A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-ANG3 in Adults With Mixed Dyslipidemia

Protocol Number: AROANG3-2001
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Product Number:	ARO-ANG3
Indication:	Mixed Dyslipidemia
IND Number:	151756
EudraCT Number:	To be determined
Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA
Sponsor's Responsible Medical Monitor:	[redacted] Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 [redacted]

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

1 PROTOCOL SYNOPSIS

TITLE OF STUDY:

A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-ANG3 in Adults With Mixed Dyslipidemia

PROTOCOL NUMBER:

AROANG3-2001

PHASE OF DEVELOPMENT:

Phase 2b

STUDY SITES:

Approximately 25 sites 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-ANG3 Injection (also referred to as ARO-ANG3). The active pharmaceutical ingredient contained in ARO-ANG3 is a synthetic, double-stranded, small 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 subcutaneously (SC), volume-matched to the corresponding ARO-ANG3 dose volume.

Doses and Number of Doses per Treatment:

Three dose levels of ARO-ANG3 will be evaluated against placebo in participants with mixed dyslipidemia, who had low-density lipoprotein cholesterol (LDL-C) ≥ 70 mg/dL (1.8 mmol/L) OR non-high-density lipoprotein cholesterol (non-HDL-C) ≥ 100 mg/dL (2.59 mmol/L) AND mean fasting triglycerides (TG) ≥ 150 mg/dL (≥ 1.69 mmol/L) but ≤ 499 mg/dL (5.61 mmol/L) at Screening.

A total of approximately 180 participants will be enrolled in the study. All dose cohorts will enroll in parallel with 60 participants per cohort randomly assigned in a 3:1 ratio to receive ARO-ANG3 or placebo. During the Double Blind Treatment Period, each participant will receive SC injection on Day 1 and Week 12 for a total of 2 injections as follows:

- ARO-ANG3 **50 mg** (n=45) or volume-matched placebo (n=15) at Day 1 and Week 12; or
- ARO-ANG3 **100 mg** (n=45) or volume-matched placebo (n=15) at Day 1 and Week 12; or
- ARO-ANG3 2**00 mg** (n=45) or volume-matched placebo (n=15) at Day 1 and Week 12.

After completing the Week 36 Visit in the Double Blind Treatment Period, participants may opt to continue receiving ARO-ANG3 in the 24-month Open-Label Extension (OLE) Treatment Period. Participants in the OLE Treatment Period will be dosed quarterly (Q3M) and except for subjects in the 200 mg dose group, all others will be assigned to receive the same dose level to which they were randomized in the Double Blind Treatment Period. Participants in the 200 mg dose group who are entering OLE and those previously assigned to the 200 mg dose group in the OLE period will be transitioned to the 100 mg dose group at the next dosing visit. Once a single dose has been selected by the Sponsor, all participants will be transitioned to the selected dose level.

STUDY OBJECTIVE:

The primary objective of the study is to evaluate the safety and efficacy of ARO-ANG3 in adults with mixed dyslipidemia and to select a dosing regimen for later stage clinical studies in this patient population. This study will also evaluate the efficacy, safety, and tolerability of long-term dosing of ARO-ANG3 in a 24-month OLE Treatment Period following the Double Blind Treatment Period.

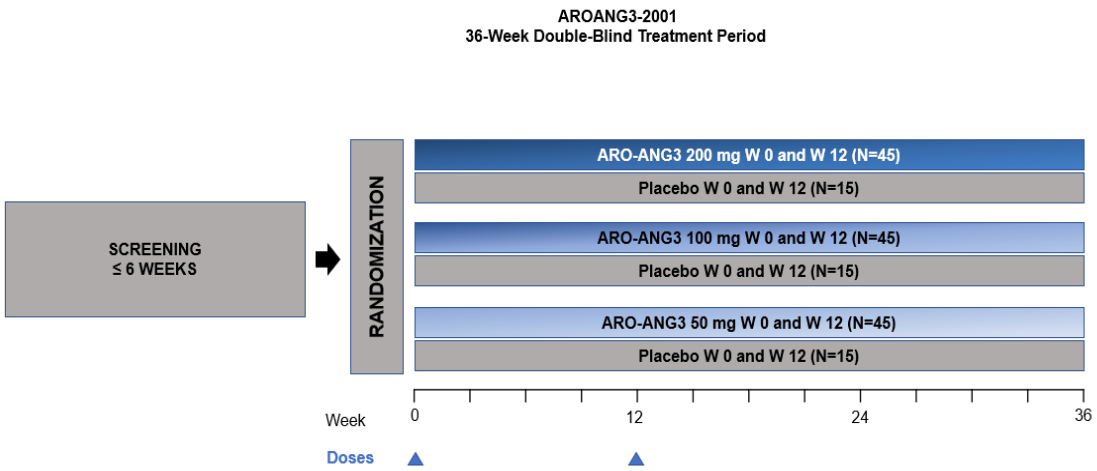
STUDY DESIGN:

This is a randomized, double-blind, placebo-controlled, Phase 2b clinical study with an OLE Treatment Period. After informed consent and at least 2 weeks on a stable diet, at least 4 weeks on a stable optimal statin regimen (unless the participant is confirmed to be statin intolerant, refer to Section 8.4) and confirmation of stable background medications, the participant will be assessed for eligibility. Participants who have met all the protocol eligibility criteria during Screening will be randomly assigned to treatment in a double-blind fashion in a 3:1 ratio to receive 1 of 3 ARO-ANG3 dosing regimens (50, 100, or 200 mg) or matched placebo (see Study Schema). During the Double-Blind Treatment Period, each participant will receive a total of 2 SC injections: 1 on Day 1 and 1 at Week 12. All dose cohorts will enroll in parallel. Enrolled participants will be counseled to remain on stable background medications and on the specified diet throughout the study, as recommended by the Investigator in accordance with local standard of care. The specifics of the diet will be at the discretion of the Investigator based on each individual's diagnosis and medical needs.

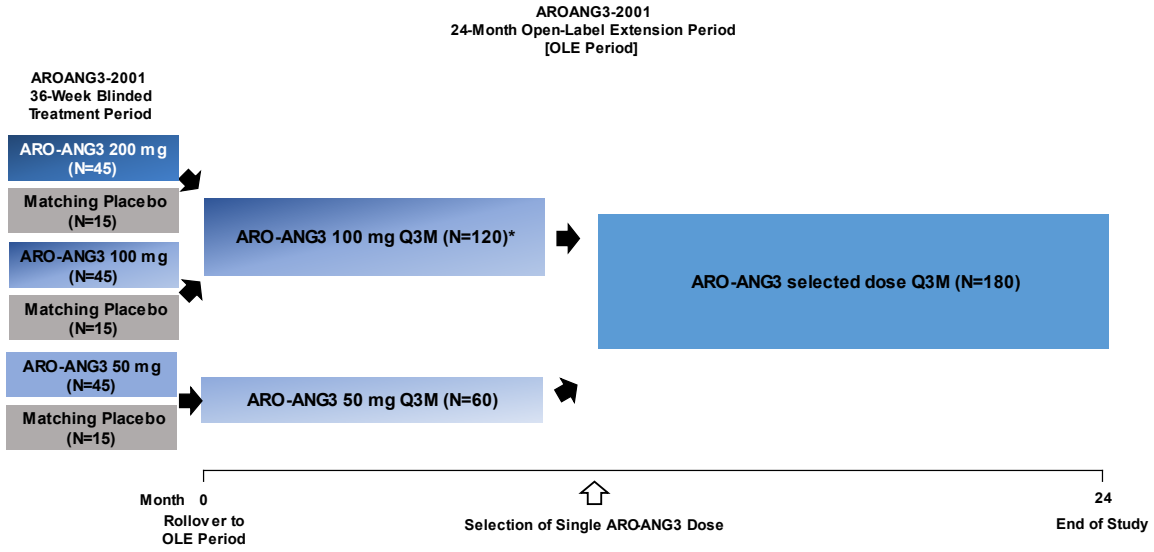
Blinding will be preserved to the extent possible; however, investigational product (IP) unblinding may occur, at the Investigator's or Medical Monitor's discretion, where deemed necessary for treatment of an adverse event (AE), for a safety-related decision, or a decision to be made regarding study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

After completing the 36-week Double-Blind Treatment Period, participants will be eligible and invited to continue in the 24-month OLE Treatment Period to evaluate the efficacy, safety, and tolerability of long-term dosing of ARO-ANG3 in participants with mixed dyslipidemia. Participants assigned to the 50 and 100 mg dose cohorts in the Double Blind treatment period will continue to receive ARO-ANG3 at the same dose level in the OLE Treatment Period. The ARO-ANG3 200 mg dose cohort will be discontinued from the AROANG3-2001 open-label treatment period. Participants currently assigned to the 200 mg dose group will be transitioned to the 100 mg dose group at the next dosing visit. Participants in the OLE Treatment Period will be dosed quarterly (Q3M) at their assigned dose until a single dose has been selected by the Sponsor.

Study Schema



Abbreviations: N = number of participants; W = week



Abbreviations: N = number of participants; Q3M = every 3 months.
*The 200 mg ARO-ANG3 dose will be discontinued in the OLE period; all participants originally receiving the 200 mg dose or volume-matched placebo control in the 36-Week Blinded Treatment period will be assigned to 100 mg dose.

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 IP discontinuation. Safety assessments will be performed at specified time points and up to study completion.

The AE/SAE reporting period for an enrolled participant begins when the participant provides informed consent. Treatment-emergent AEs (TEAEs) and SAEs are defined as those that occur following IP administration or are 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 within 24 hours of being notified. All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event causality is otherwise explained, or until the participant is lost to follow-up. If the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the IP, the Investigator will promptly notify the Sponsor. Laboratory or diagnostic assessment (eg, ECG) abnormalities will be reported as AEs if considered clinically significant (CS) by the Investigator. Laboratory or diagnostic assessment abnormalities not reported as AEs are not to be reported as CS in the study database.

TREATMENT STOPPING RULES:

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

- Any confirmed pregnancy in the study will lead to permanent discontinuation of IP dosing of that participant; or
- A need for apheresis or other emergent interventions indicated to lower TG; or
- In participants with normal (per central laboratory reference range) aspartate aminotransaminase (AST) or alanine aminotransferase (ALT) on Day 1, treatment-emergent elevations >3× 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 will lead to permanent discontinuation of IP dosing of that participant per Appendix 1. The participant will remain on study follow-up visits until EOS as per the Schedule of Assessments (SOA) (refer to Table 1 and Table 2).
    - 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

- Participants should discontinue IP if they meet the following criteria (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
  - For 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 the above criteria 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 recommendations

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 for time to evaluate safety data and recommend the action to be taken.

STUDY DURATION (PLANNED):

The duration of the Double-Blind Treatment Period is approximately 42 weeks (10.5 months) from Screening to the Week 36 examination.

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

After completing the Week 36 Visit in the Double-Blind Treatment Period, participants may opt to continue receiving ARO-ANG3 in the 24-month OLE Treatment Period. Therefore, the total duration of the study is approximately 35 months.

All placebo participants who opt to continue in the OLE Treatment Period will initially receive ARO-ANG3. The ARO-ANG3 200 mg dose cohort will be discontinued from the AROANG3-2001 open-label treatment period. Participants who were previously assigned ARO-ANG3 50 mg, 100 mg, or placebo in the Double-Blind Treatment Period, will receive ARO-ANG3 at the corresponding dose level in the OLE Treatment Period. Subjects previously assigned to the 200 mg dose group will be transitioned to the 100 mg dose group at the next dosing visit. After the last subject in the Double Blind Treatment Period completes the Week 36 Visit and a final dose has been selected by the Sponsor, all subjects in the OLE Treatment Period will be transitioned to receive ARO-ANG3 at the selected dose for the remainder of their duration in the OLE Treatment Period.

STUDY POPULATION / NUMBER OF PARTICIPANTS PLANNED:

This study will be conducted in adults with mixed dyslipidemia (LDL-C $\geq$ 70 mg/dL [1.8 mmol/L] OR non-HDL-C $\geq$ 100 mg/dL [2.59 mmol/L], after at least 4 weeks of stable optimal statin therapy, AND mean fasting TG $\geq$ 150 mg/dL [$\geq$ 1.69 mmol/L] but $\leq$ 499 mg/dL [5.61 mmol/L] at Screening). A total of approximately 180 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 $\geq$ 18 years of age;
2. Based on medical history, prior evidence of TG $\geq$ 150 mg/dL ($\geq$ 1.69 mmol/L) but $\leq$ 499 mg/dL (5.61 mmol/L);
3. Fasting levels at Screening of LDL-C $\geq$ 70 mg/dL (1.8 mmol/L) OR non-HDL-C $\geq$ 100 mg/dL (2.59 mmol/L) after at least 4 weeks of stable diet and stable optimal statin therapy (unless documented as statin intolerant per Section 8.4);

4. A mean fasting TG level of ≥ 150 mg/dL (≥ 1.69 mmol/L) and ≤499 mg/dL (5.61 mmol/L) collected at two separate and consecutive visits and at least 7 days apart and no more 17 days apart during the Screening period;
5. Able and willing to provide written informed consent prior to the performance of any study specific procedures;
6. Willing to follow diet counseling and maintain a stable diet as per Investigator judgment based on local standard of care;
7. Participants of childbearing potential must agree to use highly-effective contraception, during the study and for at least 24 weeks from last dose of IP. Males must not donate sperm during the study and for at least 24 weeks following the last dose of IP;
8. Women of childbearing potential on hormonal contraceptives must be stable on the medication for ≥2 menstrual cycles prior to Day 1;
9. Participants must be on at least 4 weeks of stable optimal statin therapy (unless statin intolerant as per Section 8.4). 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:

1. Current use or use within the last 365 days from Day 1 of any hepatocyte targeted siRNA or antisense oligonucleotide molecule;

2. Active pancreatitis within 12 weeks prior to Day 1;
3. 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. Glycated hemoglobin (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 pharmacokinetics (PK) (whichever is longer) prior to Day 1 or current participation in an interventional investigational study. Participants previously exposed to ARO-ANG3 or ARO-APOC3 will require a washout period of at least 1 year from last dose; or
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, psychiatric condition, 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.

A participant will be excluded from the OLE Treatment Period of the study if any new conditions or worsening of any existing condition (eg, renal, hematologic, gastrointestinal, endocrine, cardiovascular, pulmonary, immunologic, psychiatric) or any other situation that, in the Investigator's judgment, would make the subject unsuitable for enrollment, or which could otherwise interfere with the subject participating in or completing the study, or would make it difficult to comply with protocol requirements or put the participant at additional safety risk.

ENDPOINTS:

Primary Endpoint:

The primary endpoint of the study is:

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

Secondary Endpoints:

The following secondary endpoints will be evaluated during 36-week double-blind study period:

- Percent change from baseline in fasting TG over time through Week 36;
- Percent change from baseline at Week 24 and over time through Week 36 in fasting non--HDL-C;
- Percent change from baseline at Week 24 and over time through Week 36 in fasting total apolipoprotein (Apo) B;
- Percent change from baseline at Week 24 and over time through Week 36 in fasting LDL--C using ultracentrifugation;
- Percent change from baseline at Week 24 and over time through Week 36 in angiopoietin-like protein 3 (ANGPTL3);

- Percent change from baseline at Week 24 and over time through Week 36 in fasting HDL-C;
- Plasma concentrations of ARO-ANG3 over time through Week 12; and
- The frequency and severity of AEs and SAEs at Week 24 and over time through Week 36.

The following secondary endpoints will be evaluated in the OLE Treatment Period:

- Percent change from baseline in fasting TG, non-HDLC, total apolipoprotein (Apo) B, LDL-C using ultracentrifugation, ANGPTL3, HDL-C, and plasma ARO-ANG3 at all visits as described in Table 2 (SOA).
- The frequency and severity of AEs and SAEs through Month 24.

Exploratory Endpoints:

The following exploratory endpoints will be evaluated in this study:

- Change from baseline over time during double-blind study period as well as over time during the OLE Treatment Period 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-III, ApoC-II, ApoA-I, ApoA-V, and ApoA-1)
- Change from baseline to Week 24 and over time through Week 36 during double-blind study period as well over time in the OLE Treatment Period in fasting serum blood glucose, HbA1c, homeostatic model assessment for insulin resistance (HOMA-IR) and C- peptide
- Proportion of participants requiring emergent apheresis over time during double-blind study period as well as during the OLE Treatment Period
- Change from baseline to Week 24 in liver fat content using magnetic resonance imaging-proton density fat fraction (MRI-PDFF; only in participants with a liver fat fraction of ≥ 8% at Screening); and
- Emergence of and levels of anti-drug antibodies to ARO-ANG3 in those receiving AROANG3 over time during double-blind study period as well as over time during the OLE Treatment Period.

DATA ANALYSIS / STATISTICAL METHODS:

Statistical Considerations:

With a total of 180 participants randomly assigned in a 3:1 (active to placebo) ratio within each dosing cohort, the study will have greater than 98% power to detect at least 1 active dose cohort which is significantly different from placebo, and at least 95% power to detect all active dose cohorts which are significantly different from placebo using a two-sided test, with 5% level of significance, adjusted for multiplicity. These estimates are based on the assumption of 35% to 60% reduction from baseline in fasting TG in the 3 active dose cohorts and no change in fasting TG in the pooled placebo cohort. The standard deviation (SD) is assumed to be 65% in the pooled placebo cohort and 35% to 55% in the active treatment cohorts.

Efficacy and Pharmacodynamics Analysis:

The primary endpoint will be evaluated using mixed model repeated measures approach with a minimum model terms included for treatment group, baseline value, visit, and stratification factors. The primary analysis will be performed will evaluate the difference in means between each ARO-ANG3 dose group and pooled placebo groups in all randomized participants who receive at least 1 dose of IP (Full Analysis Set). The primary estimand of interest is the difference in means of percent change from baseline in fasting TG at Week 24 during double-blind study period in adult Mixed Dyslipidemia population (as defined by the inclusion/exclusion criteria), regardless of treatment compliance or other intercurrent events postbaseline. 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 of double-blind study period will be analyzed in a similar manner to the primary endpoint, unless otherwise noted.

Data will be summarized as applicable for the following: Serum ANGPTL3, ratio of LDL-C/HDL-C, ApoC-III, ApoC-II, LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, LP(a), TG, ApoB-48, ApoB-100, total ApoB, ApoA-I, ApoA-V, HbA1c, C-peptide, HOMA-IR, changes in serum insulin, and changes in serum glucose.

For primary endpoint (TG) analysis at Week 24 during double-blind study period, the laboratory value for endpoint analysis will be the arithmetic mean of 2 values taken during Week 24. 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 Day 1 predose assessment and two fasting assessments during screening period. For other efficacy endpoints, only Day 1 predose assessment will be used as the baseline.

After the last subject in the Double Blind Treatment Period completes the Week 36 Visit, an interim analysis will be conducted to review the efficacy and safety data in order to select a single dose level for all subjects in OLE Treatment Period and for the remainder of their participation in the trial.

For efficacy variables during open-label treatment period, the measurements and changes and/or percent changes from baseline over time will be summarized descriptively.

Descriptive statistics of biomarker changes will include mean, median SD, minimum, and maximum. Additional details will be provided in the statistical analysis plan.

Tolerability and Safety Data:

In general, safety analyses will be performed and the results summarized by dose cohort. Post-treatment safety assessments will be compared with measurements recorded at baseline. Treatment emergent AEs will be summarized using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). The incidence and frequency of AEs, SAEs, related AEs, related SAEs, and AEs leading to discontinuation, will be summarized by dose cohort per SOC, PT, and severity. All AEs will also be presented in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome. The incidence of laboratory abnormalities will be assessed using descriptive summary statistics and shift tables. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Abnormal physical examination findings will be summarized by time point and presented in participant listings. ECG parameters, changes

from baseline, and qualitative assessments will be summarized. Pregnancy and follicle-stimulating hormone (FSH) test results will be listed separately by time point.

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

Pharmacokinetics:

Plasma concentrations of ARO-ANG3 will be measured in all participants to evaluate trough and postdose levels throughout the study per the SOA (Table 1).

Full PK group: In each of the dose cohorts, 16 PK participants (12 active, 4 placebo for 48 total participants for PK) will be enrolled at the designated PK sites. Plasma concentrations will be measured predose, serially postdose on Day 1 and Week 12, as per the SOA. Only samples collected from participants receiving active treatment will be included in the PK analysis.

Sparse Sample PK group: All participants will provide a predose and postdose PK sample on Day 1 and Week 12, 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 36-Week Double-Blind Treatment Period Schedule of Assessments

Assessment	Screening Period			Double Blind Treatment Period												
	Day -42 to Day -21 S1[1]	Day -35 to Day -21 S2[1]	Day -21 to Day -1 S3	Day 1 (Pre-dose)[2]	Day 2	Wk 4[3]	Wk 8[3]	Wk 12[3]	24 hr post dose	Wk 16[3]	Wk 20[3]	Wk 24[3]	2-7 Days Post Wk 24	Wk 28[3]	Wk 36[3] or /ET	2-7 Days Post W36/ ET
Informed Consent	X															
Dietary counseling to maintain diet	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	
Demographics	X															
Medical History	X			X												
Physical Examination (symptom directed after Screening)	X			X		X	X	X		X	X	X		X	X	
Vital Signs (BP, temp, respiratory rate, heart rate)	X			X		X	X	X		X	X	X		X	X	
Concomitant Medications/Therapies	X	X	X	X		X	X	X		X	X	X		X	X	
Adverse Events (including pancreatitis, abdominal pain or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
HBV/HCV Serology Screen	X															
FSH (females not of childbearing-potential)	X															
Clinical Laboratory Tests (predose on dosing days)[5]	X			X		X	X	X		X	X	X		X	X	
Fasting Serum Triglyceride[6]		X	X													
Fasting LDL-C and non-HDL-C[6,]		X														
Fasting Lipid/Pharmacodynamic Parameters (predose on dosing days)[6,7]				X		X	X	X		X	X	X[8]	X[8]	X	X[8]	X[8]
Pregnancy test in females of childbearing potential (predose on dosing days)	X	X	X	X		X	X	X		X	X	X		X	X	

Assessment	Screening Period			Double Blind Treatment Period												
	Day -42 to Day -21 S1[1]	Day -35 to Day -21 S2[1]	Day -21 to Day -1 S3	Day 1 (Pre-dose)[2]	Day 2	Wk 4[3]	Wk 8[3]	Wk 12[3]	24 hr post dose	Wk 16[3]	Wk 20[3]	Wk 24[3]	2-7 Days Post Wk 24	Wk 28[3]	Wk 36[3] or /ET	2-7 Days Post W36/ ET
ECG[9]		X		X				X				X			X	
MRI-PDFF[10]		X										X				
IP Administration				X				X								
Postdose Follow-up					X				X							
Optional Genotype (new sample or record from source documents, if available)				X												
Anti-drug antibodies (predose on dosing days)				X		X		X		X					X	
Full PK[11]				X	X			X	X							
Sparse Sample PK[12]				X				X								

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

1 S1 and S2 visit assessments may be conducted concurrently within the S2 visit timeframe (Day -35-Day -21) as long as the participant is in a fasted stated for at least 10 hours and is on a stable diet and stable background therapy regimen as required per protocol Sections 8.1, 8.4, and 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, and 36 is ±5 days

4 Height (cm) only at Screening visit; Weight (kg) at all indicated visits.

5 Blood and urine samples will be collected after obtaining informed consent. With prior consent, a separate sample will be collected and stored for future research at the following study visits: Day 1, Week 4, and Week 12. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, laboratory samples may be collected at alternative location (eg, home health, local laboratory) using the central laboratory kit and shipped to central laboratory for analysis. If the central laboratory kit collection is not available, local laboratory safety testing may only be permitted in limited circumstances and only with prior Sponsor approval. Beginning on Day 1, clinical laboratory tests will be collected after confirming the participant has fasted (no food or drink other than water) for at least 10 hours prior to the blood draw, unless otherwise specified.

6 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 (Sections 8.1 and 8.4)

7 Beginning predose Day 1, fasting TG, LDL-C and non-HDL-C will be included as part of lipid/pharmacodynamic parameter collection

[8] At Week 24 and Week 36, whole blood for pharmacodynamic analysis of lipid parameters should be drawn **on two separate occasions, separated by 2 – 7 days after a 10 hour fast** for calculation of primary and secondary endpoints

[9] The ECGs are to be completed predose, then 30 min (± 10 minutes) and 2 hours (± 30 minutes) postdose. The ECG will be performed prior to any invasive procedures (eg, venipuncture).

[10] Selected sites (where MRI-PDFF is available) will perform MRI-PDFF assessments at Screening until up to approximately 35 participants with baseline liver fat fraction ≥ 8% have been enrolled in each of the 3 dosing cohorts after which, MRI-PDFF will no longer be included as an evaluation. If a participant terminates prior to the Week 24 visit, an unscheduled MRI-PDFF assessment should be performed.

[11] Whole blood for the plasma PK samples will be drawn in 16 participants (12 active and 4 placebo) enrolled at designated PK sites in each of the 50, 100, and 200 mg dose cohorts. 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 (see 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.

[12] All other participants (Sparse PK participants) will have PK samples drawn predose and at no less than 15 minutes postdose on dosing days.

Table 2 Open-Label Extension Treatment Period Schedule of Assessments

Study Visit Assessments	24-Month Open-Label Extension Treatment Period										
		OLE Months									
	OLE Day 1[a] (≤ 30 days after Week 36 Visit)	1[a,b]	2[a,b]	3[a,b]	6[a,b]	9[a,b]	12[a,b]	15[a,b]	18[a,b]	21[a,b]	24/EOS/ET[a]
Verify Subject Consent to OLE Treatment Period	X										
Dietary counseling / maintain diet	X	X	X	X	X	X	X	X	X	X	
Weight	X			X	X	X	X	X	X	X	X
Vital signs (BP, temperature, respiratory rate, heart rate)	X			X	X	X	X	X	X	X	X
Physical examination (symptom directed)	X			X	X	X	X	X	X	X	X
Single 12-Lead ECG[c]				X	X	X	X	X	X	X	X
Pregnancy test in women of childbearing potential (predose on dosing days)	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (predose on dosing day)[d]		X	X	X	X	X	X	X	X	X	X
Fasting Lipid parameters (predose on dosing days)[e]		X	X	X	X		X	X	X	X	X
ARO-ANG3 Administration	X			X	X	X	X	X	X	X	
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X
Anti-drug Antibodies	X	X		X	X		X		X		
Adverse events (including documentation of pancreatitis, abdominal pain or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: OLE= Open-label extension; BP = blood pressure; ECG = electrocardiogram

[a] Visits occur within ± 5 days until Month 3, then ± 14 days

[b] Assessments on dosing days are to be completed predose unless otherwise specified.

[c] Performed in the semi-supine position after the participant has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.

[d] At study visits requiring lipid parameter collection, participants will have fasted for at least 10 hours prior to blood draw. Samples collected on OLE Month 1 and 2 will be analyzed for HbA1c only. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria.

[e] At study visits requiring lipid parameter collection, participants will have fasted for at least 10 hours prior to blood draw.

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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-ANG3 in Adults With Mixed Dyslipidemia

Protocol Number: AROANG3-2001

INVESTIGATOR SIGNATURE:

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

_____

Signature Date

_____

Printed Name

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACS	Acute coronary syndrome
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like protein 3
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 ANG3	Apolipoprotein C-III
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ARO	Arrowhead Pharmaceuticals, Inc
ARO-ANG3 Injection	Clinical drug product solution ready for SC injection
ARO-ANG3	Short name for ARO-ANG3 Injection
BMI	Body mass index
CECT	Contrast-enhanced computed tomography
cGMP	current Good Manufacturing Practice
CM	Chylomicronemia
COVID	Coronavirus 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
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EL	Endothelial lipase
EOS	End-of-Study
ET	Early Termination

FAS	Full Analysis Set
FCS	Familial Chylomicronemia Syndrome
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
HOMA-IR	Homeostatic model assessment for insulin resistance
HTG	Hypertriglyceridemia
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDL	Intermediate-density lipoprotein
IFCC	International Federation of Clinical Chemistry
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ISR	Injection Site Reaction
IWRS	Interactive Web Response System
LD	Lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LIPG	Endothelial lipase
LISR	Local injection-site reactions
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LMF1	Lipase maturation factor 1
Lp	Lipoprotein
LPL	Lipoprotein lipase
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCM	Multifactorial chylomicronemia

MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
Mixed Dyslipidemia	Severe hypertriglyceridemia
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
mRNA	Messenger ribonucleic acid
NCEP	National Cholesterol Education Program
NOAEL	No observed adverse effect level
non-HDL-C	Non-Low density lipoprotein cholesterol
NYHA	New York Heart Association
OLE	Open-Label Extension
OTC	Over the Counter
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
Q12W	Once every 12 weeks
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
siRNA	Short interfering RNA oligonucleotides
SOA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TG	Triglyceride(s)
TSH	Thyroid stimulating hormone
TRL	Triglyceride-rich lipoprotein
ULN	Upper Limit of Normal
US	United States
VLDL-C	Very-low-density lipoprotein-cholesterol

Definition of Terms

Investigational Product (IP) is defined as, “A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical 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 on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

5 BACKGROUND

Patients with mixed dyslipidemia are at high risk of atherosclerotic cardiovascular disease (ASCVD), the leading cause of mortality worldwide that is associated with substantial morbidity and healthcare costs (Barquera 2015). ASCVD is commonly associated with elevated concentrations of low-density lipoprotein cholesterol (LDL-C), but even in the setting of adequate LDL-C control, considerable residual cardiovascular disease risk remains (Hussain 2020) due to elevated triglycerides (TG) and TG-rich lipoprotein levels (TRLs) (Lawler 2017, Chapman 2011, Jorgensen 2013, Nordestgaard 2016). 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 or recurrent ACS event was reduced by 2.3% when TG was lowered 10% during the first month of statin therapy (Miller 2008).

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, HMG-CoA reductase inhibitors (statins), ezetimibe, niacin, and proprotein convertase subtilisin kexin type-9 (PCSK9) inhibitors are 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% (42.0M) 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% (11.6M) of US adults have all 3 lipid abnormalities (Toth 2012).

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-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), very-low-density lipoprotein (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 meta-analysis 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. The authors reported that in randomized controlled studies, TG lowering is associated with a lower risk of major vascular events, but to a lesser extent per absolute amount of reduction than with LDL. Additionally, they found that a reduction in non-HDL-C, a measure of atherogenic LDL and VLDL particles, is strongly associated with a lower risk of major vascular events regardless of the lipid-lowering drug class (Marston 2019).

An emerging therapeutic target with relevance to mixed dyslipidemia (including hypercholesterolemia, hypertriglyceridemia) is angiopoietin like protein 3 (ANGPTL3). ANGPTL3 has emerged as an important regulator of plasma lipoprotein levels (including LDL-C, HDL-C, and VLDL-C) by inhibition of enzymes including lipoprotein lipase (LPL) and endothelial lipase (EL). ANGPTL3 is also involved in regulating ApoB particle containing synthesis and hepatocyte clearance of LDL-C through mechanisms independent of the low-density lipoprotein receptor (LDLR) (Xu 2018). This LDLR-independent feature makes ANGPTL3 inhibition interesting for LDLR-deficient hypercholesterolemic patients.

ANGPTL3 is a primarily hepatocyte-synthesized member of the angiopoietin like family of proteins. It is exclusively produced in the liver and can therefore be classified as a true hepatokine (Conklin 1999). Serum concentrations in humans average 368 ± 168 ng/mL (Robciuc 2010). Its key role is as a regulator of LDL-C, HDL-C, and TG metabolism. ANGPTL3 acts with ANGPTL8 to inhibit LPL and is most active after feeding (Quagliarini 2012). LPL is responsible for TG hydrolysis in peripheral tissues (eg, adipose tissue, muscle). Inactivation of ANGPTL3 in mice reduces plasma TG and free fatty acid levels and suppresses atherosclerosis (Graham 2017). ANGPTL3 also inhibits EL-driven HDL-C metabolism and inhibits hepatocyte uptake of ApoB-containing lipoproteins (LDL-C and VLDL-C) through mechanisms at least partially independent of the LDLR (Xu 2018). Given ANGPTL3's inhibitory role of various lipoproteins and TG, reduced expression and reduced circulating levels of ANGPTL3 would be expected to increase clearance of TGs, non-HDL-C, LDL-C and HDL-C.

In humans, homozygous loss-of-function mutations in *ANGTPL3* lead to very low or undetectable serum ANGPTL3, low plasma levels of LDL-C, HDL-C and TGs, a condition referred to as familial combined hypolipidemia (Musunuru 2010). Heterozygous carriers of loss-of-function mutations in *ANGPTL3* have a lower risk of coronary artery disease than non-carriers (Dewey 2017, Stitziel 2017). To date no adverse clinical phenotype such as hepatic steatosis, obesity or other metabolic derangements have been reported in *ANGPTL3* -deficient subjects (Dewey 2017). Importantly, the low HDL-C observed in *ANGPTL3* deficiency is due to

enhanced EL activity and does not appear to increase risk of cardiovascular disease. The low LDL-C, TG, and reduced odds of developing cardiovascular disease seen in *ANGPTL3* deficient subjects indicate that pharmacologic suppression of ANGPTL3 may hold considerable promise for the treatment and secondary prevention of ASCVD.

ANGPTL3 inhibition may also benefit patients with diseases of intracellular TG accumulation with associated insulin resistance which include metabolic syndrome and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Treatment of wild type mice with hepatic steatosis due to a high fat diet experienced and 80% reduction in liver TG when treatment with antisense oligonucleotides targeting *ANGPTL3* expression (Graham 2017). Hepatic steatosis has been proposed as the first in a cascade of 'hits' in the development of nonalcoholic steatohepatitis (NASH) (Tilg 2010). Intrahepatic targeting of ANGPTL3 may lead to reductions in hepatic fat in these subjects, therefore potentially lowering the risk of progression to NASH. Additionally, *ANGPTL3*-deficient homozygotes show lower serum insulin, lower serum glucose and improved measures of insulin resistance compared to non-carriers (Robciuc 2010).

One method of targeting serum ANGPTL3 is with a monoclonal antibody approach. Evaluations with evinacumab, targeting circulating ANGPTL3 in healthy volunteers (Dewey 2017) and in patients with familial hypercholesterolemia (Gaudet 2017), have confirmed potent reductions in LDL-C, HDL-C, and TG. However, an antibody approach would miss intra-hepatocyte ANGPTL3 which may be important for improvement of intra-hepatocyte TG accumulation and insulin resistance (Graham 2017).

5.2 Overview of ARO-ANG3 Development

A brief overview of existing information on ARO-ANG3 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.

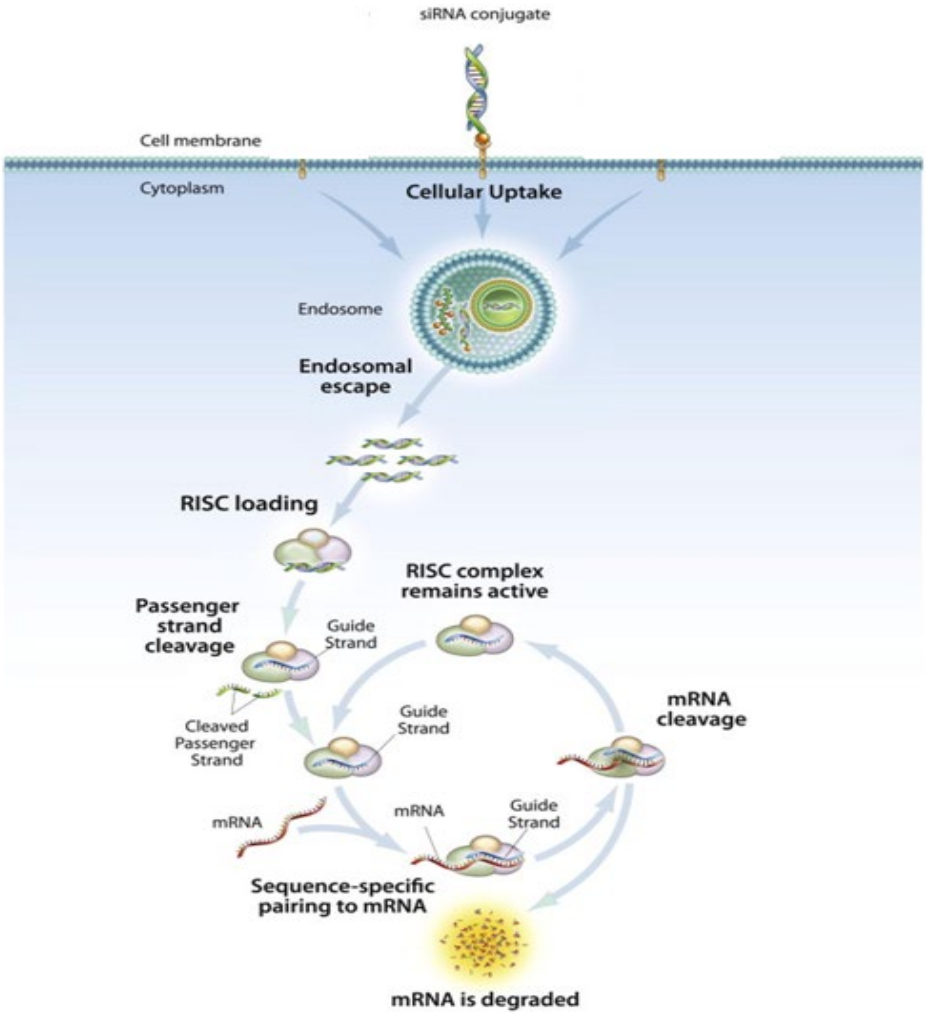
Mechanism of Action of ARO-ANG3 and Therapeutic Rationale

siRNA Mechanism of Action

An RNA interference (RNAi)-based therapeutic targeting ANGPTL3 has the potential to treat dyslipidemias in a fundamentally different manner than current therapies. RNAi is a naturally -occurring phenomenon by which siRNAs trigger a sequence-specific down-modulation of gene expression. RNAi triggers refer to synthetic siRNAs designed to target specific messenger ribonucleic acid (mRNA) expression. By delivering the RNAi trigger targeting *ANGPTL3* to the liver, it is possible to silence expression of *ANGPTL3* mRNA in hepatocytes. Since *ANGPTL3* is exclusively expressed in hepatocytes, silencing of *ANGPTL3* mRNA is expected to reduce both intrahepatic and plasma ANGPTL3 protein levels. Significant reduction in ANGPLT3 levels is expected to reduce plasma LDL-C and TG levels and may lead to the reduction of risk of coronary heart disease and cardiovascular events associated with hypertriglyceridemia and LDL-C in patients with persistent dyslipidemia. Targeting *ANGPTL3* may also improve insulin resistance and hepatic steatosis. The RNAi trigger molecule in ARO-ANG3 Injection was designed to avoid activity against other human mRNAs, microRNA

and other non-coding RNA and to avoid acting outside of the liver. Thus, ARO-ANG3 is not expected to have off-target effects.

Figure 1 siRNA Mechanism of Action



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

Preclinical Studies

The Sponsor is conducting a comprehensive preclinical program to support the subcutaneous (SC) administration of ARO-ANG3. 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 *ANGPTL3* as a potential treatment of mixed dyslipidemia. Details regarding preclinical pharmacology, pharmacokinetics (PK), and toxicology results are provided in the IB.

- Preclinical pharmacology of ADS-004, the active pharmaceutical ingredient in ARO-ANG3, shows that ADS-004 treatment in transgenic mice (TgANG3) resulted in dose-dependent reduction of hepatic *ANGPTL3* mRNA levels, which correlated with reduced serum ANG3 of > 90%. Reductions in serum ANG3 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 liver and serum ANGPTL3 were also observed after ADS-004 doses in a diet-induced dyslipidemic rhesus monkey model. ARO-ANG3 has been well tolerated in rats and in non-human primate toxicology studies.

- Results of non-Good Laboratory Practice (GLP) and GLP short term and chronic toxicology studies are reviewed in the IB.

Clinical Studies

The Sponsor has initiated a Phase 1 single and multiple dose study to evaluate the safety, tolerability, PK, and pharmacodynamic (PD) effect of ARO-ANG3 in adult healthy volunteers and patients with dyslipidemia (AROANG1001). Details regarding Phase 1 study results can be found in the IB.

5.3 Risk Assessment for Participants

- **Embryo-Fetal:** Limited GLP toxicology and clinical studies have been conducted. Accordingly, eligible participants enrolled in this study, both male and female (including partners), must agree to use 2 highly effective forms of contraception during the study, or agree to abstinence (acceptable only if this method is in alignment with the normal life style of the participant).

- **Liver Function:** ARO-ANG3 targets the liver. siRNA literature has described alanine aminotransferase (ALT) changes associated with off-target effects of the siRNA seed region on microRNAs in the hepatocyte (Janas 2018). The siRNA sequence of the ARO-ANG3 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 AROANG1001 study, transient mild to moderate elevations in ALT were occasionally seen (Refer to IB for details) without accompanying elevation in international normalized ratio (INR) or total bilirubin. To mitigate this risk, the proposed study protocol has built in stopping rules for ALT and aspartate aminotransferase (AST) elevation. Blood samples will be drawn frequently 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 and transient injection site

AEs have been reported in the AROANG1001 study (Refer to IB for details). In this study, steps will be taken to minimize injection site reactions such as rotating injection sites and allowing the ARO-ANG3 solution to come to room temperature prior to injection.

- **Glycemic Control:**
  An administrative analysis in the ongoing Phase 2 AROANG3-2001 clinical trial observed an imbalance in changes in HbA1c over time, with increased HbA1c values observed in subjects who had preexisting diabetes at baseline and particularly in a subset of subjects in the highest (200 mg) ARO-ANG3 dose group.

  To mitigate the risk of worsening glycemic control, investigators will be encouraged to evaluate 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 the protocol pre-established level, a number of criteria for study drug discontinuation have been established (Appendix 3).

  Routine monitoring of serum HbA1c and fasting glucose concentrations will be assessed as part of the clinical laboratory panels to monitor glycemic control, as specified in the SOA (Table 1 and Table 2).

5.4 Study Rationale

Interim results from the Phase 1, First in Human study AROANG1001 show that in healthy volunteers and in patients with hypertriglyceridemia, treatment with ARO-ANG3 reduces hepatic production of ANGPTL3 via RNAi, leading to reductions in serum TG, non-HDL-C, LDL-C, and HDL-C. Thirty-five (35), 100, 200, and 300 mg all demonstrated durable PD activity lasting beyond Week 12. Aside from mild and transient injection site reactions and transient, self-limited ALT elevations, single and repeat doses of ARO-ANG3 were well tolerated in healthy volunteers and the safety profile based on Phase 1 warrants additional later stage clinical evaluation.

Based on these results and given the unique ability of ARO-ANG3 to simultaneously lower both TG and LDL-C, this current study will be conducted in adults with mixed dyslipidemia, defined as patients who have LDL-C $\geq$ 70 mg/dL (1.8 mmol/L) OR non-HDL-C $\geq$ 100 mg/dL (2.59 mmol/L) AND a mean fasting TG $\geq$ 150 mg/dL ($\geq$ 1.69 mmol/L) but $\leq$ 499 mg/dL (5.61 mmol/L). The design is intended to evaluate the effects of 3 different dosing levels of ARO-ANG3 (50, 100, or 200 mg) with 3 doses administered per dose level, against volume-matched placebo in lowering TG levels on top of standard of care lipid-lowering medications and dietary

modifications. In addition, this study will evaluate whether 50, 100, or 200 mg of ARO-ANG3 improve other lipid parameters (eg, LDL-C, non-HDL-C). Plasma concentrations of ARO-ANG3 will also be measured over time to evaluate the PK profile. Administration of doses on Day 1 and Week 12 with extended follow-up will allow complete assessment of the drug effect over a long 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

Rationale for the doses selected comes primarily from the single escalating and multiple escalating dose components of the AROANG31001 phase 1 clinical study. The 35, 100, 200, and 300 mg dose levels were assessed in the Phase 1 study (AROANG1001). Based on efficacy and safety data from that study, [redacted], the dose levels of 50, 100, and 200 mg, were selected for use in this Phase 2b study. Overall, there was no appreciable difference in the safety profile of the 100 or 200 mg dose levels as described in the safety data summary provided in the IB. Furthermore, it is expected that the 50 mg dose level would have a safety profile that is comparable to the dose levels studied in Phase 1.

In the Phase 1 study evaluating ARO-ANG3 in healthy volunteers, single doses and multiple doses (Days 1 and 29) of 35, 100, 200, or 300 mg consistently reduced serum TG levels through Week 12. Reductions in TG of greater than 50% from baseline were maintained for the 200 and 300 mg doses at Week 12 with single doses. In the multi-dose cohorts, 100, 200, and 300 mg doses maintained > 60% reductions in TG through Week 16 (Day 113). A clearer dose response is seen with ANGPTL3 with dose-dependent decreases in ANGPTL3 demonstrated with increasing single doses. Summary PD data are provided in the IB. All 3 dose levels are active and reduce serum ANGPTL3 as well as TGs versus placebo.

The planned dose levels of 50, 100, and 200 mg are approximately 1/30th, 1/10th, and 1/5th, respectively, of the no observed adverse effects level (NOAEL) (15 mg/kg) from 4 week/3 dose GLP toxicology studies in rat, assuming weight-based conversion and an average 70 kg subject. The planned dose levels of 50, 100, and 200 mg are approximately 1/600th, 1/210th, and 1/105th,

respectively, of the NOAEL (300 mg/kg) from 4 week/3 dose GLP toxicology studies in monkeys, assuming weight-based conversion and an average 70 kg subject. It should be additionally noted that the dose frequency in this proposed study is only once every 12 weeks, 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.

The proposed study design is intended to evaluate the duration of effect after doses of 50, 100 or 200 mg administered on Day 1 and Week 12 with follow-up through Week 36. This design will inform on optimal dose and duration based on time for ANGPTL3 levels and other lipid parameters to return to baseline after the second dose. Details of the analyses used for dose selection are provided in the Statistical Analysis Plan. After completing Week 36, participants will be eligible and invited to continue in a 24-month open-label extension (OLE) period during which all participants, including those previously assigned to placebo, will switch to ARO-ANG3. Participants who were previously assigned ARO-ANG3 50 mg or 100 mg or placebo in the 36-week Double Blind Treatment Period, will receive ARO-ANG3 at the corresponding dose level in the OLE Treatment Period. However, participants previously assigned to the 200 mg dose group will be transitioned to the 100 mg dose group at the next dosing visit in the OLE. After the last subject in the Double Blind Treatment Period completes the Week 36 Visit and a final dose has been selected, all subjects in the OLE Treatment Period will be transitioned to receive ARO-ANG3 at the selected dose for the remainder of their duration on the OLE.

6 STUDY OBJECTIVES

The primary objective of the study is to evaluate the safety and efficacy of ARO-ANG3 in adults with mixed dyslipidemia and to select a dosing regimen for later stage clinical studies in this patient population.

Following the 36-week Double-Blind Treatment Period, participants will have the option to receive ARO-ANG3 in a 24-month OLE Treatment Period to evaluate the efficacy, safety, and tolerability of long-term dosing of AROANG3.

7 STUDY PLAN

7.1 Overall Study and Design Plan

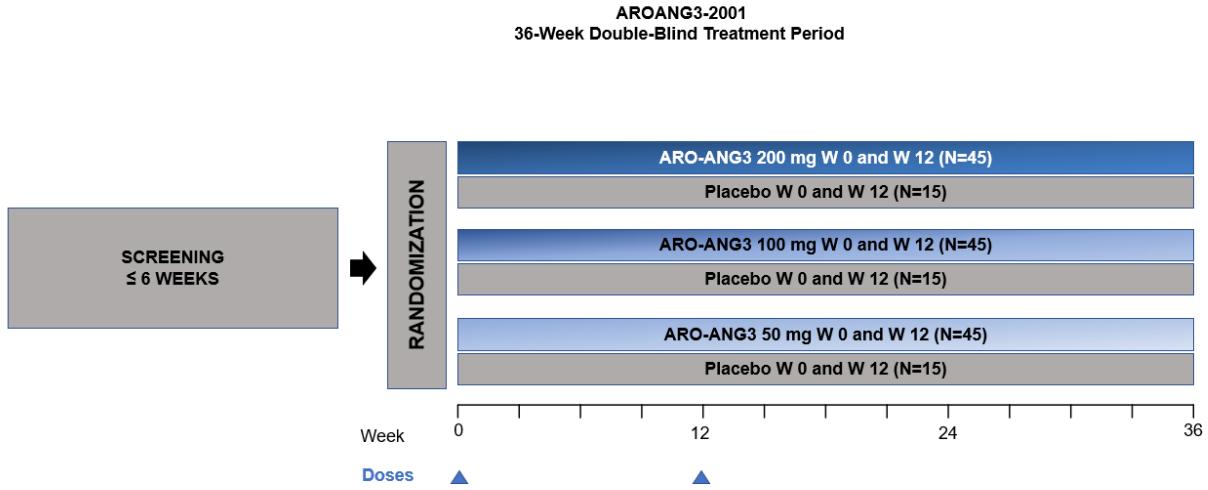
This is a randomized, double-blind, placebo-controlled, Phase 2b clinical study. Participants who have signed an Ethics Committee (EC)/Institutional Review Board (IRB) approved informed consent form may initiate screening during which eligibility assessments will be completed. Participants must maintain a stable diet and stable lipid-lowering therapy, including statins, and

other relevant background medications, as applicable (see Sections 8.1, 8.4, and 10.2), throughout the Screening Period.

Participants who have met all the protocol eligibility criteria during the Screening Period will be randomly assigned to treatment in a double-blind fashion in a 3:1 ratio to receive 1 of 3 ARO-ANG3 dosing regimens (50, 100, or 200 mg) or matched placebo (Figure 2). Each participant will receive a total of 2 SC injections, on Day 1 and Week 12 during the Double Blind Treatment Period. All dose cohorts will enroll in parallel.

Enrolled participants will be counseled to remain on stable background medications and on the specified diet throughout the study, as recommended by the Investigator in accordance with local standard of care, see the Schedule of Assessments (SOA) (Table 1). The specifics of the diet will be at the discretion of the Investigator based on each individual's diagnosis and medical needs.

Figure 2 Study Schema



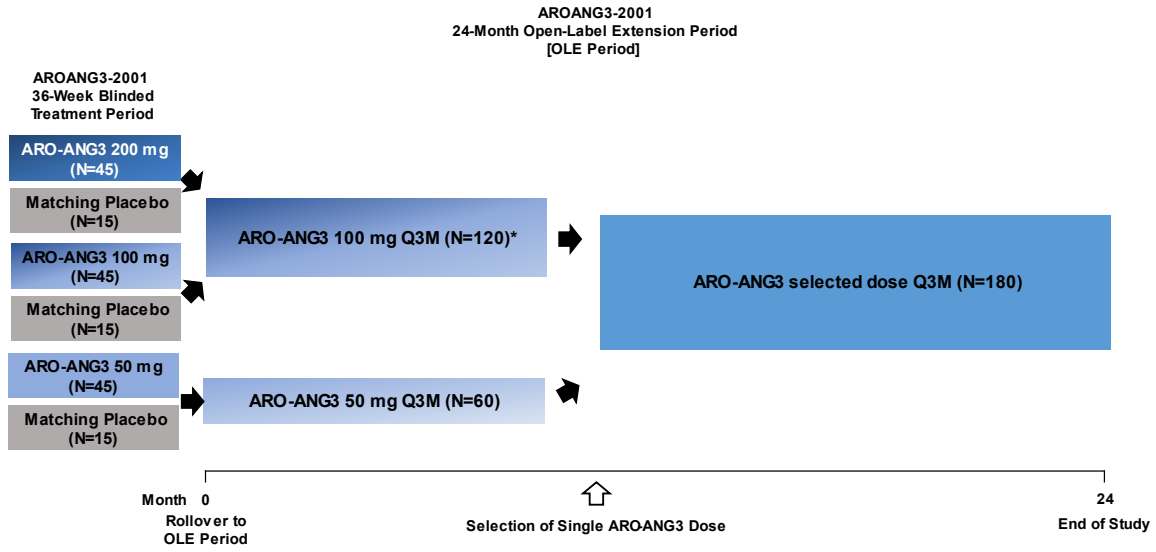
Abbreviations: N = number of participants; W = week

Blinding will be preserved to the extent possible (or unless otherwise specified); however, investigational product (IP) 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.

Following completion of the Week 36 Visit, eligible participants will be invited to continue in the 24-month OLE Treatment Period (Figure 3). The ARO-ANG3 200 mg dose cohort will be discontinued from the AROANG3-2001 open-label treatment period. Participants entering the OLE period at the 200 mg dose group (placebo or ARO-ANG3) and participants previously assigned to the 200 mg dose group in the OLE period will be transitioned to the 100 mg dose group at the next dosing visit. Participants in the OLE will be dosed quarterly and will receive

the same dose level (either 50 mg or 100 mg) to which they were randomized in the Double Blind Treatment Period until a single dose has been selected by the Sponsor. Once a single dose has been selected by the Sponsor, all subjects will be transitioned to the selected dose for the duration of their participation in the OLE Study Period (Figure 3).

Figure 3 Study Schema (OLE)



Abbreviations: N = number of participants; 3QM = every 3 months.
*The 200 mg ARO-ANG3 dose will be discontinued; all subjects originally receiving the 200 mg dose or volume-matched placebo control in the 36-Week Blinded Treatment period will be assigned to 100 mg dose in the OLE period.

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 IP 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 (TEAE) and SAEs are defined as AEs that occur following IP administration or a pre-existing condition exacerbated following IP administration. The TEAE reporting period begins after the first dose and extends until the End-of-Study visit is complete. All SAEs that occur during the reporting period, in addition to reporting via electronic case report forms (eCRFs), must also be reported to the Sponsor via the SAE report form within 24 hours of being notified. All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event causality is otherwise explained, or until

the participant is lost to follow-up. If the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the IP, the Investigator will promptly notify the Sponsor. Laboratory or diagnostic assessment (eg, ECG) abnormalities will be reported as AEs if considered 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.

Number of Study Sites

Approximately 25 centers globally.

Number of Participants

Approximately 180 participants.

Estimated Study Duration

The total estimated duration of the study, including the Double Blind Treatment Period and the OLE Treatment Period is approximately 35 months.

The total duration of the Double Blind Treatment Period is approximately 42 weeks (10.5 months) from Screening to the Week 36 Visit in the Double Blind Treatment Period.

The Screening period will last approximately up to 6 weeks (Day -42 through Day -1) consisting of dietary stabilization and other required eligibility assessments. Lipid parameter values assessed to determine eligibility during the Screening period and throughout the study will be collected from participants in a fasted state as specified in the SOA (Table 1 and Table 2).

After completing the Week 36 visit, participants will be eligible and invited to continue in the 24-month OLE Treatment period (Table 2) and will receive the dose corresponding to their study treatment dose as assigned in the Double Blind Treatment Period. Participants who had previously received ARO-ANG3 50 mg or100 mg, or volume-matched placebo, will continue to receive the corresponding dose level of ARO-ANG3 in the OLE Treatment Period. However, participants previously assigned to the 200 mg dose group (Placebo or ARO-ANG3) will be transitioned to the 100 mg dose group at the next dosing visit in the OLE. After the last participant in the Double-Blind Treatment Period completes the Week 36 Visit and a single dose has been selected by the Sponsor, all participants in the OLE will receive the selected ARO-ANG3 dose Q3M for the remainder of their participation in the study.

7.2 Discussion of Study Design, Including Choice of Control Group

The primary objective of the study is to select 1 dose and dosing regimen for later stage clinical studies based on evaluation of the safety and efficacy of 3 doses of ARO-ANG3 in participants with mixed dyslipidemia. Patients with mixed dyslipidemia is the key planned patient population for later stage clinical studies.

Participants confirmed to be on a stable diet, a stable optimal statin regimen (unless documented history of statin intolerance as per Section 8.4), and stable background medications, (see Sections 8.1, and 10.2) will complete all remaining eligibility assessments within 6 weeks (Day -42 to Day -1) prior randomization on Day 1 as specified in the SOA (Table 1). The Double Blind Treatment Period will begin on Day 1 and will continue for 36 weeks. Dietary counseling will commence at the start of the Screening Period and will be reinforced at intervals throughout the study. 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. Compared with the potent effect of ARO-ANG3 in lowering TG levels, other first-line therapies have modest effects on TGs. For example, patients with severe hypertriglyceridemia 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-ANG3 is used on top of optimal lipid lowering therapy. In this Phase 2 study, stable concomitant optimal statin therapy is required for all participants. Concomitant use of other prescription or over-the-counter (OTC) lipid management regimens (eg, nicotinic acid/niacin, omega-3 fatty acids) will be permitted as long as the participant has maintained a stable regimen for the specified timeframe (refer to Section 8.1) prior the collection of Screening lipid parameter laboratory tests and will agree to stay on this baseline regimen during the Double Blind Treatment Period (refer to Section 8.4).

The duration of the treatment is intended to ensure adequate exposure to ARO-ANG3 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 time points from Week 24 over time through Week 36 will assess the durability of the treatment effect, additional efficacy outcomes, and long-term safety. The OLE study will determine the long term safety and efficacy of the study drug.

8 PARTICIPANT SELECTION

The proposed participant population is adults with mixed dyslipidemia, defined as LDL-C $\geq$ 70 mg/dL (1.8 mmol/L) OR non-HDL-C $\geq$ 100 mg/dL (2.6 mmol/L), after at least 4 weeks of stable optimal statin therapy (unless participant has a documented history of statin intolerance as documented in medical records as per Section 8.4), AND mean fasting TG $\geq$ 150 mg/dL ($\geq$ 1.69 mmol/L) but $\leq$ 499 mg/dL (5.61 mmol/L). Patients with mixed dyslipidemia are at high risk of ASCVD, the leading cause of mortality worldwide that is associated with substantial morbidity and healthcare costs (Barquera 2015). ASCVD is commonly associated with elevated concentrations of LDL-C, but even in the setting of adequate LDL-C control, considerable residual cardiovascular disease risk remains (Hussain 2020) due to elevated TG and TRLs (Lawler 2017, Chapman 2011, Jorgensen 2013, Nordestgaard 2016). Evidence from a large prospective study of over 4,000 patients hospitalized for ACS (PROVE-IT TIMI 22 study),

indicate that the risk of death or recurrent ACS event was reduced by 2.3% when TG was lowered 10% during the first month of statin therapy (Miller 2008). 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 12.3.

8.1 Inclusion Criteria

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

1. Males or non-pregnant (who do not plan to become pregnant), non-lactating females ≥ 18 years of age;

2. Based on medical history, prior evidence of TG ≥ 150 mg/dL (1.69 mmol/L) and ≤ 499 mg/dL (5.61 mmol/L)

3. Fasting levels at Screening of LDL-C ≥ 70 mg/dL (> 1.8 mmol/L) OR non-HDL-C ≥ 100 mg/dL (> 2.6 mmol/L) after at least 4 weeks of stable diet and stable optimal statin therapy (unless documented as statin intolerant per Section 8.4);

4. A mean fasting TG level at Screening of ≥ 150 mg/dL (≥ 1.69 mmol/L) and ≤ 499 mg/dL (5.61 mmol/L) collected at two separate and consecutive visits at least 7 days apart and no more than 17 days apart during the Screening period;

5. Able and willing to provide written informed consent prior to the performance of any study specific procedures;

6. Willing to follow diet counseling and maintain a stable diet as per Investigator judgment based local standard of care;

7. Participants of childbearing potential must agree to use highly-effective contraception, during the study and for at least 24 weeks from last dose of IP. Males must not donate sperm during the study and for at least 24 weeks following the last dose of IP.

8. Women of childbearing potential on hormonal contraceptives must be stable on the medication for ≥2 menstrual cycles prior to Day 1;

9. Participants must be on at least 4 weeks of stable optimal statin therapy (unless statin intolerant as documented in medical records per section 8.4). 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.

Table 3 Stable Therapy Regimen at Screening

Medication		**Time on stable regimen prior to collection of Screening visit (S2) laboratory tests**
Lipid lowering therapies (including		≥ 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		≥ 12 weeks
Testosterone replacement therapy		≥ 16 weeks
Oral estrogens, tamoxifen, raloxifene		≥ 16 weeks
Immunosuppressants		≥ 24 weeks

NOTE: All laboratory tests used as inclusion criteria will be assessed by a central laboratory and may be repeated once and the repeat value may be used for inclusion purposes. Local laboratory testing may be permitted in limited circumstances and only with prior Sponsor approval (see Table 1).

8.2 Exclusion Criteria

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

1. Current use or use within the last 365 days from Day 1 of any hepatocyte targeted siRNA or antisense oligonucleotide molecule;
2. Active pancreatitis within 12 weeks prior to Day 1;
3. 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, or
    c. Glycated hemoglobin (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-ANG3 will require a washout period of at least 1 year from last dose; or

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.

NOTE: All laboratory tests used as exclusion criteria will be assessed by a central laboratory and may be repeated once and the repeat value may be used for inclusion purposes. Local laboratory testing may be permitted in limited circumstances and only with prior Sponsor approval (see Table 1).

A participant will be excluded from the OLE Treatment Period of the study if any new conditions or worsening of any existing condition (eg, renal, hematologic, gastrointestinal, endocrine, cardiovascular, pulmonary, immunologic, psychiatric) or any other situation that, in the Investigator's judgment, would make the subject unsuitable for enrollment, or which could otherwise interfere with the subject participating in or completing the study, or would make it difficult to comply with protocol requirements or put the participant at additional safety risk;

8.3 Participant Withdrawal Criteria

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

- the need to take medication which may interfere with study measurements;
- intolerable/unacceptable adverse experiences;
- major violation of or deviation from study protocol procedures;
- noncompliance of participant with protocol;
- participant unwilling to proceed and/or consent is withdrawn; or
- withdrawal from the study if, in the Investigator's judgment, it is in the participant's best interest.

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

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

designee, at the clinical study facility will attempt to contact the Medical Monitor or medically qualified designee for consultation. No medical help, diagnosis, or advice will be withheld from the participant due to an inability to contact the Medical Monitor. The participant will be encouraged to remain available for follow-up medical monitoring. The Sponsor will be notified as soon as possible of any participant withdrawals.

8.3.1 Data Safety Committee and Treatment Stopping Rules

An independent DSC will be assembled to review safety data after half of the total number of participants planned for enrollment have received at least 1 dose of IP. This group may also be asked by the study Sponsor to meet on an ad hoc basis to review safety data and make recommendations related to the study. Planned safety reviews will include evaluations for imbalances between active and placebo groups for AEs and SAEs. The DSC may be asked to review safety data at additional unscheduled meetings should a potential safety signal be detected. The DSC may also make recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Blinded data will be reviewed initially and if there are any concerns or unblinded review is warranted based on blinded review, the DSC may review unblinded data in a closed session. 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 to allow for time to evaluate safety data and recommend the action to be taken. The DSC's recommendation may include, but is not limited to, one of the following:

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

Sponsor or Investigator can discontinue any participant at any time.

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

- Any confirmed pregnancy in the study will lead to permanent discontinuation of IP dosing of that participant.
- A need for apheresis or other emergent interventions indicated to lower TG; or

- In participants with normal (per central laboratory reference range) aspartate aminotransaminase (AST) or alanine aminotransferase (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 will lead to permanent discontinuation of IP dosing of that participant per Appendix 1. The participant will remain on study follow-up visits until EOS as per the Schedule of Assessments (SOA) (refer to Table 1 and Table 2).
    - 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

  Please see protocol Appendix 1 for treatment modification guidelines in participants with elevated AST or ALT.

<u>Study drug discontinuation criteria for increased HbA1c</u>

- 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
- For 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 the above criteria will be followed for 6 months after their last dose per the Schedule of Assessments.

8.4 Restrictions and Concomitant Medications

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

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

3. ***Concomitant Medications***: Unless a participant has a documented history of statin intolerance, all participants must be on 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. 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. 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 taking any of the concomitant medications specified in Table 4 (below) 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. In cases where any concomitant medication specified in Table 4 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 4 during the study, are only allowed if, at the discretion of the Investigator, this is needed to provide adequate supportive care. These changes must be documented in the eCRF no later than at the next study visit. Participants will be instructed to inform the Investigator of the details (indication, dose and dates of administration) if they do take any medication, and these details will be recorded in the eCRF.

Table 4 Concomitant Medications

Background Medications	Time on stable regimen prior to collection of Screening visit (S2) laboratory tests and throughout study duration
Lipid lowering therapies (including statins)	≥ 4 weeks
Fibrates	≥ 6 weeks
PCSK9 inhibitors	≥ 8 weeks
Beta-blockers, Thiazide diuretics	≥ 4 weeks
Retinoids	≥ 8 weeks
Atypical antipsychotics	≥ 12 weeks
Diabetes Mellitus medications	≥ 12 weeks
Anticoagulation therapy	≥12 weeks
Thyroid hormone replacement therapy	≥12 weeks
Testosterone replacement therapy	≥16 weeks
Oral estrogens, tamoxifen, raloxifene	≥ 16 weeks
Immunosuppressants	≥ 24 weeks

4. ***Local laboratory lipid testing***: Central laboratory results of fasting serum ANGPTL3, as well as 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 during the Double-Blind Treatment Period as these results may potentially unblind IP assignment. After Day 1, Investigators should not perform local non-protocol testing of these analytes for the duration of the Double Blind Treatment Period and through Day 1 of the OLE Treatment Period.

   Beginning with the second OLE study visit (Month 1 Visit, refer to Table 2), lipid parameters from the central laboratory will be reported to the Investigator for the remainder of the OLE Treatment Period.

8.5 Lipid Monitoring

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

Following the Week 24 visit, in cases where a participant with a baseline LDL-C <130 mg/dL (<3.37 mmol/L) subsequently experiences an increase to ≥130 mg/dL (≥3.37 mmol/L) on two

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

In cases where any participant 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. The Investigator will contact the participant to provide appropriate medical follow-up including dietary and medication compliance counseling, which may include modification to the participant's lipid lowering regimen.

9 INVESTIGATION PRODUCT

9.1 Description, Identification, and Dosage

The Sponsor is responsible for the supply of active drug supplies together with detailed instructions (in a Pharmacy Manual) describing preparation of ARO-ANG3. Placebo (normal saline 0.9%) will be supplied by the clinical site.

Accordingly, ARO-ANG3 will be supplied as single sterile 2-mL vials containing ARO-ANG3, with the correct dose of ARO-ANG3 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-ANG3) or placebo (normal saline 0.9%), will be administered by SC injection by the Investigator or appropriately trained and qualified clinical staff designated by the Investigator. Injections will be made into the SC tissue at an appropriate site (eg, abdomen, thigh, upper arm, etc.) using a 25 to 30 gauge, ½ inch needle. The abdomen is the preferred site. Injection site is to be varied (no multiple injections into the same exact site. Alternating various locations on the abdomen is acceptable). Injection site location is to be recorded in the eCRF. Prior to IP administration, the ARO-ANG3 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 1.0 mL.

There will be no dose escalation or dose reduction (ie, the same drug dose will be administered to each participant within dose cohort) during the Double-Blind Treatment Period. During the OLE Treatment Period, participants assigned to 50 mg or 100 mg of ARO-ANG3 or placebo during the Double-Blind Treatment Period will receive ARO-ANG3 at the same dose. Participants assigned to receive 200 mg of ARO-ANG3 or placebo during the Double-Blind

Treatment Period will be assigned to receive 100 mg during the OLE Treatment Period. Participants will continue on their assigned dose in the OLE Treatment Period until the Sponsor has selected a single dose at which point all subjects will transition to the selected dose.

9.2 Supply, Preparation, Storage and Labeling of ARO-ANG3

ARO-ANG3 will be supplied as a sterile Type-1 glass 2.0-mL vial (1.2 mL nominal volume, 1.0 mL withdrawable volume).

Table 5 Investigational Product Description

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, 2ºC to 8ºC

ARO-ANG3 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-ANG3 will be supplied by the Sponsor and labeled with the drug name, batch number, expiration date (as applicable) and storage conditions. The IP will be dispensed by clinical study site staff members on the day of dosing and recorded in the drug accountability records. A Pharmacy Manual will be prepared to define the procedures for dispensing.

9.4 Allocation to Treatment

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

Eligible participants will be allocated a unique randomization number, in accordance with the randomization schedule. Each participant will be randomly assigned 3:1 to either active (ARO-ANG3) treatment in 1 of 3 dose groups (50, 100, or 200 mg) or to placebo treatment. Treatments will be administered per the randomized sequence generated by an Interactive Web Response System (IWRS). The allocation of active treatment or placebo will be performed using a block randomization algorithm.

After completing the Week 36 Visit, eligible participants may opt to enroll into the OLE Treatment Period (Table 2) and will receive the dose corresponding to their study treatment dose as assigned in the Double Blind Treatment Period. Participants who had previously received ARO-ANG3 50 mg or100 mg, or volume-matched placebo, will continue to receive the corresponding dose level of ARO-ANG3 in the OLE Treatment Period. However, participants previously assigned to the 200 mg dose group will be transitioned to the 100 mg dose group at the next dosing visit in the OLE. After the last participant in the Double-Blind Treatment Period completes the Week 36 Visit and a single dose has been selected by the Sponsor, all participants in the OLE will receive the selected ARO-ANG3 dose Q3M for the remainder of their participation in the study.

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. Injection site is to be varied (no multiple injections into the same exact site. Alternating various locations on the abdomen is acceptable).

Table 6 Injection Number and Volume Per Dose Cohort During Blinded Study Period

ARO-ANG3 Dose	Concentration	Total Injection Volume	Number of Injections per Planned Dose	Total Number of Study Injections (Blinded Period)	Total Number of Study Injections (OLE Treatment Period)
50 mg	200 mg/mL	0.25 mL	Single	2	8
100 mg	200 mg/mL	0.50 mL	Single	2	8
200 mg*	200 mg/mL	1.00 mL	Single	2	8

*The 200 mg ARO-ANG3 dose will be discontinued in the OLE period; all participants originally receiving the 200 mg dose or volume matched placebo control in the 36-Week Blinded Treatment period will be assigned to 100 mg dose.
Placebo injections of normal saline will be volume matched during Double Blind Treatment Period.

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 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-ANG3 will be retained sequestered per participant and cohort (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 IP assignment (ie, active or placebo). The pharmacy will dispense the IP 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 IP vials will be retained for an adequate period to allow accountability by the nonblinded CRA. No additional IP samples will be retained.

9.8 Blinding and Code-Break

Treatment assignment (active vs placebo) is blinded in this clinical study. Dose group assignment is not blinded, due to required injection volume differences dictated by the respective dose group. Therefore, during the Double Blind Treatment Period, participants will receive an injection of either active or placebo volume matched to the assigned dose group (Table 1). 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 Sponsor medical monitor can unblind the IP 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 assignments will be maintained under controlled access. The personnel involved in the dispensing of IP will be accountable for ensuring compliance to randomization assignment. The nonblinded CRA will review the randomization assignment in comparison to the dispensing log to 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 Subinvestigator. 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 (Double Blind Treatment Period) and Table 2 (OLE Treatment Period). Potential participants will visit the site to provide informed consent and start the Screening Period. At the Investigator's discretion and if permitted by local requirements, the first and second Screening visit (S1 and S2) assessments may be conducted concurrently within the S2 visit window (Day -35 to Day -21) as long as the participant meets stable diet, stable background medications, and fasting requirements as outlined in Sections 8.1, 8.4, and 10.2. The 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 at the Screening visit will be enrolled into the study. All dose cohorts will enroll in parallel with participants randomized 3:1 to receive ARO-ANG3 or placebo. Each participant will receive 1 SC injection on Day 1, and Week 12, for a total of 2 injections during the Double Blind Treatment Period as follows:

- ARO-ANG3 **50 mg** (n=45) or volume-matched placebo (n=15) on Day 1 and Week 12;
- ARO-ANG3 **100 mg** (n=45) or volume-matched placebo (n=15) on Day 1 and Week 12; or
- ARO-ANG3 **200 mg** (n=45) or volume-matched placebo (n=15) on Day 1 and Week 12.

All participant Screening visits and dosing visits during the Double Blind Treatment Period and OLE Treatment Period 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.

All participants will have predose and postdose PK samples collected at Day 1 and Week 12 as specified in the SOA. In a subset of participants undergoing full PK (12 active, 4 placebo in each dose cohort), PK will be measured predose and postdose on Day 1 and Week 12 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 time point: ± 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 the SOA in Table 1 and Table 2. 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 predose for non-HDL-C, HDL-C, LDL-C, VLDL-C, TG, and other specified lipid or metabolic parameters, hematology, serum lipase and insulin, HbA1c, C-peptide, coagulation, chemistry analysis, and urinalysis. Blood samples will also be collected for PK and immunogenicity analysis. Participants will have fasted for at least 10 hours prior to blood sample collection.

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

10.2 Screening Diet Stabilization Period

Confirmation of ≥ 2 weeks diet stabilization will precede lipid parameter laboratory assessments collected at Screening visits (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 American Heart Association/American College of Cardiology (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 and Table 2).

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

10.3 Selection and Screening

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

Informed consent will be performed per the Principles of the ICH GCP procedures. Documentation of the participant's fulfillment of the entry criteria, for all participants considered for the study and subsequently included or excluded, is to be completed by the Investigator, or medically qualified designee. Documentation of screening failure details will be recorded using eligibility screening forms or a participant screen failure log. Procedures outlined in the SOA

(Table 1 and Table 2) will be performed. Timing will abide by fasting restrictions outlined in Sections 8.1, 8.4, and 10.2.

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

10.4 On-Study Procedures/Assessments

Efficacy Assessments

Serum Triglycerides and Other Lipid Parameters

Fasting serum TG, LDL-C, and non-HDL-C, will be collected at the Screening after a 10-hour fast in order to evaluate lipid parameters. In order to determine the average (arithmetic mean) TG level during Screening, two fasting serum TG levels will be collected separately and consecutively at least at least 7 days but no more than 17 days apart in accordance with the SOA (Table 1).

Fasting serum TG will be measured as per the SOA (Table 1, Table 2) and assessed by a central laboratory standard method. LDL-C will be measured as per the SOA and assessed by a central laboratory. During Screening, either ultracentrifugation methodology or Martin -Hopkins methodology may be used to determine eligibility. In the event of logistical disruptions (eg, coronavirus 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, ApoA-V, and ANGPTL3) will be collected on Day 1 prior to dosing after a 10-hour fast.

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.

Magnetic Resonance Imaging

Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) for the evaluation of percentage liver fat will be conducted at Screening, after completion of the S2 visit, and at Week 24 as outlined in the SOA (Table 1) and in accordance with procedural standards detailed in the Imaging Acquisition Manual. Selected sites (where MRI-PDFF is available) will perform MRI-PDFF assessments at Screening until approximately 35 participants with baseline liver fat fraction ≥ 8% have been enrolled in each of the 3 dosing cohorts after which, MRI--PDFF will no longer be included as an evaluation. The MRI protocol used should be consistent across all

individual participant visits (same MRI imaging technique/protocol will be used predose and at Week 24 on a participant-by-participant basis). Please refer to the Imaging Acquisition Manual for further instructions.

Blood Sampling for Pharmacodynamic Analysis

Blood samples will be collected from participants through an indwelling cannula or through a fresh vein puncture. The actual blood collection time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections, for the actual time of sample collection will be incorporated at the time of data analysis. Blood samples will be collected at time points outlined in the SOA (Table 1, Table 2).

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.

Pharmacokinetic Assessments

Plasma samples for analysis of circulating ARO-ANG3 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.

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.

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-ANG3 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 IP discontinuation due to toxicity.

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

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 a blood sample drawn for these analyses.

Physical Examination

A complete physical examination will be performed at Screening and as per SOA (Table 1, Table 2). At Screening, height (centimeters, without shoes) and weight (kilograms, without shoes) will be measured. At all other time points outlined in the SOA, a symptom-directed physical examination will be performed if indicated.

Vital Signs

Systolic/diastolic blood pressure (mmHg), temperature (°C), heart rate (beats/minute), respiratory rate (breaths/minute) will be obtained at time points outlined in the SOA (Table 1, Table 2) after the participant is sitting for at least 3 minutes. Vitals signs will be obtained prior to venipuncture and other invasive procedures.

Electrocardiogram

A single 12-lead ECG measurement will be obtained at time points outlined in the SOA (Table 1, Table 2) 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 other invasive procedures.

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, Table 2). Refer to the laboratory manual for additional details on clinical laboratory tests.

Biochemistry: Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, calculated eGFR, creatine kinase, uric acid, phosphate, total calcium, anion gap, cholesterol, 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: 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, prothrombin time with INR and fibrinogen.

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

Microscopic urinalysis will be performed if indicated: White blood cells, RBC, epithelial cells, bacteria.

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

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

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

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

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

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, Table 2) will be completed. Participants who discontinue ARO-ANG3 due to SAE will be encouraged to remain available for follow-up for medical monitoring until resolution.

Follow-Up Procedures

Contact will be made to each participant and documented to verify AEs occurring over the 24 hours following doses at Day 1 and at Week 12 (Table 1) during the Double Blind Treatment Period and following doses administered Q3M (Table 2) during the OLE Treatment Period.

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, noninvasive 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:

Table 7 Assessment Windows

Predose	Any time during the study visit, and before first dose

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

Abbreviation: PK = pharmacokinetic.

[1]Only for Full PK assessments.

10.6 Pregnancy Testing and Contraception Requirements

Female participants of childbearing potential will have urine pregnancy tests at each Screening visit, Day 1 (baseline), and at subsequent study visits as indicated in Table 1 and Table 2. Females not of childbearing potential must be either surgically sterile or postmenopausal (defined as cessation of regular menstrual periods for at least 12 months) 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 during the Screening Period or on Day 1 predose will not be enrolled 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 contraception during the study and for at least 24 weeks following the last dose of IP.

- Using twice the normal protection of birth control by using a condom AND one other form of contraception; either birth control pills (The Pill), or injectable birth control, birth control patch, vaginal contraceptive ring, or contraceptive implant associated with inhibition of ovulation, or intrauterine device.
- Surgical sterilization as a single form of birth control: ie, tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy or equivalently effective surgical form of birth control.
- True sexual abstinence for the duration of the study and for at least 24 weeks following the last dose of IP, is acceptable only when in line with the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not considered "true" abstinence and are not acceptable methods of contraception.

11 ADVERSE EVENTS

The Investigator and clinical facility staff are responsible for detection, recording, and reporting of events that meet the criteria and definition of various AEs as listed below. AEs will be recorded from time of signed consent through to end of the 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.

Adverse events 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 (eg, 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;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is a medically important event or reaction.

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

11.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events

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

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

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

11.3 Timing, Frequency, and Method of Detecting Adverse Events

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

All AEs occurring after informed consent and on or before the final visit must be reported as AEs; only AEs that occur postdose will be considered treatment emergent. All AEs must be recorded irrespective of whether they are considered drug related.

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

11.4 Recording of Adverse Events

When an AE occurs, it is the responsibility of the Investigator or medically qualified designee to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator or medically qualified designee will then record the AE on the AE CRF. Additional reporting requirements for an AE meeting any serious criterion 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

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.

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 Times as provided in Appendix 2. For data analysis purposes, AEs at the injection site with reported terms of bruising or hematoma will not be considered LISRs. Injection site reactions are graded based on CTCAE.

- Grade 1: Tenderness with or without associated symptoms (eg, warmth, erythema, itching).
- Grade 2: Pain; lipodystrophy; edema; phlebitis.
- Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Results in death.

Assessment of Causality

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

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

The Investigator (or medically qualified designee) will provide the assessment of causality utilizing 3 possible categories: Not Related, Possibly Related, and Probably Related.

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

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

An AE will be considered “Possibly related” when there is a reasonable possibility that the incident, experience, or outcome may have been caused by the product under investigation.

An AE will be considered "Probably related" when there are facts, evidence, or arguments to suggest that the event is related to the product under investigation.

Follow-up of Adverse Events

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

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

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

11.6 Prompt Reporting of Serious Adverse Events

Any AEs meeting serious criteria MUST be reported promptly to the designated Pharmacovigilance Contract Research Organization (CRO), and the IRB/EC.

Completion and Transmission of the Serious Adverse Events Reports

Once an Investigator becomes aware that an SAE has occurred in a study participant, he/she will report the information on an SAE report form to the designated Pharmacovigilance CRO within 24 hours. 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.

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

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

Sponsor Emergency Contact

[redacted]

Pregnancy Reporting

Pregnancy occurring in a participant or in the female partner of a male participant during the study must be reported on a pregnancy reporting form or on an SAE form to the designated Pharmacovigilance CRO within 24 hours of initially becoming aware of the pregnancy by the Investigator.

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

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.

Serious Adverse Event Reports to the IRB/EC

The Investigator, or responsible person per local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the EC.

11.7 Regulatory Requirements for Reporting of Serious Adverse Events

The Investigator or medically qualified designee will promptly report all SAEs in accordance with the procedures detailed in Section 11.6. 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 the Sponsor to relevant regulatory authorities, Investigators and IRBs/ECs in accordance with the Sponsor's procedures and local regulatory requirements.

11.8 Poststudy Adverse Events

A poststudy AE is defined as any event that occurs outside of the AE detection period defined in Section 11.3.

Investigators are not obligated to actively seek AEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the IP, the Investigator will promptly notify the Sponsor.

11.9 Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests, a change in existing therapy), even if it occurs during the pretreatment or post-treatment period, will be reported promptly (refer Section 11.7).

12 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Statistical analyses and descriptive summaries will be presented for primary, secondary and exploratory endpoints using appropriate methods. Any proposed amendments to the Statistical Analysis Plan will only occur prior to database lock. Descriptive statistics will be presented for all analyses unless otherwise specified. For continuous variables, data will be presented as number (n), mean, median, standard deviation (SD), minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percent. Data will be analyzed by treatment groups of ARO-ANG3 50, 100, and 200 mg and placebo.

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

12.1 Endpoints

Primary Endpoint

The primary endpoint in this study is:

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

Secondary Endpoints

The following secondary endpoints will be evaluated during 36-week double blind study period:

- Percent change from baseline in fasting TG over time through Week 36
- Percent change from baseline at Week 24 and over time through Week 36 in fasting non–HDL-C

- Percent change from baseline at Week 24 and over time through Week 36 in fasting total apolipoprotein (Apo) B
- Percent change from baseline at Week 24 and over time through Week 36 in fasting LDL-C using ultracentrifugation;
- Percent change from baseline at Week 24 and over time through Week 36 in angiopoietin-like protein 3 (ANGPTL3)
- Percent change from baseline at Week 24 and over time through Week 36 in fasting HDL-C;
- Plasma concentrations of ARO-ANG3 over time through Week 12; and
- The frequency and severity of AEs and SAEs at Week 24 and over time through Week 36.

The following secondary endpoints will be evaluated in the OLE portion of the study:

- Percent change from baseline in fasting TG, non–HDLC, total apolipoprotein (Apo) B, LDL-C using ultracentrifugation, ANGPTL3, HDL–C, and plasma ARO-ANG3 at all visits as described in Table 2 (SOA).
- The frequency and severity of AEs and SAEs through Month 24.

Exploratory Endpoints

The following exploratory endpoints will be evaluated in this study:

- Change from baseline over time during double-blind study period as well as open-label treatment period 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-III, ApoCII, ApoA-I, ApoA-V, and ApoA-1
- Change from baseline to Week 24 and over time through Week 36 during the double-blind study period as well as over time in the open-label treatment period in fasting serum blood glucose, HbA1c, homeostatic model assessment for insulin resistance (HOMA-IR) and C-peptide;
- Proportion of participants requiring emergent apheresis over time during the double-blind study period as well as during the OLE treatment period;
- Change from baseline to Week 24 in liver fat content using magnetic resonance imaging-proton density fat fraction (MRI-PDFF; only in participants with a liver fat fraction of ≥ 8% at Screening); and
- Emergence of and levels of anti-drug antibodies to ARO-ANG3 in those receiving ARO-ANG3 over time during the double-blind study period as well as over time during the open-label treatment period.

12.2 Analysis Populations

The following study populations are defined for 36-week double blind study period and OLE Treatment Period in this study, respectively:

- ***Full Analysis Set (FAS)***: All randomized participants who receive at least 1 dose of IP during the study period. 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 during the study period. 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 180 participants randomly assigned to treatment in a 3:1 (active to placebo) ratio within each dosing cohort, the study will have greater than 98% power to detect at least 1 active treatment dose cohort which is significantly different from placebo, and at least 95% power to detect all treatment dose cohorts which are significantly different from placebo using a two-sided test, with 5% level of significance, adjusted for multiplicity. These estimates are based on the assumption of 35% to 60% reduction from baseline in fasting TG in the 3 active treatment dose cohorts and no change in fasting TG in the pooled placebo cohort. The SD is assumed to be 65% in the pooled placebo group and 35% to 55% in the active treatment groups (Graham 2017).

12.4 Stratification

Enrollment will be stratified into placebo and active groups based on:

- Level of LDL-C at Screening ≥ 100 versus < 100 mg/dL (≥ 2.59 versus < 2.59 mmol/L).

Prespecified subgroup analyses will be conducted for:

- Participants with reported history of ASCVD (coronary artery disease, symptomatic peripheral artery disease, Stroke/transient ischemic attack).

12.5 Analysis Methods

Screening Data

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

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

Efficacy and Pharmacodynamics Analysis

The primary analysis will be performed using a mixed-model repeated measures approach with treatment, study visit, stratification factor, and baseline TG level included as model terms. The model will also include treatment by visit and treatment by baseline interaction terms. The primary estimate of interest will be the difference in means between each active treatment dose group and pooled placebo group, evaluated at Week 24 during double-blind study period. 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 during double-blind study period will be analyzed in a similar manner to the primary endpoint, unless otherwise noted. Descriptive statistics of biomarker changes will include mean, median SD, minimum, and maximum. The frequency and severity of AEs and SAEs at Week 24 and over time through Week 36 during double-blind study period will be summarized with descriptive statistics.

For efficacy variables during open label treatment period, the measurements and changes and/or percent changes from baseline over time will be summarized descriptively.

Data will be summarized as applicable for the following: serum ANGPTL3, ApoC-II, ApoCIII, LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, LDL-C/HDL-C, LP(a), TG, ApoB-48, ApoB-100, total ApoB, ApoA-I, ApoA-V, HbA1c, C-peptide, changes in serum insulin, HOMAIR, and changes in serum glucose.

For primary endpoint (TG) analysis at Week 24 during double-blind study period, the laboratory value for endpoint analysis will be the arithmetic mean of 2 values taken during Week 24. 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 Day 1 predose assessment and two fasting assessments during screening period. For other efficacy endpoints, only Day 1 predose assessment will be used as the baseline.

After the last subject in the Double Blind Treatment Period completes the Week 36 Visit, an interim analysis will be conducted to review the efficacy and safety data in order to select a single dose level for all subjects in OLE Treatment Period and for the remainder of their participation in the trial.

For efficacy variables during open-label treatment period, the measurements and changes and/or percent changes from baseline over time will be summarized descriptively.

Pharmacokinetic Analysis

Plasma concentrations of ARO-ANG3 will be measured in all participants to evaluate trough and postdose levels through the study (see SOA in Table 1).

Full PK group: In each of the dose cohorts, 16 PK participants (12 active, 4 placebo for a total of 48 participants for PK) will be enrolled at the designated PK sites. Plasma concentrations will be measured predose and serially postdose on Day 1 and Week 12 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 ≥15 minutes postdose on Day 1 and Week 12 as per the SOA.

Safety/Tolerability Analysis

In general, safety analyses will be performed and the results summarized by treatment groups. Post-treatment safety assessments will be compared with measurements recorded at baseline. Treatment-emergent AEs will be summarized using the latest version of the MedDRA by System Organ Class (SOC) and PT. The incidence of AEs, SAEs, related AEs, related SAEs, and AEs leading to discontinuation, will be summarized by treatment group and by dose level per SOC, PT, and severity. All AEs will also be presented in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome. The incidence of laboratory abnormalities will be assessed using descriptive summary statistics and shift tables. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Abnormal physical examination findings will be summarized by time point and presented in listings. The ECG parameters, changes from baseline, and qualitative assessments will be summarized. Pregnancy and FSH test results will be listed separately by time point.

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.

12.6 Data Recording and Quality Control

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

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

13 STUDY APPROVAL AND CONDUCT

The following conditions will be met.

13.1 Regulatory Approval

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

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

Prior to initiation of the study, written IRB/EC approval of the Protocol and Informed Consent Forms, based on the principles of ICH GCP, will be received. A copy of the signed and dated letter of approval will be provided to the clinical site and 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 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 lab reference ranges may only be permitted in limited circumstances and only with prior Sponsor approval.

13.8 Protocol Deviations

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

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

- Failure to adhere to study exclusion and inclusion criteria;

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

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

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

13.9 Termination of the Study

The Sponsor reserves the right to discontinue the study at any time. Reasons will be provided in the event of this happening. The circumstances under which the study may be terminated include:

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

The Investigator reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.

14 STUDY ADMINISTRATION

14.1 Study Monitoring

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

In accordance with applicable regulations, GCP and 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 visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity and enrollment rate.

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

During these site visits, the study monitor will:

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

This will be done to verify that the:

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

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

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

- Return of all study data to the Sponsor;
- Data queries;
- Accountability, reconciliation and arrangements for unused IP(s);

- Inventory and final disposition (eg, destruction, shipping to repository, etc.); and
- Review of site study records for completeness.

14.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and clinical site agree to notify Sponsor as soon as possible following awareness of an impending regulatory inspection. The Investigator and clinical site agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

14.3 Records Retention

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

The Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor 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 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]

[redacted]

15.3 Publication

[redacted]

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17 Appendix 1

Table 8: Liver Related Study Modification and Follow-Up Guidelines for Participants

Treatment-Emergent AST or ALT	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
Normal baseline: AST or ALT >3× ULN Elevated baseline: AST or ALT >2× baseline or ≥300 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome or hemolysis- no change in baseline TBL	None	Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies[1] Follow-up for symptoms.
Normal baseline: AST or ALT >5× ULN Elevated baseline: AST or ALT >3× baseline or ≥300 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome or hemolysis- no change in baseline TBL	None	Discontinue IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies[1] Refer to guidelines for close observation below. Follow-up for symptoms.
Normal baseline: AST or ALT >3× ULN Elevated baseline: AST or ALT >2× baseline or ≥300 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome or hemolysis- no change in baseline TBL	Symptoms of clinical hepatitis – severe fatigue, nausea, vomiting, right upper quadrant pain or; immunologic reactions (eg rash, >5% eosinophilia)	Interrupt IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies.[1] IP can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred. Refer to guidelines for close observation below. Follow-up for symptoms.
Normal baseline: AST or ALT >3× ULN Elevated baseline: AST or ALT >2× baseline or ≥300 U/L (whichever occurs first)	TBL >2× ULN or increased INR to >1.5 In participants with Gilbert's syndrome or hemolysis- doubling of direct	None	Interrupt IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies.[1]

Treatment-Emergent AST or ALT	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
	bilirubin if baseline >0.5 mg/dL		Initiate close observation and workup for competing etiologies.[1] IP can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred.

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

[1] 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 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, alkaline phosphatase, 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.

18 Appendix 2

Table 9: Local Injection Site Reactions (LISRS)

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

Injection site discomfort	Injection site abscess
Injection site discoloration	Injection site abscess sterile
Injection site erythema	Injection site atrophy
Injection site irritation	Injection site calcification
Injection site inflammation	Injection site cellulitis
Injection site induration	Injection site dermatitis
Injection site paint	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 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:

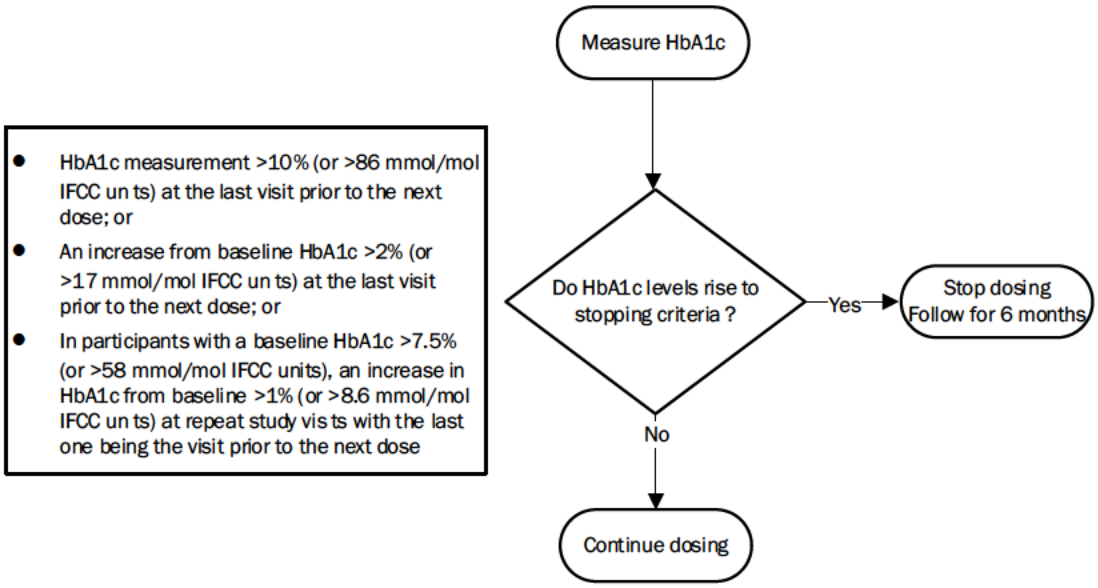
(A/B)*, where A = number of injections with a local injection site reactions, and B = total number of injections.

19 Appendix 3

Study drug discontinuation criteria for increased HbA1c

- Participants should discontinue IP if they meet the following criteria (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
  - For 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 the above criteria will be followed for 6 months after their last dose per the Schedule of Assessments.



Guidelines for Excessive Increases in HbA1c

The following guidelines should be followed for increases in HbA1c:

- Investigators are encouraged to evaluate diabetes status and adjust diabetes treatment according to clinical practice and diabetes care guidance.
- At the Investigator's discretion, any participants with worsening diabetic control may return for an unscheduled visit for evaluation of HbA1c prior to the next planned dose to confirm continued treatment eligibility.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL NUMBER:	**AROANG3-2001**
STUDY TITLE:	**A Double-blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-ANG3 in Adults with Mixed Dyslipidemia**

Protocol Amendment 1, Dated 1-March-2021

- Established minimum time on stable statin regimen to ≥4 weeks
- Revised treatment stopping rules due to liver transaminase elevations
- Revised possible outcomes of Data Safety Committee meetings
- Revised key inclusion criteria relating to triglyceride (TG) level upper limit, refined restrictions on lipid lowering medicadtion and other background therapies;
- Extended duration of contraceptive use by 12 weeks and requires minimum hormonal contraceptive use duration for women of child-bearing potential prior to enrollment
- Revised exclusion criterion related to medical history and laboratory signs;
- Removed PK sample collection timepoint at Week 36/EOS and revised associated secondary endpoint
- Removed TG stratification and associated prespecified subgroup analyses
- Extended contraception requirement to 24 weeks after last administration of investigstional product
- Revised the Schedule of Assessments (Table 1) to:
    - include three distinct screening visits
    - add pregnancy testing for women of childbearing potential at each study visit
    - add urine protein dipstick test
    - clarify fasting requirements relative to assessments and timepoints
    - separate TG, LDL-C, HDL-C and non-HDL-C testing and clarify timepoints
    - require waiing at least 15 minutes prior to postdose Sparse sample PK collection
- Removed option for home study visit at Week 12 dosing
- Clarified baseline values for TG, HDL-C, and non-HDL-C
- Revised restrictions on concomitant medications during treatment period

Protocol Amendment 2, Dated 11-November-2021

- Added the 24-month Open-Label Extension (OLE) Treatment Period with quarterly dosing (Q3M) following the Blinded Treatment Period for a total study duration of approximately 35 months and clarified plans for dose level assignment in the OLE Treatment Period
- Updated Treatment Stopping Rules
- Updated eligibility criteria:
    a) Updated requirement for prior evidence of fasting TG

b) Allowed for participants documented as statin interolerant
c) Extended time between qualifying TG collections during Screening
d) Added anticoagulation therapy, testoerone replacement therapy, and thyroid hormone replacement therapy to the list of restricted medications
e) Clarified hypertension exclusion criterion
f) Replaced urine protein exclusion with spot urine protine/spot urine creatinine ratio
g) Revised alcohol unit definitions and allowable daily consumption limit
h) Added eligibility criterion for OLE Treatment Period

- Updated Table 1, 36-Week Double-Blind Period Schedule of Assessments as follows:
  a) Adjusted Screening Visit (S1) window to permit overlap with S2 Visit
  b) Allowed flexibility to combine S1 and S2 where permitted
  c) Clarified collection timing of second lipid collection after Week 24 and Week 36
- Added Table 2: Open-Label Extension Treatment Period Schedule of Assessments
- Clarified that qualifying LDL-C value at Screening may be based on either Martin-Hopkins method or ultracentrifiguation method.
- Updated lipid monitoring parameters for increased LDL-C results following the Week 24 visit from baseline to notify the investigator and Medical Monitor and unblind LDL-C participant values as needed to provide appropriate medical follow-up
- Revised lipid testing restrictions to allow for provision of lipid results to Investigator in the OLE Treatment Period
- Updated Statisticial section to include interim analysis at Week 36
- Added secondary endpoints in the OLE portion of the study
- Updated exploratory endpoints to include both blinded and OLE portions of the study
- Clarified that the mean of the two fasting screening values together with the fasting Day 1 TG value will serve as the baseline value for the primary endpoint analysis
- Updated the circumstances under which the sponsor may terminate the study
- Revised pregnancy reporting and collection of information for up to 1 year
- Updated Liver Related Study Modification and Follow-Up Guidelines for Participants (Appendix 1)

Protocol Amendment 3, Dated 22-November-2022

- Removed 200 mg dose from the 24-Month OLE treatment period
- Speified plan to transition subjects assigned to the 200 mg dose cohort to the 100 mg dose cohort in the OLE
- Added guidelines for new study drug discontinuation critieris in response to HbA1c elevation
- Added HbA1c laboratory test at Month 1 and Month 2 of the OLE treatment period
- Updated risk assessment for study participants in response to HbA1c elevation