Statistical Analysis Plan

Investigational Product:	ARO-APOC3
Protocol Title:	A Double-blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia
Study Number:	AROAPOC3-2002
Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA
Author:	[redacted] Arrowhead Pharmaceuticals, Inc.
Protocol Version/Date:	Amendment 3/26 January 2023
SAP Version/Date:	Version 2.0 / 08 September 2023

Signature Page

Protocol Title:	A Double-blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia
Protocol Number:	AROAPOC3-2002
SAP Version/Date:	Version 2.0 / 08 September 2023

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
DocuSigned by: [redacted] FB45E83C0ED849389588536F92DC9F4F	08-Sep-2023 | 16:09:44 PDT
[redacted] Arrowhead Pharmaceuticals, Inc DocuSigned by: [redacted] 696C2FFCF1284FD5A947E93C194178A4	11-Sep-2023 | 08:00:42 PDT
[redacted] Arrowhead Pharmaceuticals, Inc DocuSigned by: [redacted] 29440081A1B338F4839299	08-Sep-2023 | 19:00:35 PDT
[redacted] Arrowhead Pharmaceuticals, Inc	

Version Number	Date	Summary of Changes
1.0	14 April 2023	Original
2.0	08 September 2023	• Adding the definition of 'worsening of preexisting diabetes mellitus' and the subgroup analysis • Updating the definition of PPS

Table of Contents

List of abbreviations and definitions of terms

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug Antibody
AE	Adverse event
ALT	Alanine aminotransferase
Apo(B)	Apolipoprotein B
ApoA-I	Apolipoprotein A-I
ApoA-V or APOA5	Apolipoprotein A-V
ApoB-48	Apolipoprotein B 48
ApoB-100	Apolipoprotein B 100
ApoC-II or APOC2	Apolipoprotein C-II
ApoC-III or APOC3	Apolipoprotein C-III
ARO-APOC3 Injection	Clinical drug product solution ready for SC injection
ARO-APOC3	Short name for ARO-APOC3 Injection
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the limit of quantification
BMI	Body mass index
CHD	Coronary heart disease
CM	Concomitant medication
COVID	Corona virus disease
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic Blood Pressure
DPP-4	Dipeptidyl peptidase-4
DSC	Data Safety Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FCS	Familial Chylomicronemia Syndrome
FSH	Follicle-stimulating hormone
GPIHBP1	Glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment for insulin resistance

HR	Heart Rate
hsCRP	high sensitivity C-reactive protein
HTG	Hypertriglyceridemia
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
LFT	Liver Function Test
LIPG	Endothelial lipase
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
MD	Mixed Dyslipidemia
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing not at random
NODM	New Onset Diabetes Mellitus
non-HDL-C	Non-high-density lipoprotein cholesterol
OC	Observed cases
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred Term
Q12W	Once every 12 weeks
Q24W	Once every 24 weeks
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
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure

SC	Subcutaneous
SD	Standard deviation
SGLT	Sodium-glucose transporter
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TG	Triglyceride(s)
TLF	Tables, Listings, and Figures
TRL	Triglyceride-rich lipoprotein
ULN	Upper limit of normal
UN	Unstructured
VLDL	Very-low-density lipoprotein
VLDL-C	Very-low-density lipoprotein cholesterol
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Background

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

1.2. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on Protocol AROAPOC3-2002 Amendment 3 dated 26 January 2023.

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 after the time of treatment unblinding, will be documented as such in the study report.

1.3. Changes from Planned Analyses in the Protocol

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

2. STUDY OVERVIEW

2.1. Primary Objectives

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

2.2. Study Endpoints

2.2.1. Primary

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

2.2.2. Secondary

The following secondary endpoints will be evaluated:

- Percent change from baseline at each scheduled assessment in fasting TG;
- Percent change from baseline at Week 24 and over time through Week 48 in apolipoprotein (Apo)C-III;
- Percent change from baseline at Week 24 and over time through Week 48 in fasting non-high-density lipoprotein cholesterol (non-HDL-C);

- Percent change from baseline at Week 24 and over time through Week 48 in fasting high-density lipoprotein cholesterol (HDL-C);
- Percent change from baseline at Week 24 and over time through Week 48 in fasting total apolipoprotein B (ApoB);
- Percent change from baseline at Week 24 and over time through Week 48 in fasting low-density lipoprotein-cholesterol (LDL-C)*;
- Subject incidence of treatment-emergent adverse events (TEAEs)

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

2.2.3. Exploratory

The following exploratory endpoints are defined in this study:

- Change from baseline over time through Week 48 in other fasting lipid parameters (total cholesterol, LDL/HDL ratio, very-low-density lipoprotein cholesterol [VLDL-C], ApoB-48, lipoprotein [Lp][a], ApoB-100, ApoC-II, ApoA-I and ApoA-V [all values drawn after at least 8-hour fast]);
- Change from baseline to Week 24 and overtime through Week 48 in fasting serum blood glucose, glycated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR) and C-peptide;
- Change from baseline over time through Week 48 in high sensitivity C-reactive protein (hsCRP);
- Incidence of anti-drug antibodies (ADA) to ARO-APOC3
- Plasma pharmacokinetics (PK) of ARO-APOC3

2.3. Study Design

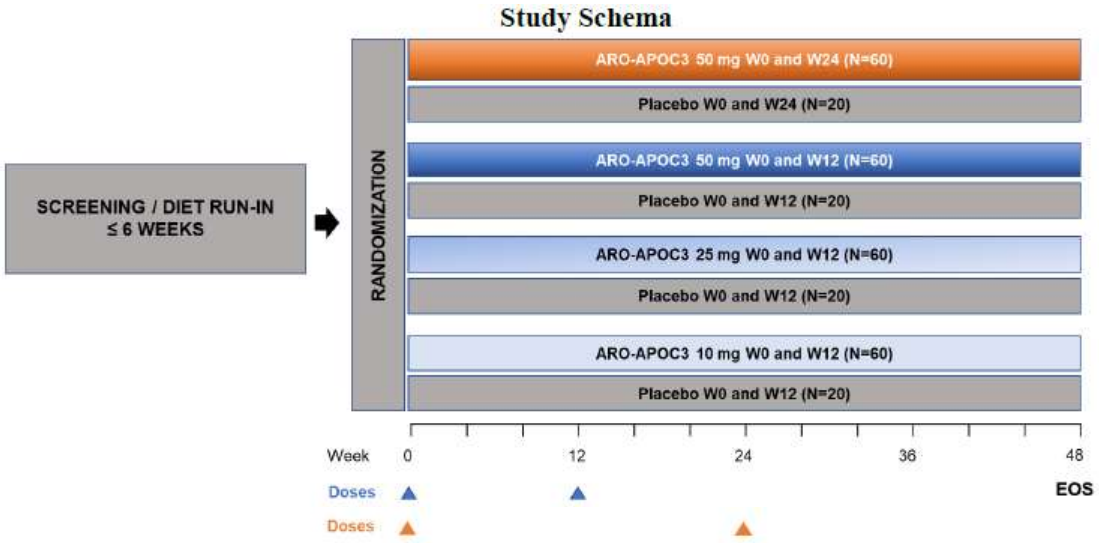
2.3.1. Design Overview

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, as well as diabetes mellitus therapies and other background medications, as applicable, throughout the Screening period and for the duration of the 48-week Treatment period.

A total of approximately 320 participants will be enrolled in the study. All dose cohorts will enroll in parallel with 80 participants per dose cohort randomly assigned in a 3:1 ratio to receive ARO-APOC3 (10 mg, 25 mg, 2 cohorts at 50 mg) or placebo. Each participant will receive

Subcutaneous (SC) injections on Day 1 and Week 12. In one additional 50 mg cohort, each participant will receive SC injection on Day 1 and Week 24 for a total of 2 injections as follows:



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

2.3.2. Study Population

This study will be conducted in adults with MD (150 mg/dL [1.69 mmol/L] ⩽ fasting TGs ⩽ 499 mg/dL [5.64 mmol/L] and fasting non-HDL-C ⩾ 100 mg/dL [2.59 mmol/L] or fasting LDL-C ⩾ 70 mg/dL [1.8 mmol/L]). A total of approximately 320 participants will be enrolled in the study in 35 centers globally to receive ARO-APOC3 or placebo in 3:1 ratio.

2.3.3. Sample Size Predictions

With a total of 320 participants, where 80 will be randomly assigned to treatment in a 3:1 (60 active to 20 placebo) ratio within each dose cohort, the study will have 99% power to detect at least 1 active treatment group which is significantly different from placebo, and at least 91% power to detect all treatment groups which are significantly different from placebo using a two-sided test, with family-wise 5% level of significance, adjusted for multiplicity. These estimates are based on the expected 30%, 45%, 60%, and 70% reduction from baseline in fasting TG in the 4 active treatment dose arms and no change in fasting TG in the pooled placebo group. The standard deviation (SD) is assumed to be 50% in all treatment groups.

2.3.4. Treatment Randomization

Eligible participants will be randomly assigned 3:1 to either active (ARO-APOC3) treatment in 1 of 4 dose cohorts (10, 25, or 2 cohorts at 50 mg) or to placebo treatment. No stratification factor is used, but randomization will be performed separately based on subject participation in full PK sub-study (Yes, No). 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 allowing for subject replacement (in the full PK sub-study only), as detailed in the IWRS vendor's Randomization Requirements Specification.

2.3.5. Assessment Schedule

The duration of the study is approximately 54 weeks from Screening to the Week 48 End-of-Study examination. Participants will attend study visits on Day -42 (Screening 1), Day -35 (Screening 2), Day -21 (Screening 3) during screening phase, Day 1, 2, week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 36 and week 48 (end of study [EOS]/ early termination) during treatment phase. Detailed Schedule of Assessments are included in clinical study protocol Table 1.

3. STATISTICAL METHODOLOGY

3.1. General Analytical Considerations

3.1.1. Data Sources

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 done under non-fasting status will be excluded from summary and analysis.

Data will be analyzed by treatment groups of ARO-APOC3 10 mg, 25 mg, 50 mg (Day 1 and Week 12 [Q12W]) and 50 mg (Day 1 and Week 24 [Q24W]), and Placebo (pooled).

3.1.2. 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" 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 average (i.e. geometric mean) of Day 1 predose assessment and two fasting TG values collected during the Screening period. If more than 3 predose assessments are available, the average will be taken from the last 3 available results. If fewer than 3 predose assessments are available, the average will be taken from the available results. For lipid related, lipoprotein and serum pharmacodynamic (PD) assessments, baseline is defined as the predose value on Day 1.

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 of discontinuation as recorded in the electronic case report form (eCRF).

End of study (EOS)

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

3.1.3. 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. For efficacy endpoints, 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 48, 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 48 values will be used for analysis.

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

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 – Day 295
Week 48	337	≥ 296

3.1.4. 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 adverse events (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.

Adverse events (AEs):

- AEs occur on Day 1 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.

Below the Limit of Quantification (BLQ):
In lipid and other clinical laboratory parameters, if the BLQ or < lower limit of quantification (LLOQ) is reported, half of LLOQ values will be used.

3.1.5. 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.

3.1.6. Covariate Adjustment in Primary Analysis

The primary and secondary efficacy analyses will be adjusted the relevant baseline values.

Additional covariates that may be considered are:

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

Details will be provided as described in relevant sections below.

3.1.7. Sample Size Reassessment

Not applicable.

3.1.8. Interim Analyses

An interim analysis is planned for this study after all participants completed the Week 24 visit. The interim analysis will be conducted by an unblinded independent biostatistician and reviewed by the unblinded individual(s) from sponsor or their designee. Safety data and select PD data, will be reviewed in aggregate, comparing the treatment groups: ARO-APOC3 10 mg, 25 mg, 50 mg (Day 1 and Week 12) or 50 mg (Day 1 and Week 24) to pooled placebo. Following receipt of the interim analysis data, recipients will not be involved in further planning or conduct of the study so as to maintain the study blind. The primary endpoint will be evaluated and, therefore, no adjustment to the alpha level for the final analysis is necessary.

3.1.9. 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 serious AEs (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.

3.1.10. 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.

3.1.11. Multiple Comparisons

When performing the primary analysis, the adjustment for multiplicity of testing ARO-APOC3 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.

3.1.12. Analysis Populations

The following study populations are defined in this study:

3.1.12.1. Full Analysis Set (FAS)

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

3.1.12.2. Safety Analysis Set

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

3.1.12.3. Per-protocol Set (PPS)

All participants in the FAS population who have completed the Week 24 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:

- Missing Week 24 geometric mean measurement of TG;
- Not completing all 2 injections of the study drug for Q12W treatment groups;
- Not satisfying major Inclusion/Exclusion criteria;
- Taking the study drug that the subject is not randomized to;
- Usage of restricted medications/treatments; and
- Any other major protocol deviation.

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

3.1.12.4. 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.

3.1.13. Subgroups of Analysis Populations

The subgroup 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. Selected subgroup analysis will be plotted by visit.

Prespecified subgroup analyses will be based on:

- Mean value of TG at Baseline (Tertiles)
- LDL-C using Friedewald at Baseline (Tertiles)
- LDL-C using Friedewald at Baseline (<70 mg/dL, 70 to <100 mg/dL, 100 to <130 mg/dL, ≥130 mg/dL)
- Age at Screening (<65 years, ≥65 years)
- Sex (female, male)
- Race (White, Asian, all other races)
- Baseline BMI (<25 kg/m^2, ≥25 kg/m^2)
- Region (North America, Europe, other)
- 10-year coronary heart disease (CHD) Risk (<10%, 10 to ≤20%, >20%)
- 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 15 mg	20 to 40 mg
Simvastatin (Zocor)	10 mg	20 to 40 mg	NA

Any additional subgroup may be considered.

3.1.14. 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 treatment (ARO-APOC3 dose group [10 mg, 25 mg, 50 mg Q12W and 50 mg Q24W] and pooled placebo group), participant number, and time of assessment.

Summary tables will display summary statistics calculated for each of the ARO-APOC3 dose group (10 mg, 25 mg, 50 mg Q12W and 50 mg Q24W), and a pooled placebo group, unless described otherwise in following sections.

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.

3.2. Participant Accountability

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

3.2.1. 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, Europe, 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, grouped as follows: <150 mg/dL, 150 to <499 mg/dL, and ≥499 mg/dL
- ApoC-III at baseline (mg/dL)
- non-HDL-C at baseline (mg/dL)
- HDL-C at baseline (mg/dL)
- total ApoB at baseline (mg/dL)
- LDL-C* at baseline (mg/dL)
- LDL-C* at baseline category: <70 mg/dL, 70 to <100 mg/dL, 100 to <130 mg/dL ≥130 mg/dL
- VLDL-C at baseline (mg/dL)
- Remnant Cholesterol*^ at baseline (mg/dL)
- Remnant Cholesterol*^ at baseline category: <39 mg/dL, ≥39 mg/dL
- Participating in Full PK sub-study: Yes, No
- Concomitant Statin Use: high intensity, moderate intensity, low intensity, none
- Concomitant Anti-PCSK9 Inhibitor Use (Yes, No)
- Concomitant Niacin Use (Yes, No)

- Concomitant Diabetic Medication Use (Metformin/combo[1], Insulin, GLP1 receptor agonists[2], Dipeptidyl peptidase-4 [DPP-4] inhibitors[3], Sodium-glucose transporter [SGLT] 2 inhibitors[4], Others)

  1. Includes metformin-alogliptin (Kazano), metformin-canagliflozin (Invokamet), metformin-dapagliflozin (Xigduo XR), metformin-empagliflozin (Synjardy), metformin-glipizide, metformin-glyburide (Glucovance), metformin-linagliptin (Jentadueto), metformin-pioglitazone (Actoplus), metformin-repaglinide (PrandiMet), metformin-rosiglitazone (Avandamet), metformin-saxagliptin (Kombiglyze XR), metformin-sitagliptin (Janumet)

  2. Includes albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Byetta), exenatide extended-release (Bydureon), liraglutide (Victoza), semaglutide (Ozempic)

  3. Includes alogliptin (Nesina), alogliptin-metformin (Kazano), alogliptin-pioglitazone (Oseni), linagliptin (Tradjenta), linagliptin-empagliflozin (Glyxambi), linagliptin-metformin (Jentadueto), saxagliptin (Onglyza), saxagliptin-metformin (Kombiglyze XR), sitagliptin (Januvia), sitagliptin-metformin (Janumet and Janumet XR), sitagliptin, vildagliptin and simvastatin (Juvisync)

  4. Includes dapagliflozin (Farxiga), dapagliflozin-metformin (Xigduo XR), canagliflozin (Invokana), canagliflozin-metformin (Invokamet), empagliflozin (Jardiance), empagliflozin-linagliptin (Glyxambi), empagliflozin-metformin (Synjardy), ertugliflozin (Steglatro)

- Regular Use of Alcohol (Yes, No)

- Regular Use of Tobacco (Yes, No)

- 10-year CHD risk (based on ATP III Guidelines): <10%, 10 to ≤20%, >20%

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

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

Medical History: Medical history (MH) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or higher. Medical Histories will be summarized for the FAS using system organ class (SOC) and preferred term (PT).

Genotype: Genotype results will be summarized for historic results and new samples collected at Screening. 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 (Yes, No)

- Post-heparin LPL activity (normal, abnormal)
- Participants with a genotype consistent with Familial Chylomicronemia Syndrome (FCS) (Yes, No)

3.2.2. Disposition and Population Inclusions

Participant disposition will be summarized as the number and percentage of patients who were screened, failed screening (together with reason for screen failure), randomized, completing treatment, completing the study, discontinued treatment (together with the reasons for discontinuation), discontinued from the study (together with the reasons for discontinuation), and in each analysis population by each ARO-APOC3 treatment group each placebo dose group (together with a pooled placebo group). Participants 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 treatment and participant. All enrolled participants will be displayed in a listing that includes the protocol version under which they enrolled, and whether or not all inclusion exclusion criteria were satisfied. Screen failures and participants not randomized will also be listed.

3.2.3. Protocol Deviations

Protocol deviation listing will be presented by participant.

3.2.4. Visit Attendance and corona virus disease (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

3.3. Efficacy Analyses

All efficacy analyses will be performed using FAS. Participants will be analyzed according to the treatment assigned at randomization.

3.3.1. Primary Efficacy Outcome Analysis

The primary analysis of the primary endpoint will evaluate the difference in means between each ARO-APOC3 dose cohort and pooled placebo cohort.

3.3.1.1. Primary Estimand

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

Attribute	Description
Treatment	4 ARO-APOC3 treatment groups (10 mg, 25 mg, 50 mg Q12W and 50 mg Q24W) vs placebo
Population	Adult MD population 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

3.3.1.2. Primary Efficacy Analysis

The μ_0, μ_1, μ_2, μ_3 and μ_4 be the population means of the percent change from baseline at Week 24 in fasting TG levels under pooled placebo, ARO-APOC3 10 mg, 25 mg, 50 mg Q12W and 50 mg Q24W treatment groups, respectively.

The null hypothesis H_{01}, H_{02}, H_{03}, H_{04} give below will be tested against the alternative hypothesis H_{A1}, H_{A2}, H_{A3}, H_{A4}

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}: $\mu_3 - \mu_0 \neq 0$

H_{04}: $\mu_4 - \mu_0 = 0$ vs H_{A4}: $\mu_4 - \mu_0 \neq 0$

The primary analysis will be performed based on all observed cases (OC) from baseline through Week 48 using a mixed model repeated measures (MMRM) approach with treatment, study visit,

and baseline TG value included as model terms. Additional covariates (age, sex, race, BMI, and baseline LDL-C) as described in Section 3.1.6 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-APOC3 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-APOC3 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-APOC3 50 mg Q24W, 10 mg, 25 mg, 50 mg Q12W) 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.

3.3.1.3. 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. 10 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 (Friedewald) values, and TG values observed at post-baseline visits.

```
proc mi data = indata out = mono nimpute = 10 seed = &seed;

  var trt01pn basenh baseh basel basetg w4 w8 w12 w16 w20 w24 w28
w36 w48;

  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;

  monotone reg(/details);

  mnar model(basetg w4 w8 w12 w16 w20 w24 w28 w36 w48/
modelobs=(trt01pn='0'));

  var basenh baseh basel basetg w4 w8 w12 w16 w20 w24 w28 w36
w48;

run;


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

3. 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.

<u>Multiple imputation with tipping point approach</u>

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. 10 “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 (Friedewald) values, and TG values observed at post-baseline visits.

```
proc mi data = indata out = mcmc nimpute = 10 seed = &seed;

  var trt01pn basenh baseh basel basetg w4 w8 w12 w16 w20 w24
w28 w36 w48;

  mcmc;

run;
```

2. For each of the 10 completed datasets, apply a shift parameter S_1 in the ARO-APOC3 groups only. A positive adjustment assumes a worsened outcome for the imputed values in the ARO-APOC3 groups. The MNAR statement with the ADJUST option in PROC MI will be used to apply the shift parameter.

3. Each of the 10 completed datasets applying the shift parameter will be analyzed using an MMRM analysis as described above.

4. The results of the 10 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-APOC3 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 ≥ 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-APOC3 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.

Nonparametric approach

A nonparametric approach will be used as the sensitivity analysis for the primary efficacy endpoint. As an extension to the Wilcoxon rank-sum test, the Hodges-Lehmann method will be used to estimate the median difference and its corresponding 95% CI for percent changes between ARO-APOC3 doses and placebo.

The SAS code for Hodges-Lehmann estimates is listed below:

```
proc npar1way data = indata hl alpha=0.05;

class trt01pn;
```

```
var pchg;

run;
```

The same referenced (placebo) based multiple imputation method will be used to impute the missing values for the nonparametric approach.

3.3.1.4. Other Sensitivity Analysis

Sensitivity analyses for secondary endpoints (TG, non-HDL-C, HDL-C, LDL-C) may also be performed following the same method as described for primary endpoint.

3.3.2. Secondary Efficacy Outcome Analyses

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

- Percent change from baseline at each scheduled assessment in fasting TG
- Percent change from baseline at Week 24 and over time through Week 48 in ApoC-III
- Percent change from baseline at Week 24 and over time through Week 48 in fasting non-HDL-C
- Percent change from baseline at Week 24 and over time through Week 48 in fasting HDL-C
- Percent change from baseline at Week 24 and over time through Week 48 in fasting total ApoB
- Percent change from baseline at Week 24 and over time through Week 48 in fasting LDL-C*

*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 48 including treatment, study visit, stratification factor, and the corresponding baseline level. Additional covariates as described in Section 3.1.6 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-APOC3 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, 36, and 48).

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.

3.3.3. Exploratory Efficacy Outcome Analyses

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 from baseline over time through Week 48 in TG and other fasting lipid parameters (total cholesterol, LDL/HDL ratio, VLDL-C, ApoB-48, Lp[a], ApoB-100, ApoC-II, ApoA-I and ApoA-V)

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.

3.3.4. 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 3.1.13.

3.4. Safety Analyses

Safety analyses will use data from the Safety Analysis Set.

3.4.1. Exposure and Compliance

Study drug administration data will be listed by participant. The number and percentage of participants receiving 1 dose and both doses of the study drug will be summarized by treatment arm. 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)

3.4.2. Adverse Events

AE terms will be coded using the MedDRA dictionary version 23.1 or higher. A TEAE is defined as an AE that occurs following investigational product (IP) administration or a pre-existing condition exacerbated following IP administration.

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 treatment and participant, detailing the verbatim term given by the investigator, the PT, 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, seriousness and criteria for seriousness. 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 present 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 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 on the day 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 LISR:

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 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).

3.4.3. Clinical Laboratory Results

The glycemic status at baseline is defined as the following:

- Diabetic: Having HbA1c ≥6.5% or Fasting Glucose ≥126 mg/dL or with medical history of 'diabetes' or receiving diabetic medications at baseline
- Non-diabetic: Not meeting any of the criteria for diabetes at baseline

The non-diabetic subjects include the subjects with prediabetes and normoglycemia at baseline:

- Prediabetes: No diabetes and having HbA1c ≥5.7% and <6.5%, or Fasting Glucose ≥100 mg/dL and <126 mg/dL at baseline
- Normoglycemia: No diabetes and not meeting the criteria for prediabetes at baseline

The New Onset Diabetes Mellitus (NODM) is defined as the subjects who did not have diabetes at baseline (i.e., non-diabetes), but develop postbaseline new onset diabetes mellitus, defined as having HbA1c ≥6.5% or Fasting Glucose ≥126 mg/dL at any postbaseline visits.

Worsening of preexisting diabetes mellitus will be identified and evaluated for the subjects who have diabetes at baseline by the following:

- Worsening of HbA1c that is considered clinically significant by the investigator to modify or change the anti-diabetic regimen
- New adverse events (AEs) related to hyperglycemia or complications of hyperglycemia
- Initiation of an anti-diabetic medication in study subjects not known to have preexisting diabetes mellitus

The actual values, changes from baseline and percent changes from baseline will be summarized by treatment and visit on

- Worsening of preexisting diabetes mellitus with diabetic subjects at baseline
- NODM subjects with prediabetes at baseline
- NODM subjects with normoglycemia at baseline

and overall for the following endpoints:

- Change from baseline to Week 24 and overtime through Week 48 in fasting serum blood glucose, HbA1c, HOMA-IR and C-peptide

Mean (+/-SD) change from baseline for fasting serum blood glucose and HbA1c will also be plotted by visit.

In additional, the number and percentage of participations who meet the following criteria will be summarized by treatment on worsening of preexisting diabetes mellitus with diabetic subjects at baseline, NODM subjects with prediabetes at baseline, NODM subjects with normoglycemia at baseline and overall:

- HbA1c measurement >10% at any post-baseline visit
- An increase from baseline with HbA1c >2% at any post-baseline visit

- An increase from baseline with HbA1c >1% for at least 2 post-baseline visits

The actual values, changes from baseline and percent changes from baseline will be summarized by treatment and visit for the following endpoint:

- Change from baseline over time through Week 48 in hsCRP

Other 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 will be presented by each ARO-APOC dose group and pooled placebo group for each assessment time point, beginning with the Screening visit.

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

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

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (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 international normalized ratio (INR) > 1.5

3.4.4. 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 participant.

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

3.4.5. 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 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.

3.4.6. Physical Examination

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

3.4.7. Prior and Concomitant Medications

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

Prior medications are defined as medications with start time prior to the time of study drug administration, regardless of when the medication stops.

Concomitant medications are defined as medications with a start times at or after the time of study drug administration or medications with a start times prior to study drug administration, regardless of when the medication stops.

The number and percentage of participants with prior or concomitant will be summarized by WHO-DD ATC classification and PT for each ARO-APOC3 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.

3.4.8. Other Safety Analyses

Pregnancy and Follicle-Stimulating Hormone (FSH) Results:

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

3.5. Immunogenicity (Anti-drug Antibodies) Analysis

All immunogenicity data will be listed by participant for safety population which has at least one ADA data reported.

For subjects that were ADA-negative at baseline, treatment-emergent ADA incidence will be summarized (number and percent of subject with positive ADA) at each time point for each treatment group, and pooled placebo. 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 postdose 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, spaghetti plots of individual plasma concentrations versus actual time will be presented by ADA category for each treatment group for PK analysis set.

3.6. 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, which will be supported by separate analysis plan and combined with PK from other clinical studies.

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

Concentrations BLQ will be set to zero for summary statistics. Plasma PK concentration for ARO-APOC3 will be summarized by treatment descriptively, including n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV(%)], geometric mean, geometric CV%;

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 LLOQ will be included in plots, as appropriate.

3.7. References

Gaudet D, Alexander VJ, Baker BF, Brisson D, Tremblay K, Singleton W, et al.. "Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia. N Engl J Med. 2015;373:438-47.

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

Stone N J, Robinson J G, Lichtenstein A H, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines[J]. Journal of the American College of Cardiology, 2014, 63(25 Part B): 2889-2934.