Statistical Analysis Plan

Investigational Product:	ARO-APOC3
Protocol Title:	A Phase 2 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of ARO-APOC3 in Adults With Dyslipidemia
Study Number:	AROAPOC3-2003
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Signature Page

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



eSignature for approval is applied. Signatures are attached at the end of this document.

Version Number	Date (DDMMYYYY)	Summary of Changes
V1.0	13DEC2024	Original

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
APOA-I	apolipoprotein A-I
APOA-V	apolipoprotein A-V
APO	apolipoprotein
APOB	apolipoprotein B
APOB-100	apolipoprotein B 100
APOB-48	apolipoprotein B 48
ApoC-II	apolipoprotein C-II
ApoC-III	apolipoprotein C-II
AST	aspartate aminotransferase
BMI	body mass index
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
EC	ethics committee
ECG	electrocardiogram
eDISH	evaluation of drug-induced serious hepatotoxicity
EOS	end of study
FAS	Full Analysis Set
HbA1c	glycosylated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment for insulin resistance
ICF	Informed consent form
IPD	important protocol deviations
IRB	institutional review board
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LISR	local injection site reaction
LP(a)	lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
OLE	open-label extension
PT	preferred term
Q1	first quartile
Q3	third quartile
Q3M	every 3 months
Q6M	every 6 months
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TG	triglycerides
ULN	upper limit of normal
VLDL-C	very low-density lipoprotein cholesterol
WHO DRUG	World Health Organization Drug

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined in the protocol for the study AROAPOC3-2003 dated 25SEP2024. The scope of this plan includes the planned final analyses for the Clinical Study Report (CSR) as well as an interim analysis in support of an interim report.

2. STUDY OVERVIEW

2.1. Study Objectives

The primary objectives of the study are to evaluate the safety and efficacy of long-term treatment with ARO-APOC3 in adults with dyslipidemia.

2.2. Study Design

2.2.1. Overview

This is an open-label extension (OLE) Phase 2b clinical study. Subjects who have signed an Ethics Committee (EC)/Institutional Review Board (IRB) approved informed consent form (ICF) may be enrolled after completing either AROAPOC3-2001 or AROAPOC3-2002 (parent studies). Subjects must continue to maintain a stable diet and stable lipid-lowering therapy in accordance with local standard of care, as well as other background medications taken during the parent study, throughout the duration of the 24-month OLE period.

The study design is shown in Figure 1. Subjects previously assigned to 10 mg ARO-APOC3, 25 mg ARO-APOC3, or placebo once every 3 months (Q3M) in the parent study receive ARO-APOC3 at the same frequency in this OLE study. Subjects previously assigned to 50 mg ARO-APOC3 or placebo Q3M or 50 mg ARO-APOC3 or placebo once every 6 months (Q6M) in the parent study, transition to 25 mg ARO-APOC3 in this OLE at the same frequency in this OLE study. Any participants in the 50 mg dose group (Q3M or Q6M) enrolled in this OLE prior to the discontinuation of the 50 mg dose cohort (Amendment 2, dated 22 November 2022) transition to ARO-APOC3 25 mg Q3M or Q6M. After the last subject in the parent study reaches the Month 12/end of study (EOS) visit of the parent study and a single dose has been selected, all subjects in this OLE study transition to the selected ARO-APOC3 dosing regimen.

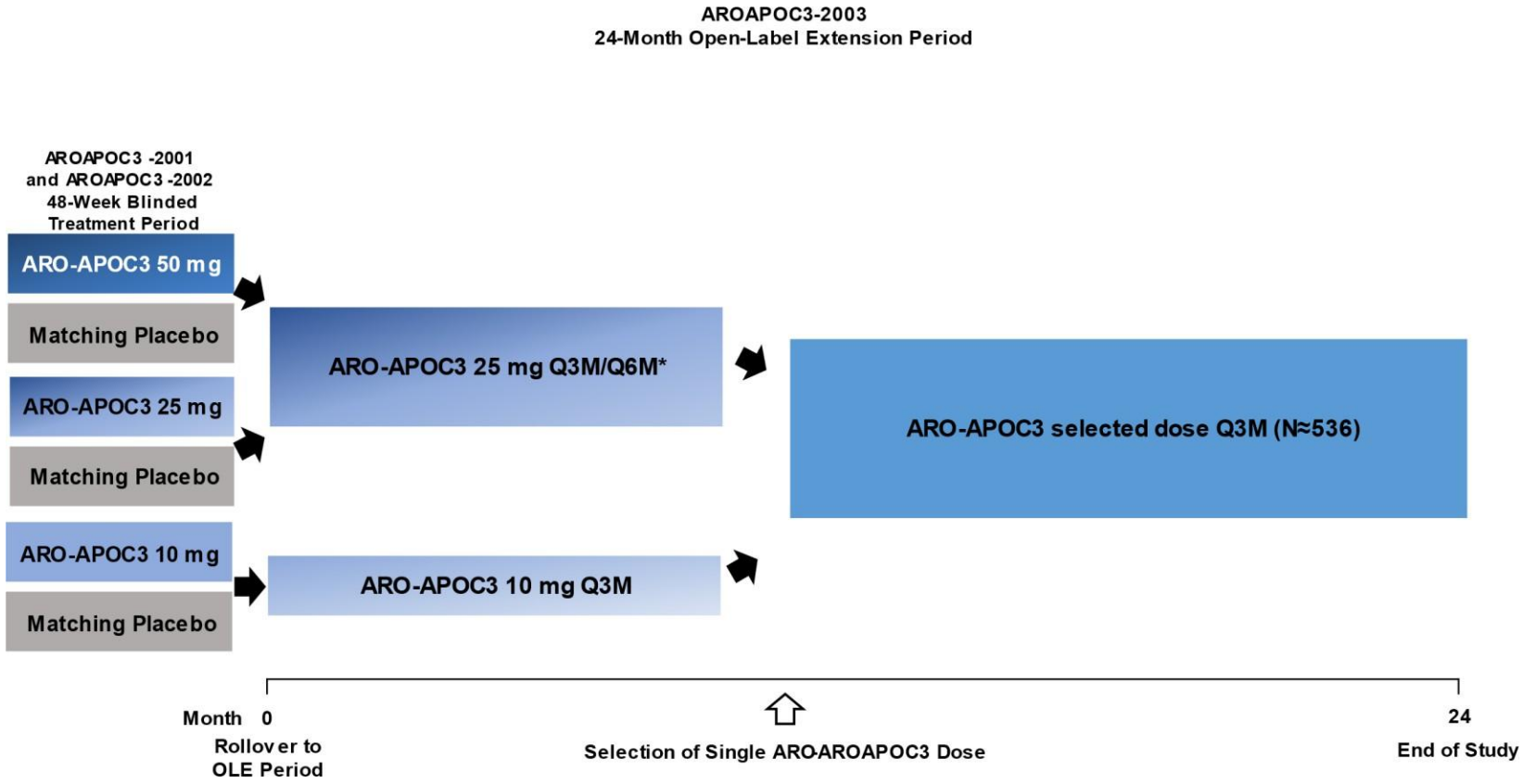
Under Amendment 2 of the protocol (dated 22 November 2022), following an administrative analysis of the AROAPOC3-2001 and AROPOC3-2002 studies, dosing of the subjects in the 50 mg dose cohort of this OLE (AROAPOC3-2003) was adjusted as follows:

- The 50 mg dosing group was discontinued.
- If assigned to the 50 mg dose group, a subject transitioned to the 25 mg dose group at the next dosing visit as long as glycosylated hemoglobin (HbA1c) discontinuation criteria have not been met.
- Discontinuation criteria were added for subjects with elevated HbA1c during the OLE.

Under AROAPOC3-2003 Clinical Study Memorandum (dated 27 November 2023), the single dose was selected as 25 mg. On 04 December 2023, all active subjects were assigned to 25 mg Q3M for the remainder of the study.

Subjects discontinued due to elevations in HbA1c during the study will be asked to continue with study follow-up assessments until 6 months have passed since receiving their last dose.

Figure 1: Study Schema



Abbreviations: Q3M=once every 3 months; Q6M=once every 6 months.

Note: Subjects assigned to the 50 mg ARO-APOC3 dose or placebo in the parent studies (AROAPOC3-2001 and AROAPOC3-2002) receive the 25 mg dose. The dosing frequency will remain the same.

Table 1: Schedule of Assessments

Assessment	24-Month Treatment Period									
	Day 1 [a] (within 30 days of EOS visit for parent study [b])	Study Months								
		1	2	3 [a]	6 [a]	9 [a]	12 [a]	15 [a]	18 [a]	21 [a]	24/ET
		Days (±5 days until Month 3, then ±14 days)									
		30	60	90 [a]	180 [a]	270 [a]	360 [a]	450 [a]	540 [a]	630 [a]	720
Informed consent	X										
Eligibility criteria	X										
Dietary counseling/maintain diet	X	X	X	X	X	X	X	X	X	X	
Review with subject signs/symptoms of pancreatitis and when to seek medical care	X	X	X	X	X	X	X	X	X	X	X
Weight	X			X	X	X	X	X	X	X	X
Vital signs (blood pressure, temperature, respiratory rate, heart rate)	X			X	X	X	X	X	X	X	X
Medical history	X										
Physical examination (symptom directed after Day 1)	X			X	X	X	X	X	X	X	X
Single 12-lead electrocardiogram [c]	X			X	X	X	X	X	X	X	X
Pregnancy test (women of childbearing potential)	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests [d]	X	X	X	X	X	X	X	X	X	X	X
Lipid parameters [d]	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies [a]	X	X		X	X		X		X		X
Investigational product administration, **Q3M** dosing cohort (subjects who received ARO-APOC3 Q3M in parent study) [e]	X			X	X	X	X	X	X	X	
Investigational product administration, **Q6M** dosing cohort (subjects who received ARO-APOC3 Q6M in parent study) [e]	X				X		X		X		
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain, or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: COVID-19=coronavirus disease 2019; ECG=electrocardiogram; EOS=end of study; ET=early termination; HbA1c=glycated hemoglobin; IP=investigational product; Q3M=once every 3 months; Q6M=once every 6 months.

[a] Assessments completed on dosing days **are to be done predose**, unless otherwise specified.

[b] Assessments completed at the EOS visit (Month 12) of the parent study may be used for Day 1 of this study. If Month 12/EOS of the parent study is used as Day 1 for this study, then informed consent must be obtained and eligibility for this study must be confirmed before any protocol-specific procedure is initiated and before IP is administered. If Day 1 of this study is different from Month 12/EOS of the parent study, then Day 1 will occur no later than 30 days after the Month 12/EOS visit in the parent study, and assessments must be repeated on Day 1 of this study, after informed consent is obtained and eligibility for this study is confirmed.

[c] Single 12-lead ECG will be performed in the semi-supine position after the subject has rested comfortably for 3 minutes. ECGs will be collected prior to any blood draws.

[d] Blood and urine samples will be collected on Day 1 after obtaining informed consent. In the event of logistical disruptions (eg, COVID-19-related) where a subject does not have direct access to the site, lab samples may be collected at alternative location (eg, home health, local lab) using the central laboratory kit and shipped to the central laboratory for analysis. If central laboratory kit collection is not available, local laboratory safety testing may be permitted only in limited circumstances and only with prior sponsor approval. Beginning on Day 1, at study visits with blood draws for clinical laboratory tests or lipid parameter measurements, subjects will have fasted for at least 10 hours prior to blood draw unless otherwise specified. Samples collected at Month 1 and 2 will be analyzed for HbA1c only. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Protocol Appendix 4).

[e] Subjects will transition to a single dose based on review of data from the parent studies. Once the single dose is selected by the sponsor, all participants will transition to the Q3M dosing schedule.

2.3. Study Endpoints

2.3.1. Primary Endpoint

- Subject incidence of treatment-emergent adverse events (TEAEs)

2.3.2. Secondary Endpoints

- Change and percent change from baseline over time in fasting triglyceride (TG)
- Change and percent change from baseline over time in apolipoprotein C-III [ApoC-III]
- Change and percent change from baseline over time in fasting non-high-density lipoprotein cholesterol (non-HDL-C)
- Change and percent change from baseline over time in fasting HDL-C
- Change and percent change from baseline over time in fasting total apolipoprotein B (ApoB)
- Change and percent change from baseline over time in fasting low-density lipoprotein cholesterol (LDL-C) using ultracentrifugation

2.3.3. Exploratory Endpoints

- Change and percent change from baseline over time in other fasting lipid parameters (total cholesterol, low-density lipoprotein cholesterol [LDL-C] measured using Martin-Hopkins methodology, LDL/HDL ratio, very-low-density lipoprotein cholesterol [VLDL-C], ApoB-48, lipoprotein[a] [Lp{a}], apolipoprotein B 100 [ApoB-100], apolipoprotein C-II [ApoC-II], apolipoprotein A-I[ApoA-I], and apolipoprotein A-V[ApoA-V] [all values drawn after at least a 10-hour fast])
- Change from baseline over time in fasting serum blood glucose, hemoglobin A1c (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and C peptide
- Change and percent change from baseline over time in high sensitivity C-reactive protein
- Emergence of and titers of anti-drug antibodies to ARO-APOC3 over time
- Incidence of positively adjudicated events of acute pancreatitis
- Incidence of hospitalizations for abdominal pain
- Subject incidence of emergent apheresis

3. STATISTICAL METHODOLOGY

3.1. General Considerations

3.1.1. Analysis Visits

An analysis visit window is defined based on the scheduled target day. Within an analysis visit window, if a scheduled visit occurs, the measurement from this scheduled visit will be used as the measurement for the visit window. If an unscheduled visit occurs within a visit window, the measurement from the visit closest to the scheduled visit within the visit window will be used. If

there is more than one measurement with equal distance to the scheduled measurement, the last one will be used. If no visits occur within a visit window, the measurement for the visit will be treated as missing.

Visit	Target Day	Analysis Window (Study Day)
Day 1	1	OLE Day 1
Month 1	30	(Post OLE Day 1, 45]
Month 2	60	(45, 75]
Month 3	90	(75, 135]
Month 6	180	(135, 225]
Month 9	270	(225, 315]
Month 12	360	(315, 405]
Month 15	450	(405, 495]
Month 18	540	(495, 585]
Month 21	630	(585, 675]
Month 24	720	>675

For early termination visit, it will be treated as analysis visit +1 if more than one visits are measured within one analysis visit window.

3.1.2. Definitions

Study Day

- For each subject, and for a given date of interest, study day from OLE is defined as the number of days from OLE Day 1: Study day = (date of interest – OLE Day 1 date) + 1.

Parent Study Baseline of Lipid and Lipid-related Parameters

- For TG, baseline is defined as the average of the last 2 non-missing values prior to the first dose or the last non-missing value prior to the first dose if only a single value is available from the parent study.
- For other lipid related, lipoprotein and serum PD assessments, baseline is defined as the last non-missing predose value from the parent study.
- For fasting ApoC-III, if the measured value at baseline visit is below the limit of quantification, then the baseline ApoC-III will be missing, and this subject will not be included in the efficacy summary and analysis of ApoC-III.

Other Parent Study Baseline Values

- For HbA1c, baseline is defined as the worst value measured any time during screening or at Day 1.
- For all other variables, baseline is defined as the last non-missing value obtained prior to the first dose from the parent study.

OLE Baseline

- For lipid parameter and other measurements, if needed for exploratory purpose, OLE baseline will be used to evaluate the change during the OLE period. For TG, OLE baseline is defined as the average of all non-missing values at Week 48, 2-7 days post Week 48 of the parent study and OLE Day 1. For other lipid parameter, OLE baseline is defined as the last non-missing value at Week 48, 2-7 days post Week 48 of the parent study and OLE Day 1.

OLE Study Exposure in Months

- (End of Study [EOS] date – OLE Day 1 date + 1) / 365×12

TEAE

- TEAEs are defined as adverse events (AEs) that start on or after the first dose date of study drug.

3.1.3. Summary Statistics

Descriptive statistics on categorical variables will be reported using frequencies and percentages. All percentages will be presented with one-decimal point. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies, but the categories whose counts are zero will be displayed for the sake of completeness.

Descriptive statistics on continuous variables will be summarized using the mean, median, standard deviation (SD), standard error of the mean (SEM), first quartile (Q1), third quartile (Q3), minimum and maximum values. The same number of decimal places as in the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD, SEM and standard error (SE).

In the OLE, TEAEs will be summarized according to the most recent treatment received prior to the TEAE onset. For efficacy and other analyses, data will be analyzed by treatment in the randomized period/treatment in the OLE, with summary groups of placebo/ARO-APOC3, ARO-APOC3/ARO-APOC3, and total. Subjects from the AROAPOC3-2001 and AROAPOC3-2002 studies will be analyzed separately for subject data summaries (Section 3.3) and the efficacy endpoint analyses (Section 3.4).

3.2. Analysis Sets

3.2.1. Full Analysis Set (FAS)

The Full Analysis Set (FAS) includes all enrolled subjects.

3.2.2. Safety Analysis Set

The Safety Analysis Set includes all subjects who are exposed to study intervention during this study. This population will be used to summarize all safety data.

3.3. Subject Data and Study Conduct

3.3.1. Subject Disposition

The number and the percent of subjects who entered the OLE, received treatment, discontinued treatment, completed treatment, discontinued the study, and completed the study will be summarized.

Discontinuation will be tabulated separately by reason for discontinuing the treatment and reason for discontinuing the study.

The number of subjects included in each analysis set will be summarized.

3.3.2. Protocol Deviations

Important protocol deviations (IPDs) categories are defined by the clinical study team before the first subject's first visit and updated during the IPD reviews throughout the study prior to database lock (DBL).

Counts and percentages of subjects with IPDs by deviation category will be summarized using the Safety Analysis Set.

A data listing of protocol deviations will be provided by subject.

3.3.3. Demographics and Baseline Characteristics

All demographics and baseline data will be summarized using the Safety Analysis Set.

Demographics data will include but not be limited to:

- Age (in years), also categorized as <50, 50 to <65, and ≥65 years
- Sex (male, female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Region (North America, Europe, Other)

Baseline characteristics and disease history will include but not be limited to:

- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)
- BMI category (<30 kg/m^2 vs ≥30 kg/m^2)
- Geometric mean TG at parent study baseline (mg/dL)
- TG at OLE baseline (mg/dL)
- ApoC3 at baseline (mg/dL)
- HDL-C at baseline (mg/dL)
- non-HDL-C at baseline (mg/dL)
- VLDL-C at baseline (mg/dL)

- LDL-C at baseline (mg/dL)
- HbA1c at baseline (%)
- HbA1c at baseline category (<5.7%, ≥5.7% to <6.5%, ≥6.5%)
- Liver function test (LFT) at baseline (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ≤1 × upper limit of normal [ULN] [>1 to 2 × ULN, and >2 × ULN)
- Diabetic medications use at parent study baseline (Yes, No)

3.3.4. Medical History

Medical history will be summarized by system organ class (SOC) and preferred term (PT), and displayed in descending order of overall frequency by SOC and PT. The Safety Analysis Set will be used to summarize medical history.

A by-subject listing of medical history will be provided.

3.3.5. Concomitant Medications

The number and proportion of subjects receiving therapies of interest will be summarized by PT as coded by the World Health Organization Drug (WHO DRUG) dictionary. The Safety Analysis Set will be used to summarize concomitant medications.

A by-subject listing of concomitant medications will be provided.

A list of all subjects experiencing an addition or change in lipid lowering therapies will be provided. This listing will include administration dates.

A list of all subjects who had addition of a new diabetes therapy will be provided. This listing will include administration dates and will be segregated by subjects who were assigned to the placebo group or to the ARO-APOC3 group in the parent studies.

3.3.6. Investigational Product Exposure

Study drug exposure will be summarized descriptively using the Safety Analysis Set, and will include the following parameters:

- Number of injections received (category)
- Total number of injections received (continuous)
- ARO-APOC3 exposure during the OLE (continuous)
- ARO-APOC3 exposure during the OLE (categorical): 0 to 4 months, >4 to 7 months, >7 to 10 months, >10 to 13 months, >13 to 16 months, >16 to 19 months, >19 to 22 months, and >22 months

A list of subjects who had dose interruption or missed dose will be provided.

3.4. Efficacy Endpoint Analyses

All analyses will be performed based on the FAS unless otherwise specified.

For efficacy endpoints, change and percent change from baseline in fasting lipid parameters (TG, ApoC-III, non-HDL-C, HDL-C, total ApoB, LDL-C using ultracentrifugation, total cholesterol,

LDL-C measured using Martin-Hopkins methodology, LDL/HDL ratio, VLDL-C, ApoB-48, Lp[a], ApoB-100, ApoC-II, ApoA-I, ApoA-V) over time will be summarized. Baseline is defined as the study baseline from parent studies AROAPOC3-2001 and AROAPOC3-2002. The change or percent change from the measurements at enrollment of this OLE study will also be explored.

The incidence of subjects with positively adjudicated events of acute pancreatitis, incidence of hospitalizations for abdominal pain, and incidence of emergent apheresis during the OLE period will be summarized.

Subgroup analyses of selected efficacy endpoints may be conducted, including age group, gender, and race and any other factors of interest.

3.5. Safety Endpoint Analyses

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Analysis Set in OLE.

3.5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later will be used to code all events categorized as AEs to a SOC and a PT.

An overall summary of AEs will be provided. The overall summary will include the number and percentage of subjects reporting at least one: TEAE; related TEAE; treatment-emergent serious adverse event (TESAE); related TESAE; TEAE by severity; TEAE leading to study treatment discontinuation; TEAE leading to study discontinuation; and deaths.

Subject incidence of all TEAEs, related TEAEs, TESAEs, related TESAEs, TEAEs leading to discontinuation of study treatment, TEAE leading to study discontinuation, and deaths will be tabulated by SOC and PT in alphabetical order.

Summaries of TEAEs and serious adverse events (SAEs) by PT in any treatment arm will be provided in descending order of frequency.

Descriptive statistics summaries of subject incidence of TEAE by SOC, PT, and severity will be provided. Subjects will be counted once under the worst severity reported within each SOC and PT.

Descriptive statistics summary of subject incidence of TEAEs for Arrowhead Standardized MedDRA Query (SMQ) for Worsening of Glycemic Control and for Local Injection Site Reaction (LISR) by PT will be provided.

All AEs and SAEs will be presented in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome.

If any AE start date is missing, the start date will be imputed following the procedure described in Section 8.1 Appendix A. Tabulation of AEs summaries will be based on imputed AE start dates if there are any. Listing of AEs will only contain non-imputed AE start date.

TEAEs on PFS will be also summarized for ARO-APOC3 PFS.

3.5.2. Laboratory Tests Results

The actual value and the derived change and percent change from parent study baseline to each protocol-specified scheduled visit will be summarized with descriptive statistics for each clinical laboratory parameter, including hematology and clinical chemistry.

Lab shift tables for selected analytes of interest will be generated, following Common Terminology Criteria for Adverse Events (CTCAE) criteria.

The actual values and changes from parent study baseline in fasting serum blood glucose, HbA1c, HOMA-IR, and C-peptide from baseline over time will be summarized.

LFT abnormalities will be summarized by any post baseline incidence for the following categories:

- ALT or AST >3 × ULN,
- Alkaline Phosphatase >2 × ULN
- Total bilirubin >2 × ULN
- Gamma-glutamyl transferase >2 × ULN
- International Normalized Ratio >1.5 × ULN

To evaluate drug-induced liver injury, evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be generated for LFTs during the OLE period.

3.5.3. Vital Signs and Physical Measurements

Systolic and diastolic blood pressure, heart rate, and physical examination results will be summarized using descriptive statistics at each scheduled visit. Pregnancy and follicle-stimulating hormone test results will be listed.

3.5.4. 12-Lead Electrocardiograms

PR, QRS, QT, QTc, and RR interval and their change from parent study baseline will be summarized by scheduled visit. Electrocardiogram (ECG) findings will be summarized based on worst post-baseline result for the categories (QT interval >450 ms, >480 ms, >500 ms; increases from baseline >30 ms, >60ms).

3.6. Immunogenicity Analysis

For immunogenicity, changes from assay negative to positive will be summarized by dose and dosing cohort (Q3M and Q6M). Descriptive statistics of immunogenicity parameters will include mean, SD, minimum, and maximum.

Immunogenicity data will be provided in a by-subject listing.

4. SAMPLE SIZE DETERMINATION

All subjects from AROAPOC3-2001 and AROAPOC3-2002 studies who have met all protocol eligibility criteria were invited to consent and enroll in this AROAPOC3-2003 OLE study. No formal power analysis is conducted for sample size considerations.

5. INTERIM ANALYSES

In order to provide OLE study information for marketing authorization for the European Medicines Agency and for the 4-Month Safety Update for New Drug Application for the Food and Drug Administration, an interim analysis is planned. The data cutoff date for this interim analysis will be 08 Nov 2024, and the interim analysis will be reported. The interim analysis will provide the summary of the efficacy and safety data for the OLE period, including disposition, demographics, lipid parameters, and TEAEs as well as SMQs, liver function tests, renal function tests, ECG, and other safety information.

6. CHANGE FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan.

7. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

8. APPENDIX

8.1. Appendix A: Handling of Missing and Incomplete Data

Subjects 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.

The procedure outlined below describing what will be done when data are missing may be refined during the blinded review of data.

AEs:

- Adverse events 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 subject's Day 1 date.
    - If all year, month, and day are missing then use the subject'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:

- 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.
- Start date:
  - If all year, month, and day are missing then use the subject'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.

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 subject'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.

