Arrowhead Pharmaceuticals, Inc.
Protocol #: AROANG3-2001

A Double-blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-ANG3 in Adults with Mixed Dyslipidemia

Statistical Analysis Plan

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Prepared by:

[redacted]

Approved by:

[redacted]

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List of Abbreviations and Definitions of Terms

Abbreviation	Term
ADA	Anti-drug Antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
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
ARO-ANG3 Injection	Clinical drug product solution ready for SC injection
ARO-ANG3	Short name for ARO-ANG3 Injection
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the concentration-time curve
BLQ	Below the limit of quantification
BMI	Body mass index
CI	Confidence interval
CM	Concomitant medication
COVID	Corona virus disease
CTCAE	Common Terminology Criteria for Adverse Events
CS	Clinically significant
CV	Coefficient of variation
DB	Double-Blind
DBP	Diastolic blood pressure
DSC	Data Safety Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
FCS	Familial Chylomicronemia Syndrome
FSH	Follicle-stimulating hormone
GM	Geometric mean
GPIHBP1	Glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1
HbA_{1c}	Glycosylated hemoglobin
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment for insulin resistance

HR	Heart rate
IDL	Intermediate density lipoprotein
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
LFT	Liver function test
LISR	Local injection site reaction
LLOQ	Lower limit of quantification
LMF1	Lipase maturation factor 1
Lp(a)	Lipoprotein (a)
LPL	Lipoprotein lipase
LS	Least-squares
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing not at random
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
NCA	Noncompartmental analysis
non-HDL-C	Non-low density lipoprotein cholesterol
OC	Observed cases
OLE	Open-Label Extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred Term
QT	QT interval - a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOA	Schedule of Assessments
SOC	System Organ Class
SBP	Systolic blood pressure
TEAE	Treatment-emergent adverse event
TG	Triglyceride(s)
TLF	Tables, listings, and figures
TRL	Triglyceride-rich lipoprotein
ULN	Upper limit of normal
VLDL	Very low density lipoprotein
VLDL-C	Very low density lipoprotein cholesterol

I. Introduction

A. 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. 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 due to elevated triglycerides (TG) and TG-rich lipoprotein levels (TRLs).

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 lipoprotein(a) (Lp[a]). Epidemiologic studies have shown that non-HDL-C is a stronger predictor of ASCVD morbidity and mortality than LDL-C.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on Protocol AROANG3-2001 Amendment 2 dated 11th November 2021.

This SAP will not repeat all the definitions given in the protocol but will provide further details of the summaries and analyses planned therein. The plan may be modified until the time of treatment unblinding. Any deviations from the analysis plan, including any time after the time of treatment unblinding, will be documented as such in the study report.

C. Changes from Planned Analyses in the Protocol

No deviations from the planned analyses in the protocol have been noted.

II. Protocol Objectives

A. Primary 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.

III. Study Endpoints

A. Primary

The primary endpoint is percent change from baseline at Week 24 in fasting TG.

B. Secondary

The following secondary endpoints will be evaluated during the 36-week Double-Blind (DB) Treatment 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*
- 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
- The frequency and severity of AEs and SAEs over time through Week 36.

*LDL-C will use Friedewald formula, Martin-Hopkins methodology and ultracentrifugation.

The following secondary endpoints will be evaluated in the open-label extension (OLE) Treatment Period:

- Percent change from baseline in fasting TG, non-HDL-C, total apolipoprotein (Apo) B, LDL-C*, ANGPTL3, HDL-C, and plasma ARO-ANG3 at all scheduled visits
- The frequency and severity of AEs and SAEs through Month 24.

*LDL-C will use Friedewald formula, Martin-Hopkins methodology and ultracentrifugation.

C. Exploratory

The following exploratory endpoints are defined in this study:

- Change from baseline over time during DB Treatment Period as well as over time during 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 DB Treatment Period as well over time in the OLE Treatment Period in fasting serum blood glucose, HbA_{1C}, homeostatic model assessment for insulin resistance (HOMA-IR) and C-peptide
- Proportion of participants requiring emergent apheresis over time during DB Treatment Period as well as during the OLE Treatment Period
- Change and percent 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)
- Emergence of and levels of anti-drug antibodies to ARO-ANG3 in those receiving ARO-ANG3 over time during DB Treatment Period as well as over time during the OLE Treatment Period.

IV. Study Design

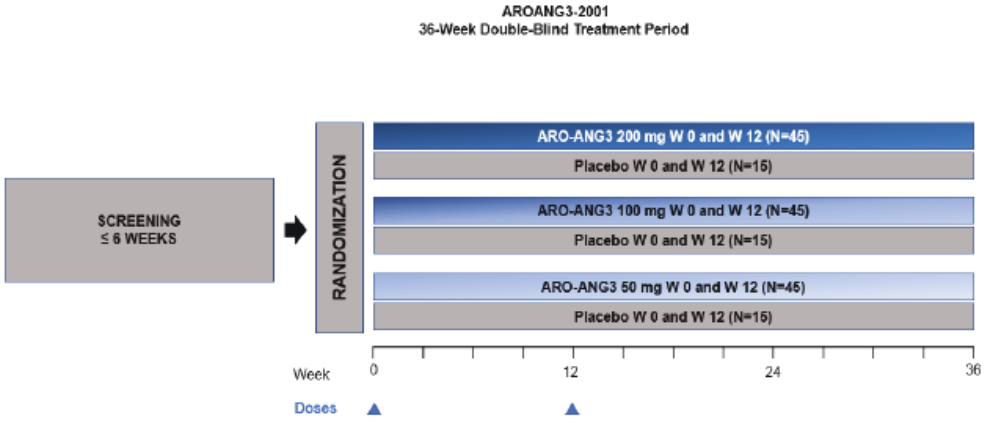
A. Design Overview

This is a randomized, double-blind, placebo-controlled, Phase 2b clinical study with OLE Treatment Period. 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.

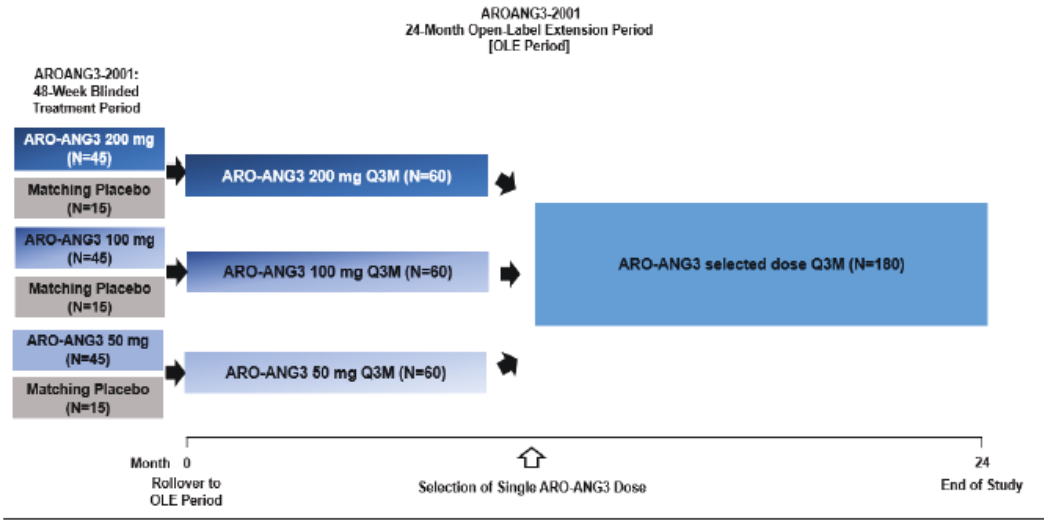
Participants must maintain a stable diet and stable lipid-lowering therapy, including statins (unless considered statin intolerant per protocol section 8.4), and other relevant background medications, as applicable, throughout the Screening Period.

A total of approximately 180 participants will be enrolled in the study. All dose cohorts will enroll in parallel with 60 participants per dose cohort randomly assigned in a 3:1 ratio to receive ARO-ANG3 (50 mg, 100 mg, or 200 mg) or matched placebo. Each participant will receive Subcutaneous (SC) injections: 1 on Day 1 and 1 at Week 12 for a total of 2 injections during the 36-Week Double-Blind Treatment Period as follows:

Study Schema



Abbreviations: N = number of participants; W = week



Abbreviations: N = number of participants; Q3M = every 3 months.

Following completion of the Week 36 Visit, eligible participants will be invited to continue in the 24-Month OLE Treatment Period. Participants in the OLE will be dosed quarterly and will receive the same dose level to which they were randomized in the DB Treatment Period until a single dose has been selected by the Sponsor. After the last subject in the DB 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 on the OLE.

B. Study Population

This study will be conducted in adults with mixed dyslipidemia (LDL-C ≥ 70 mg/dL [1.8 mmol/L] OR non-HDL-C ≥ 100 mg/dL [2.59 mmol/L], after at least 4 weeks of stable optimal statin therapy (unless documented as statin intolerant per protocol section 8.4), AND mean fasting 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 in 25 centers globally receiving ARO-ANG3 or placebo in 3:1 ratio per dosing regimen.

C. Sample Size Predictions

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.

D. Treatment Randomization

Eligible participants 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, stratified based on level of LDL-C at Screening (≥100 mg/dL versus <100 mg/dL). 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 minimization randomization algorithm initially and using block randomization for subject replacement, as detailed in the IWRS vendor's Randomization Requirements Specification.

E. Assessment Schedule

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

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

During the 36-Week DB Treatment Period, participants will attend study visits on Day -42 to Day -21 (Screening 1), Day -35 to Day -21(Screening 2), Day -21 to Day -1 (Screening 3) during screening phase, Day 1, 2, week 4, week 8,

week 12, 24 hour post week 12, week 16, week 20, week 24, week 28, and week 36 / early termination. Detailed Schedule of Assessments is included in clinical study protocol Table 1.

During the 24-Month OLE Treatment Period, participants will attend study visits on Day 1, month 1, month 2, month 3, month 6, month 9, month 12, month 15, month 18, month 21 and month 24 (end of study/ early termination). Detailed Schedule of Assessments is included in clinical study protocol Table 2.

V. General Analytical Considerations

A. Data Sources

Statistical analysis will be performed following IQVIA Biotech standard operating procedures and on the IQVIA Biotech computer network. All statistical analysis will be performed using SAS® Version 9.4 with program code prepared specifically for the project by qualified IQVIA Biotech statisticians and SAS programmers. Normality and other statistical assumptions for statistical analyses will be evaluated as appropriate.

All observed and derived variables (e.g., change from baseline, percentage change from baseline, and response status) that are analyzed or summarized will be listed by participant as appropriate. Descriptive statistics will provide an overview of the safety and efficacy results. For categorical parameters, the number and percentage of participants in each category will be presented. For continuous parameters, descriptive statistics will include number of patients, mean, standard deviation (SD), median, minimum, and maximum.

Assessments for fasting lipid and other lab parameters done under non-fasting status will be excluded from summary and analysis.

Data will be analyzed by treatment groups of ARO-ANG3 50, 100, and 200 mg, ARO-ANG3 (pooled), and Placebo (pooled).

B. Baseline and Study Day

Day 1

Day 1 is defined as the date of first administration of study drug. If the date of first study drug administration is missing, date of randomization will be used as Day 1. Study day is calculated relative to the date of Day 1 as follows:

- For any events on or after the first administration of the study drug, study day is calculated as: event date – date of first administration of study drug + 1.

- For any events before the first administration date, study day is calculated as: event date – date of first administration of study drug. As such, one day before the first administration date is study day – 1.

Baseline

Unless otherwise specified, baseline (Overall Baseline) is defined as the last observed value of the parameter of interest prior to the first administration of study treatment (this includes unscheduled visits).

- In particular, for fasting TG, baseline is defined as the geometric mean of Day 1 predose assessment and two fasting TG values collected during the Screening period. If fewer than 3 predose assessments are available, the geometric mean will be taken from the available results. For other efficacy variables, baseline is defined as the predose value on Day 1.

Where applicable, baseline is further defined for the OLE Treatment Period (OLE Baseline) as the last observed value of the parameter of interest prior to the first administration of study treatment in OLE Treatment Period (OLE Day 1).

For each type of Baseline, change from baseline is calculated as post-baseline values minus baseline values. Percentage change from baseline is calculated as ratio of change from baseline and baseline expressed as a percentage.

Percent change from baseline = ((post-baseline – baseline)/baseline) *100%

End of treatment (EOT)

EOT is the date of treatment completion or discontinuation as recorded in the eCRF.

End of study (EOS)

EOS is the date of study completion or discontinuation as recorded in the eCRF.

C. Analysis Visit Window

All efficacy and safety endpoints will be analyzed according to the nominal visits (i.e. assigned visit) except for assessments collected on early termination and unscheduled visits. Early termination and unscheduled visits will be re-numbered to an analysis visit based on their windowed visits defined by actual study day. If more than one visit or assessment (scheduled or unscheduled) occurs within a single visit window, then the analysis will take

the one closest to the target day. If the 2 visits are equidistant from the target day, the visit with later date and time will be used.

At Week 24 and Week 36, fasting lipid/pharmacodynamic endpoints will be collected twice, separated by at least 2 days and no more than 7 days after a 10 hour fast. For fasting TG, the geometric mean of two values will be using for analysis. If only one value is available, then this value will be used for endpoint analysis at that visit. For other endpoints, the scheduled Week 24 and Week 36 values will be used for analysis.

The following analysis visit windows will apply to early termination and unscheduled visits:

DB Treatment Period

Visit	**Target Day**	**Analysis Window**
Day 1	1	On or prior to Day 1
Week 4	29	Post first dose – Day 43
Week 8	57	Day 44 – Day 71
Week 12	85	Day 72 – Day 99
Week 16	113	Day 100 – Day 127
Week 20	141	Day 128 – Day 155
Week 24	169	Day 156 – Day 183
Week 28	197	Day 184 – Day 225
Week 36	253	≥ Day 226

OLE Treatment Period

Visit	**Target Day**	**Analysis Window**
Day 1	1	Nominal only (≤ 30 days after week 36 visit in Double-Treatment Period)
Month 1	31	Post Day 1 – Day 47
Month 2	62	Day 48 – Day 77
Month 3	92	Day 77 – Day 138
Month 6	184	Day 139 – Day 230
Month 9	275	Day 231 – Day 321
Month 12	366	Day 322 – Day 412
Month 15	458	Day 413 – Day 504
Month 18	549	Day 505 – Day 595
Month 21	640	Day 596 – Day 686
Month 24	732	≥ Day 687

Certain efficacy and safety endpoints are not scheduled to be assessed at each post-baseline visit, such as the ECGs. If the date of an early termination or unscheduled visit does not fall into the analysis window of any scheduled visit, the assessment will be mapped to the scheduled post-baseline visit closest to the assessment date.

D. Missing Data

Participants may be missing specific data points for various reasons. Queries will be made to the sites to distinguish true missing values from other unknown values (e.g. due to measurement of sample processing error). All attempts will be made to capture missing or partial data for the study prior to database lock.

Missing values will not be imputed except for missing or partial dates of AEs, concomitant status for medication and procedures, and for missing or partial dates where a complete date is required for calculations. When relevant, sections below will address how missing data will be handled for the particular analyses.

Non calculable or missing values for LDL-C using Friedewald formula will be imputed with LDL-C using ultracentrifugation.

Adverse events (AEs):

- AEs will be flagged as treatment emergent AEs (TEAEs) using valid answers to the questions “For events that occurred on Day 1, did the event occur before start of study drug administration?” on the eCRF regardless of whether or not the AE onset date is complete. AEs that cannot be definitely determined as occurring prior to study drug administration will be counted as TEAEs unless either the partial start date/time or a partial or complete end date/time documents the AE as occurring prior to treatment.

- TEAE start date:
  - TEAE imputed dates will not be earlier than the participant's Day 1 date.
  - If all year, month, and day are missing then use the participant's Day 1 date.
  - If year is available but day and month are missing, the day and month for the start date will be set to the 1st of January of the onset year.
  - If year and month are available but day is missing, the day will be set to the 1st of the month of the onset year.

- End date will not be imputed

Concomitant medications (CM):

- Medications with missing or partial end dates will be assumed to be concomitant unless a partial end date documents it as ending prior to treatment.

- CM start date:
  - If all year, month, and day are missing then use the participant's Day 1 date.
  - If year is available but day and month are missing, the day and month for the start date will be set to the 1st of January of the onset year.
  - If year and month are available but day is missing, the day will be set to the 1st of the month of the onset year.

- End date will not be imputed

Procedures

- Procedures with missing or partial end dates will be counted as concomitant unless a partial end date documents it as ending prior to the participant's Day 1 date.

The original missing or partial date, the imputed complete date, and an indicator variable that indicates which dates were imputed will be retained in the database.

E. Multiple Study Centers

Descriptive summaries of the primary efficacy endpoint will be presented for each individual study center to explore any potential heterogeneity across sites.

F. Covariate Adjustment in Primary Analysis

The primary and secondary efficacy analyses will be adjusted for stratification factor (level of LDL-C at Screening [≥100 mg/dL versus <100 mg/dL], and the relevant baseline values.

Additional covariates that may be considered are:

- Age (years)
- Sex (male, female)
- Race (White, Asian, all other races)
- BMI (kg/m^2)

Details will be provided as described in relevant sections below.

G. Sample Size Reassessment

Not applicable.

H. Interim Analyses or Timing of Analyses

After the last subject in the DB 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.

I. Data Safety Committee (DSC)

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.

Further details (e.g., frequency of data reviews and study committee composition and membership) will be provided in the DSC charter. The charter will define the criteria, frequency of reviews, data, and source documentation required to adjudicate all events.

J. Test Sizes

Any tested hypotheses will be tested against two-sided alternatives, using procedures that provide an expected probability of Type I error (α) of 0.05. All inferential statistics (ie, p-values) will be considered as exploratory.

K. Multiple Comparisons

When performing the primary analysis, the adjustment for multiplicity of testing ARO-ANG3 arms versus placebo will be carried out using Holm's step-down procedure.

Aside from the control of Type I error in the primary analysis of the primary endpoint, no control for the effect of multiple comparisons is planned. Any inferential statistics (ie, p-values) for secondary and exploratory endpoint analyses will be considered only as exploratory.

L. Analysis Populations

The following study populations are defined in this study:

1. Full Analysis Set Overall (FAS Overall)

All randomized participants who receive at least 1 dose of IP during the study period. All DB Treatment Period efficacy analyses will be performed using FAS. Participants will be analyzed according to the treatment assigned at randomization.

2. Safety Analysis Set

All participants who receive at least 1 dose of IP during the study period. All overall and DB Treatment Period safety and tolerability analyses will be performed using this set. Participants will be analyzed according to the treatment they actually received.

3. Full Analysis Set OLE (FAS OLE)

All randomized participants who receive at least 1 dose of IP during the OLE Treatment Period. All OLE Treatment Period efficacy, safety, and tolerability analyses will be performed using this set.

4. Per-protocol Population (PPS)

All participants in the FAS population who have completed the Week 36 visit without any major protocol violations that could influence the validity of the data for the primary and secondary efficacy evaluations. All criteria to exclude participants from the PPS will be made based on a blinded review of the data prior to the unblinding of the study.

A participant may be excluded from the PPS if any of the following criteria are met:

- Not meeting Inclusion/Exclusion criteria
- Usage of restricted medications/treatments
- Noncompliance with the trial treatment regimen

Analyses on PPS will be of supportive purpose and limited to the primary endpoint and the secondary endpoints.

5. PK Analysis set

PK Analysis Set includes all participants who have received at least one dose of active drug and have at least one PK concentration data. Participants are assigned to “Full PK Analysis Set” or “Sparse sample PK Analysis Set” as defined in the study protocol.

6. MRI-PDFF Analysis Set

FAS participants with baseline liver fat fraction ≥8% who have at least one assessment for MRI-PDFF.

M. Subgroups of Analysis Populations

Data from subgroups of participants in the FAS will be analyzed as specified below. These analyses will comprise descriptive summaries; the goal will be to identify signals of additional effects that the primary analysis does not consider. Such analyses will be considered exploratory and will not involve hypothesis testing.

Prespecified subgroup analyses will be based on:

- Stratification factor of LDL-C level at Screening: ≥100 mg/dL, <100 mg/dL. If level of LDL-C at Screening is different than the category actually used in the randomization due to errors, the actual category used in IXRS will be used.
- Age at Screening (<65, ≥65)
- Sex (female, male)
- Race (White, Asian, all other races)
- Baseline BMI (<25 kg/m^2, ≥25 kg/m^2)
- Region (North America, Asia Pacific other)
- Reported history of ASCVD (Yes, No)
- Genotype consistent with FCS (including but not limited to homozygous, compound heterozygous, or double heterozygous loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase (LPL) activity including LPL, APOC2, APOA5, GPIHBP1, LIPG, GPD1, or LMF1)
- Concomitant Statin Use (high intensity, moderate intensity, low intensity, none).

  Stable statin regimen is allowed for indicated participants from prior to Screening and throughout the Treatment Period. Concomitant statin use and its intensity will be identified from lipid management medications (see below) recorded on the eCRF that start before Day 1 and continue into Treatment Period regardless of end date.

Intensity of statin therapy will be determined based on total daily dose according to the below guideline:

Statin	Low Intensity	Moderate Intensity	High Intensity
Atorvastatin (Lipitor)	NA	10 to 20 mg	40 to 80 mg
Fluvastatin (Lescol)	20 to 40 mg	80 mg	NA
Lovastatin (Mevacor)	20 mg	40 mg	NA
Pitavastatin (Livalo)	1 mg	2 to 4 mg	NA
Pravastatin (Pravachol)	10 to 20 mg	40 to 80 mg	NA
Rosuvastatin (Crestor)	NA	5 to 10 mg	20 to 40 mg
Simvastatin (Zocor)	10 mg	20 to 40 mg	NA

N. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes.

Data listings will simply list the data recorded on the eCRF or derived for each patient. They will be ordered by randomized treatment in the DB Treatment Period (ARO-ANG3 dose group [50, 100, and 200 mg] and pooled placebo group), participant number, and time of assessment.

In general, for the DB Treatment Period, summary tables will display summary statistics calculated for each of the ARO-ANG3 dose group (50, 100, and 200 mg), a pooled ARO-ANG3 group, and a pooled placebo group, unless described otherwise in following sections. For the OLE Treatment Period, summary tables will display the ARO-ANG3 dose group (50, 100, and 200 mg) (before the determination of a single ARO-ANG3 dose) and a pooled ARO-ANG3 group.

Descriptive statistics will be presented 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.

The Standard Display of tables, listings, and figures (TLFs) and Precision of Data Displayed are documented in the appendix of SAP TLF shell.

VI. Participant Accountability

The participant characteristics defined below will be presented in summary tables and data listings for participants in the FAS separately. No formal statistical comparisons will be performed.

A. Participant Characteristics

Demography:

- Age (years): Age at time of consent, calculated as the difference between birth year and the year of inform consent date.
- Age group: <65, ≥ 65 years
- Sex: Male, Female.
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown, Other.
- Race group: White, Asian, and all other races
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown
- Region: North America, Asia Pacific, other

Baseline Characteristics

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI group: <25 kg/m^2, ≥ 25 kg/m^2
- Mean value of TG at baseline (mg/dL)
- Mean level of TG at baseline category: <1000 mg/dL and ≥1000 mg/dL
- Value of LDL-C at baseline (mg/dL)*
- Level of LDL-C at baseline category*: <70 mg/dL, 70-<100 mg/dL, ≥100 mg/dL
- Level of LDL-C at screening category used as stratification factor (from IWRS): <100 mg/dL, ≥100 mg/dL
- Value of HDL-C at baseline (mg/dL)
- Value of non-HDL-C at baseline (mg/dL)
- Value of Remnant Cholesterol at baseline (mg/dL)^
- Level of Remnant Cholesterol at baseline category^: <39 mg/dL, ≥39 mg/dL
- Value of ApoB at baseline (mg/dL)
- Value of ANGPTL3 at baseline (mg/dL)
- Value of ApoA1 at baseline (mg/dL)
- Participating in Full PK sub-study: Yes, No

- Participating in MRI-PDFF sub-group: Yes, No
- Concomitant Statin Use: high intensity, moderate intensity, low intensity, none
- Concomitant Anti-PCSK9 Inhibitor Use: Yes, No
- Regular Use of Alcohol (Yes, No)
- Regular Use of Tobacco (Yes, No)

^Remnant Cholesterol = (Total cholesterol – HDL-C – LDL-C*).

*LDL-C using Friedewald formula, Martin-Hopkins methodology and ultracentrifugation will be summarized separately.

Medical History: Medical history will be coded using MedDRA version 23.1 or higher. Medical Histories will be summarized for the FAS using system organ class (SOC) and preferred term (PT). Subjects with ASCVD (Atherosclerotic cardiovascular disease) history will also be summarized with frequencies and proportions.

Genotype: Genotype results will be summarized for historic results and new samples collected at visit Day 1 at DB Treatment Period. Summaries will be provided for the following:

- Participants with mutations for the following genes: LPL (lipoprotein lipase), GPD1, APOE, GPIHBP1, ApoC2, ApoA5, LMF1, LDLR, APOB, PCSK9, LDLRAP1, LIPA, ABCG5, ABCG8 (Yes, No)
- Post-heparin LPL activity (normal, abnormal)
- Participants with a genotype consistent with Familial Chylomicronemia Syndrome (FCS) (Yes, No)

B. Disposition and Population Inclusions

Participant disposition will be summarized, by each ARO-ANG3 dose level (together with a pooled ARO-ANG3 group) and each placebo dose group (together with a pooled placebo group), as the number and percentage of patients who were:

- Screened
- Failed screening (together with reason for screen failure)
- Randomized
- Completing treatment at DB Treatment Period
- Discontinued treatment at DB Treatment Period (together with the reasons for discontinuation)
- Completing DB Treatment Period
- Discontinued study at DB Treatment Period (together with the reasons for discontinuation)
- Entering OLE Treatment Period

- Completing treatment at OLE Treatment Period
- Discontinued treatment at OLE Treatment Period (together with the reasons for discontinuation)
- Completing OLE Treatment Period
- Discontinued study at OLE Treatment Period (together with the reasons for discontinuation)

Participants who were in each analysis population, and who were excluded from the PPS and reason for exclusion will be listed and separately summarized in the disposition table.

Enrollment and disposition will be listed by study period, cohort, treatment and participant. All enrolled participants will be displayed in a listing that includes the protocol version under which they enrolled to each study period, and whether or not all inclusion exclusion criteria were satisfied. Screen failures and participants not randomized will also be listed.

C. Protocol Deviations

Protocol deviation listing will be presented by participant.

D. Visit Attendance and COVID-19 Impact Assessment

Due to the outbreak of COVID-19 pandemic, COVID-19 related visit attendance and disposition events will be summarized for the following:

- Number of participants who discontinued treatment for reasons related to COVID-19
- Number of participants who discontinued study for reasons related to COVID-19
- At each scheduled visit, the number of participants attending the visit for overall and by type of visit (clinic, remote) and performer of the visit (site staff, home health)
- At each scheduled visit, number of participants with visits missed for reasons related to COVID-19

VII. Efficacy Analyses

All efficacy analyses will be performed using FAS Overall (DB Treatment Period) or FAS OLE (OLE Treatment Period). Participants will be analyzed according to the treatment assigned at randomization for the DB Treatment Period.

A. Primary Efficacy Outcome Analysis

The primary analysis of the primary endpoint will evaluate the difference in means between each ARO-ANG3 dose cohort and pooled placebo cohort.

1. Primary Estimand

The primary estimand of interest is the difference in means of percent change from baseline in fasting TG at Week 24 in population of adults with mixed dyslipidemia, regardless of treatment compliance or other intercurrent events post-baseline, defined by the following attributes:

Attribute	Description
Treatment	3 ARO-ANG3 dose levels (50, 100, and 200 mg) vs placebo
Population	Population of adults with mixed dyslipidemia as defined by the inclusion/exclusion criteria in the protocol
Endpoint	Fasting serum TG at Week 24*
Intercurrent events	Noncompliance with treatment and use of prohibited medications. The occurrence of intercurrent events is considered irrelevant in defining treatment effect; the values of the endpoint will be used regardless of whether subject experiences an intercurrent event. This corresponds to a *treatment policy strategy*.
Population-level summary	Difference in the mean percent change from baseline at Week 24

*serum TG at Week 24 collected under non-fasting status as indicated by dietary and fasting form will be considered as missing

2. Primary Efficacy Analysis

The μ_0, μ_1, μ_2 and μ_3 be the population means of the percent change from baseline at Week 24 in fasting TG levels under pooled placebo, ARO-ANG3 50 mg, 100 mg, and 200 mg dose levels, respectively.

The null hypothesis H_{01}, H_{02}, H_{03} give below will be tested against the alternative hypothesis H_{A1}, H_{A2}, H_{A3}

H_{01}: $\mu_1 - \mu_0 = 0$ vs H_{A1}: $\mu_1 - \mu_0 \neq 0$

H_{02}: $\mu_2 - \mu_0 = 0$ vs H_{A2}: $\mu_2 - \mu_0 \neq 0$

H_{03}: $\mu_3 - \mu_0 = 0$ vs H_{A3}: $\mu_3 - \mu_0 \neq 0$

The primary analysis will be performed based on all observed cases (OC) from baseline through Week 36 using a mixed model repeated measures (MMRM) approach with treatment, study visit, stratification factor (level of LDL-C at Screening [≥100 mg/dL versus <100 mg/dL]), and baseline TG value included as model terms. Additional covariates (age, sex, race, and BMI) as described in Section V.F will be included as appropriate. The model

will also include treatment by visit and treatment by baseline interaction terms. An unstructured (UN) covariance structure will be applied for MMRM. In case, the model will not converge with the UN covariance structure, the appropriate covariance structure will be used instead such as the Toeplitz and AR(1) covariance structures.

If there are convergence or estimation issues due to the number of participants at certain covariate levels (e.g., race), then that covariate may be pooled or removed from the model. Additional covariates or factors may be removed if there are still issues (e.g., strong collinearity).

Contrasts will be constructed to compare each of the three ARO-ANG3 treatment groups to the placebo group at each visit. The least-squares (LS) mean percent change from baseline with the associated standard errors will be displayed for each treatment group. Estimated treatment differences (ARO-ANG3 vs. Placebo) along with corresponding two-sided 95% CIs and p-values will also be presented for Week 24.

When performing the primary analysis, a family wise error rate will be controlled at alpha=0.05. The adjustment for multiplicity of testing multiple arms (ARO-ANG3 50 mg, 100 mg, 200 mg) versus placebo will be carried out using Holm's step-down procedure.

Supportive analyses will be performed for PPS population in a similar manner to the primary efficacy analysis using MMRM approach.

No adjustments for multiplicity will be considered for any other efficacy analyses.

Change from baseline and percent change from baseline in fasting TG will also be plotted by visit.

3. Sensitivity Analyses Using Multiple Imputation (MI)

The primary analysis of MMRM using OC of the data is based on the assumption of missing at random (MAR) and that participants who drop-out would behave similarly to those in the same treatment group who do not.

Multiple imputation (MI) based sensitivity analyses may be performed when the amount of missing data for the primary endpoint at any visit is deemed substantial, e.g., exceeding a tentative threshold of 10%. The sensitivity analyses will assess the robustness of the primary analysis considering the data as missing not at random (MNAR) using the MI procedure in SAS 9.4. Two MI analyses will be performed, as follows:

<u>Referenced (placebo) based multiple imputation</u>

1. Intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. 100 imputed datasets with monotone missing pattern will be generated. The variables to be used in the imputation model are treatment, baseline TG values, baseline non-HDL-C values, baseline HDL-C values, baseline LDL-C values, and TG values observed at post-baseline visits.

```
proc mi data = indata out = mono nimpute = 100 seed = &seed;
  var trt01pn basetgc basenh baseh basel base w4 w8 w12 w16 w20
w24;
  mcmc impute = monotone;
run;
```

2. Then all the monotone missing values will be multiply-imputed using the imputation model built from the control group, i.e., assuming the missing data in the treatment groups will have a profile that equals the profile of the control group for all timepoints. The missing data imputation will be implemented using PROC MI in SAS 9.4 with the MNAR statement.

```
proc mi data= mono seed=&seed nimpute=1 out= outdata;
  by  imputation ;
  class trt01pn basetgc;
  monotone reg(/details);
  mnar model(base w4 w8 w12 w16 w20 w24/
modelobs=(trt01pn='0'));
  var basetgc basenh baseh basel base w4 w8 w12 w16 w20 w24;
run;
```

Note: `trt01pn='0'` indicates placebo subjects.

Once the competed datasets are formed, the same MMRM analysis model as specified for the primary analysis will be applied to each completed set and inference drawn using PROC MIANALYZE.

Multiple imputation with tipping point approach

A tipping point analysis will be performed to investigate the robustness of departures from the MAR assumption in the MI model by applying a specified sequence of shift parameters that modify the imputed TG values, as follows:

1. Missing values will be imputed using the MCMC methodology. 100 “complete” datasets will be generated. The variables to be used in the imputation model are treatment, baseline TG values, baseline non-HDL-C values, baseline HDL-C values, baseline LDL-C values, and TG values observed at post-baseline visits.

```
proc mi data = indata out = mcmc nimpute = 100 seed = &seed;
```

```
  var trt01pn basetgc basenh baseh basel base w4 w8 w12 w16 w20
w24;
  mcmc;
run;
```

2. For each of the 100 completed datasets, apply a shift parameter S_1 in the ARO-ANG3 groups only. A positive adjustment assumes a worsened outcome for the imputed values in the ARO-ANG3 groups. The MNAR statement with the ADJUST option in PROC MI will be used to apply the shift parameter.

3. Each of the 100 completed datasets applying the shift parameter will be analyzed using an MMRM analysis as described above.

4. The results of the 100 completed datasets will be combined for inference using PROC MIANALYZE.

5. Repeat Steps 1-4, with adjustment by a different shift parameter to the imputed TG values in the ARO-ANG3 groups only, as follows: $S_1 = 0$ (no shift), 50, 150, 200, 250, 300, ….and 1000 mg/dL

6. The shift parameter that result in a reversed study conclusion (i.e., p-value increases from <0.05 to $\geqslant$0.05) will be flagged.

7. Alternate series of shift parameters may be applied based on the actual data. Alternate tipping approach may be explored based on the actual data, e.g., applying shift parameters to the placebo group in addition to applying those to the ARO-ANG3 groups.

A pre-specified seed number of 6012021 will be used in all imputation procedures as described above. Alternative model specifications may be used based on the actual data if there is an issue in model convergence.

B. Secondary Efficacy Outcome Analyses

DB Treatment Period

The following continuous secondary endpoints will be analyzed in a similar manner to the primary endpoint using MMRM approach:

- 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*

- 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

*LDL-C using Friedewald formula, Martin-Hopkins methodology and ultracentrifugation will be summarized separately.

The MMRM model will be based on OC of the data from baseline through Week 36 including treatment, study visit, stratification factor, and the corresponding baseline level. Additional covariates as described in Section V.F will be included as appropriate. The model will also include treatment by visit and treatment by baseline interaction terms. The LS mean change from baseline with the associated standard errors will be displayed for each treatment group. Estimated treatment differences (ARO-ANG3 vs. Placebo) along with corresponding two-sided 95% CIs and p-values will also be presented at each post-baseline timepoint (weeks 4, 8, 12, 16, 20, 24, 28, and 36).

Supportive analyses will be performed for PPS population for all secondary endpoints using MMRM approach.

Descriptive summary statistics for secondary variables will be provided by treatment and visit. Secondary efficacy endpoints will also be plotted by visit.

OLE Treatment Period

Descriptive summary statistics will be provided for the following continuous secondary endpoints by treatment and visit. Plots will also be provided.

- Percent change from baseline in fasting TG, non-HDL-C, total apolipoprotein (Apo) B, LDL-C*, ANGPTL3, and HDL-C at all visits

*LDL-C using Friedewald formula, Martin-Hopkins methodology and ultracentrifugation will be summarized separately.

C. Exploratory Efficacy Outcome Analyses

DB Treatment Period

For the analysis of exploratory endpoints, descriptive summaries will be provided by treatment and visit, as applicable, and any inferential statistics (ie, p-values) will be considered only as exploratory. The following endpoints will be analyzed in a similar manner to the primary endpoint using MMRM:

- Change and/or percent change from baseline over time 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 in fasting serum blood glucose, HbA1C, homeostatic model assessment for insulin resistance (HOMA-IR) and C-peptide

The exploratory endpoint of proportion of participants requiring emergent apheresis over time during the double-blind study period will be summarized by treatment arms. Chi-square test will be used for the analysis. Odds ratio (ARO-ANG3 vs. Placebo), along with corresponding two-sided 95% CIs and p-values will also be presented.

The following will be analyzed based on the MRI-PDIFF Analysis Set using an analysis of covariance (ANCOVA) model including treatment, stratification factor, and baseline level as covariate:

- Change and/or percent 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)

The LS mean estimates for each treatment arm will be displayed together with standard errors and their corresponding 95% CIs. Treatment differences with 95% CIs will also be produced.

Exploratory efficacy endpoints will also be plotted by visit.

OLE Treatment Period

For the analysis of exploratory endpoints, descriptive summaries will be provided by treatment and visit.

- Change and/or percent change from baseline over time 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 and/or percent change from baseline over time in fasting serum blood glucose, HbA1C, homeostatic model assessment for insulin resistance (HOMA-IR) and C-peptide

Exploratory efficacy endpoints will also be plotted by visit.

D. Efficacy Analysis on Subgroups of Participants

Summary statistics will be presented for the primary efficacy endpoint in each subgroup by treatment arm. The same MMRM analysis as described for the primary analysis will be applied in each subgroup.

Details of subgrouping are described in Section V.M.

VIII. Safety Analyses

Safety analyses will use data from the Safety Analysis Set if analyzing the whole study or DB Treatment Period, and FAS OLE if analyzing OLE Treatment Period.

A. Exposure and Compliance

Study drug administration data will be listed by participant. The number and percentage of participants will be summarized by number of doses of the study drug received, treatment arm, and study period. Participants not receiving planned volume will also be summarized at each visit, for overall and by reason (AE, dosing error, other).

Because study drug will be administered subcutaneously to the participants in accordance with the protocol, compliance will not be assessed.

Dietary counselling and fasting status data will be summarized at each visit for:

- Participants who have maintained a stable diet (Yes, No)
- Participants who have been on a stable dosing regimen for applicable CM (Yes, No)

B. Adverse Events

AE terms will be coded using the MedDRA dictionary version 23.1 or higher. A treatment-emergent AE (TEAE) is defined as an AE that occurs following investigational product (IP) administration or a pre-existing condition exacerbated following IP administration. Further, TEAEs will be categorized by study period (DB Treatment Period, OLE Treatment Period) as follows:

- TEAEs that occur before the first administration of IP in the OLE Treatment Period (OLE Day 1) are considered to be in the DB Treatment Period
- TEAEs that occur or exacerbate after the first administration of IP in the OLE Treatment Period are to be in the OLE Treatment Period.

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.

If relationship to treatment is missing, the event will be conservatively treated as related to study drug. Missing severity will be summarized as separate category.

All AEs will be listed by study period, treatment and participant, detailing the verbatim term given by the investigator, the preferred term (PT), system organ class (SOC), onset date and time, end date and time, severity grade, outcome, relationship to study drug, action taken with study drug, other action taken to treat the event, acute pancreatitis event, seriousness and criteria for seriousness. Serious AEs (SAEs), TEAEs leading to study drug discontinuation, TEAEs related to study drug, and local injection site reactions (LISR) will also be listed separately.

An overall AE summary will be presented, by study period and overall, by the number and percent of patients with the following:

- All TEAEs
- Treatment-related TEAEs
- Serious TEAEs
- TEAEs leading to study drug discontinuation
- Deaths
- LISR

The following AE summaries will be produced, by study period and overall, by SOC (alphabetical order) and PT (descending order of the overall frequency):

- All TEAEs
- Serious TEAEs
- TEAEs leading to study drug discontinuation
- Treatment-related TEAEs
- TEAEs by maximum severity grade
- TEAEs by maximum relationship to the study drug

At each level of summarization, a participant will be counted once if he/she reported one or more events. The severity grade and relationship to study drug will be summarized in a similar manner.

Local injection site reactions (LISR)

LISRs will only include events that start within 24 hours of injection and persist for at least 48 hours post injection. Events with onset date on the day of injection and missing resolution date will also be included in the summary.

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

Injection site discomfort	Injection site abscess
Injection site discoloration	Injection site abscess sterile

Injection site erythema	Injection site atrophy
Injection site irritation	Injection site calcification
Injection site inflammation	Injection site cellulitis
Injection site induration	Injection site dermatitis
Injection site 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	

The number and percentage of participants reporting LISRs, as well as the number of LISRs will be summarized by study period, PT and maximum severity grade. The percentage of injections leading to LISR will be summarized, as follows:

(A/B)*, where A = number of injections with a LISR, and B = total number of injections (each dose will be administered as a single injection).

C. Clinical Laboratory Results

Laboratory test results (hematology, chemistry, coagulation, urinalysis, serology) and abnormal laboratory values will be presented in data listings by participant. Summaries of actual values and changes from baseline in the DB Treatment Period will be presented by dose level and the pooled ARO-ANG3 and pooled placebo group for each assessment time point, beginning with the Screening visit. The same summaries will also be presented for the OLE Treatment Period with baseline defined both as the Overall Baseline and OLE Baseline.

Lab shift tables using the CTCAE grading will be used for selected analytes of interest, when applicable, for each study period.

In additional, liver function test (LFT) abnormalities will be assessed by the incidence overall, by study period, and by visits of the following categories:

- ALT or AST > 5 × ULN
- ALT or AST > 3 × ULN
- Total bilirubin > 2 × ULN
- (ALT or AST > 3 × ULN) and Total bilirubin > 2 × ULN
- (ALT or AST > 3 × ULN) and INR > 1.5

D. Vital Signs

Vitals Signs results (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiration rate and temperature) and change from baseline values will be presented in data listings by study period and participant.

Summaries of actual values and changes from baseline from baseline will be presented by study period, treatment and visit/at scheduled timepoint.

E. Electrocardiogram (ECG)

ECG parameters (heart rate [HR], PR, RR, QRS, QT, QTcF and QTcB intervals) will be summarized descriptively in summary tables as actual and change from baseline by study period, treatment and timepoints.

ECG results (HR, PR, RR, QRS, QT, QTcF, QTcB, and classification of Normality, Abnormality with Clinical Significance, or Abnormality without Clinical Significance) will be presented in data listings by participant.

F. Physical Examination

Clinically important abnormal physical examination results will be recorded as MH or AEs and analyzed accordingly.

G. Prior and Concomitant Medications

Prior and Concomitant Medications will be coded using the World Health Organization Drug Dictionary version B3 Global September 2020 into drug class (Anatomical Therapeutic Chemical level 4) and preferred term.

Prior medications are defined as medications with start and stop times prior to the time of study drug administration.

Concomitant medications are defined as medications with a start time at or after the time of study drug administration or medications with a start time prior to study drug administration but continuing after treatment.

The number and percentage of participants with prior or concomitant will be summarized by WHO-DD Anatomical-Therapeutic-Chemical (ATC) classification and preferred term (PT) for each ARO-ANG3 dose level, a pooled placebo group and overall. The summary table will display counts and percentages of participants who reported using at least 1 CM in each represented pharmacological subgroup.

The data will be listed by participant.

H. Other Safety Analyses

Pregnancy and FSH Results:

Female participants of childbearing potential will have urine pregnancy tests at each Screening visit (S1-S3), Day 1 (baseline) during the 36-Week Double-Blind Treatment Period, and at subsequent study visits prior to dosing throughout the study as indicated in the schedule of assessment Table 1 and Table 2 of protocol.

Pregnancy and FSH test results will be listed separately by treatment and visit/time point.

Substance use:

Substance use results collected at Screening will be listed.

IX. Immunogenicity (Anti-drug Antibodies) Analysis

All immunogenicity data will be listed by participant for Safety Analysis Set which has at least one ADA data reported.

For each study period, for subjects that were ADA-negative at baseline (Overall Baseline, OLE Baseline), treatment-emergent ADA incidence will be summarized (number and percent of subject with positive ADA) at each time point for each treatment group, pooled placebo and pooled treatment. Also, the titer values will be summarized descriptively for each time point by treatment if data available. If ADA positive were observed at baseline, the post-dose titer values will be compared with baseline and plotted vs time point to see if a treatment-boosted ADA happening to the subject.

If any ADA positive observed during the study, spaghetti plots of individual plasma concentrations versus actual time will be presented by ADA category for each treatment group for PK analysis set.

X. Pharmacokinetics Analyses

For the PK analysis set which includes full PK analysis set and sparse PK analysis set, all the PK concentration data will be listed. All PK data may be used for Population PK analysis and/or PK/PD analysis later, which will be supported by separate analysis plan and combined with PK and PD data from other clinical studies.

For Full PK Analysis set, the PK concentration data will also be summarized and plotted.

Concentrations below the limit of quantification (BLQ) will be set to zero for summary statistics. Plasma PK concentrations for ARO-ANG3 will be summarized by treatment descriptively, including n, arithmetic mean, SD, minimum, median,

maximum, coefficient of variation [CV(%)], geometric mean (GM), and geometric CV%.

For each dose, mean plasma concentrations (+SD) will be plotted on a linear and semi-logarithmic scale versus nominal time points by treatment. Individual plasma concentrations will be plotted on semi-logarithmic scale versus actual sampling times by treatment. For each treatment, spaghetti plots of individual plasma concentrations on semi-logarithmic scale will also be presented. A reference line indicating the lower limit of quantification (LLOQ) will be included in plots, as appropriate.

The following PK parameters will be calculated using Noncompartmental analysis (NCA) for Full PK Analysis Set, whenever data applicable:

AUC0–24	The area under the plasma concentration versus time curve from the zero to 24 hours
AUClast	The area under the plasma concentration versus time curve from zero to the time of the last quantifiable concentration
Cmax	maximum observed concentration
Tmax	time to reach maximum plasma concentration
T1/2	terminal elimination half-life
Vz/F	apparent volume of distribution during terminal phase after extravascular dosing
CL/F	apparent systemic clearance after extravascular dosing

Additional PK Parameters may also be calculated as appropriate.

The Sponsor (AH Clinpharm) will provide NCA for Full PK Analysis Set, and details about NCA are in Appendix A.

Plasma PK parameters for ARO-ANG3 will be listed and summarized by treatment descriptively, including n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV(%)], geometric mean (GM), and geometric CV%; For Tmax, only n, minimum, median, and maximum will be reported.

XI. References

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XII. Appendix

A. Noncompartmental Pharmacokinetic Analysis

Handling Missing or Non-Quantifiable Data

For Noncompartmental analysis (NCA), plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0. The following rules apply with special situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a pre-dose plasma concentration is missing, it may be set to zero by default, for first dose only.
- If an embedded BLQ value is considered anomalous within the concentration time profile, this value will be set as missing and excluded from the summary statistics

Pharmacokinetic Parameter Calculation

Standard PK parameters will be determined, where possible, from the plasma and urine concentrations of ARO-ANG3 using noncompartmental methods (NCA) in validated software program Phoenix WinNonlin (Certara USA, Inc. version 8.1 or higher).

Pharmacokinetic analysis will be carried out where possible using actual blood sampling times post-dose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

Cmax and tmax will be obtained directly from the concentration-time profiles. For multiple peaks, the highest postdose concentration will be reported as Cmax. In the case that multiple peaks are of equal magnitude, the earliest tmax will be reported.

AUC will be estimated using the linear trapezoidal rule for increasing concentrations and the log-trapezoidal rule for decreasing concentrations (i.e., “linear up / log down” trapezoidal rule in Phoenix WinNonlin).

Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of area under the concentration-time curve (AUC) will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow Cmax.

Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable pre-dose concentration value before the first dose will be considered anomalous and set to missing for the PK analysis.

STATISICAL ANALYSIS PLAN SUMMARY OF CHANGES VERSION 1 TO VERSION 2

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**

- Updated definition of "baseline" for TG value from "average" to "geometric mean" of Day 1 predose assessment and two fasting TG values collected during the screening period.
- Clarified that the geometric mean of the two collection timepoints associated with Week 24 and Week 36 will be used for the analysis. Further clarified that for all other lipid/pharmacodynamic endpoints, the analysis will be based on the reported value for the Week 24 and Week 36 visit.
- Clarified that non-calculable or missing values for LDL-C using Friedewald formula will be imputed with LDL-C using ultracentrifugation.
- Clarified the definition of Full and Sparse PK analysis will align with study protocol definitions
- Updated Baseline Characteristics to be presented in summary tables and listings as follows:
  - Added level of LDL-C baseline category of <70 mg/dL, 70-<100 mg/dL and ≥100 mg/dL
  - Added value of Remnant Cholesterol at baseline
  - Added level of Remnant Cholesterol at baseline category of <39 mg/dL, ≥39 mg/dL
  - Added value of ApoB at baseline
  - Added value of ANGPTL3 at baseline
  - Added value of ApoA1 at baseline
  - Added concomitant use of PCSK9 inhibitor: Yes, No
  - Removed level of LDL-C at screening and screening category of <100 mg/dL, ≥100 mg/dL
  - Removed level of non-HDL-C at screening and screening category of <100 mg/dL, ≥100 mg/dL

- The Exploratory Efficacy Outcome Analyses section was updated to add the proportion of subjects requiring emergent apheresis during the double-blind treatment period.
- Updated the analyses of clinical laboratory results, vital signs, and electrocardiogram by removing the percent change from baseline for the summaries.
- The Pharmacokinetics Analyses section was updated to:
    - Include PK samples collected outside the sampling window in the PK parameters calculation.
    - Add the following PK parameters:
        - Terminal elimination half-life (T 1/2)
        - Apparent volume of distribution during terminal phase after extravascular dosing (Vz/F)
        - Apparent systemic clearance after extravascular dosing (CL/F)