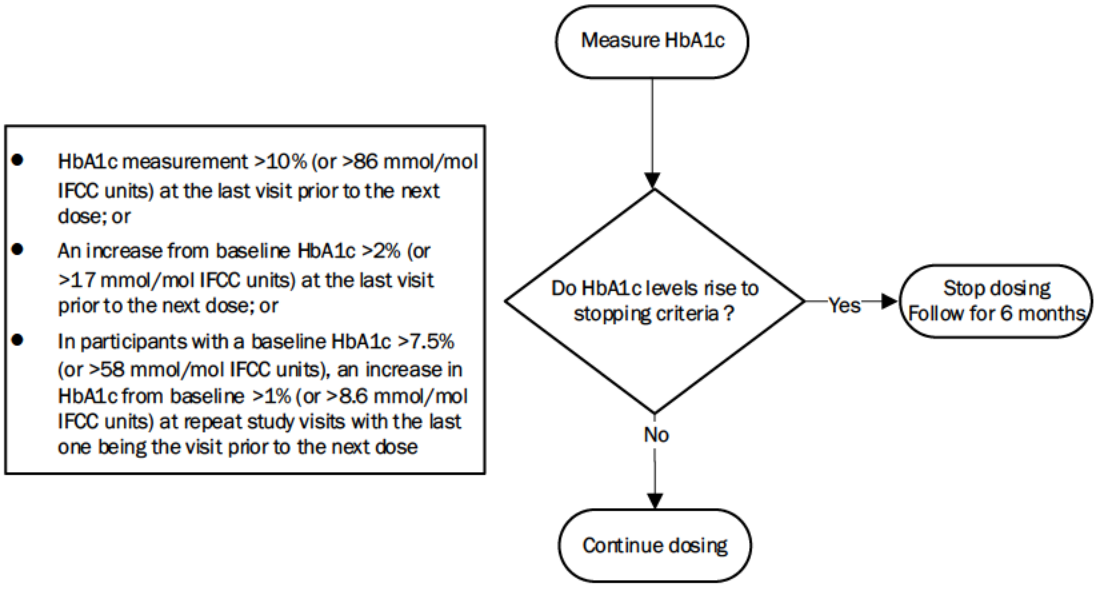
(A/B)*, where A = number of injections with a local injection site reactions, and B = total number of injections.

# APPENDIX 3. GLYCEMIC CONTROL-RELATED GUIDELINES

**Glycated Hemoglobin (HbA1c) Investigational Product Discontinuation Criteria**

Participants should discontinue Investigational Product (IP) if they meet the following criteria:

- 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
- 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 participant 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.

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| Approval | [redacted] 2023 01:25:19 GMT+0000 |
| Approval | [redacted] 2023 17:09:35 GMT+0000 |
| Approval | [redacted] 2023 17:12:41 GMT+0000 |

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