Statistical Analysis Plan

Investigational Product:	ARO-ANG3
Protocol Title:	Phase 2 Study to Evaluate the Safety and Efficacy of ARO-ANG3 in Subjects with Homozygous Familial Hypercholesterolemia (HoFH)
Study Number:	AROANG3-2003
Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA
Author:	[redacted]
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Signature Page

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

Signature	**Date**
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Version Number	Date	Summary of Changes
1.0	23 May 2023	Original

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List of abbreviations and definitions of terms

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANGPTL3	angiopoietin-like protein 3
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
ApoC	Apolipoprotein C
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the limit of quantification
BMI	Body mass index
CK	Creatine kinase
CM	Concomitant medication
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CVD	Cardiovascular disease
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ET	Early termination
EU	European Union
FAS	Full Analysis Set
FH	Familial hypercholesterolemia
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
HR	Heart Rate
INR	International normalized ratio
IP	Investigational product
ISR	Injection site reaction
IWRS	Interactive Web Response System
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein (a)

MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin kexin type-9
PK	Pharmacokinetic
PT	Preferred Term
PUC	Preparative ultracentrifugation
Q12W	Once every 12 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
SD	Standard deviation
SOA	Schedule of Assessments
SOC	System Organ Class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride(s)
ULN	Upper limit of normal
VLDL	Very-low-density lipoprotein
VLDL-C	Very-low-density lipoprotein cholesterol
WHO-DD	World Health Organization Drug Dictionary

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 Amendment 4 for study AROANG3-2003 dated 08MAR2023. The scope of this plan includes the planned final analyses to be included in the Clinical Study Report (CSR).

2. STUDY OVERVIEW

2.1. Primary Objectives

The primary objective of the study is to evaluate the efficacy and safety of ARO-ANG3 in subjects with homozygous familial hypercholesterolemia (HoFH).

This study will also evaluate the efficacy, safety, and tolerability of long-term dosing of ARO-ANG3 in a 24-month Extension Treatment Period following the 36-week Treatment Period.

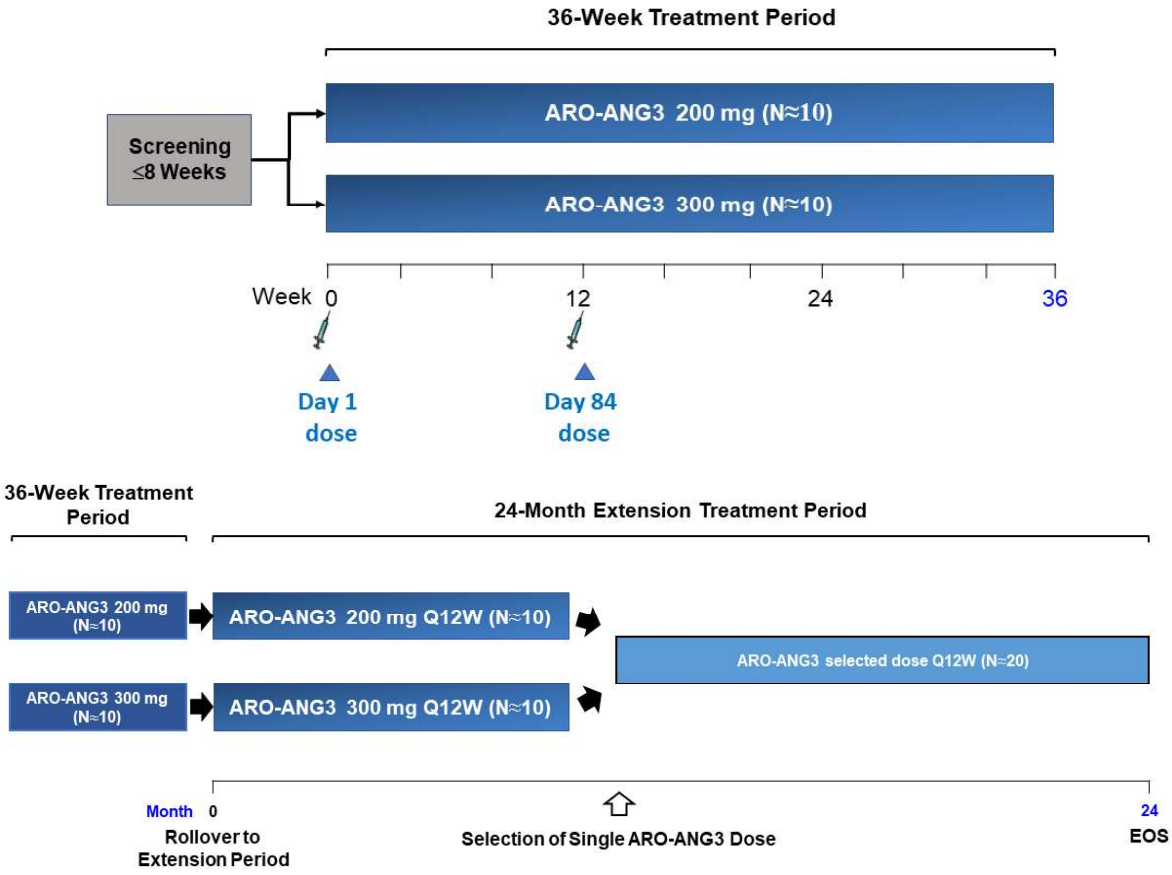
2.2. Study Design

2.2.1. Overview

This is an open-label clinical study with an optional Extension Treatment Period. This study will be conducted in subjects with documented HoFH based on genotype or clinical criteria at Screening. The duration of the study is approximately 34 months from Screening. The study activities and durations will be Screening (up to 8 weeks), Treatment Period (up to 36 weeks), and to the End of Study (EOS) Extension Treatment Period (up to 24 months).

After completing the Week 36 Visit, subjects may opt to continue in the 24-month Extension Treatment Period (see Study Schema). Unless otherwise specified, a month refers to 28 consecutive days. Subjects who do not opt to continue in the Extension Treatment Period will complete Week 36/Early Termination (ET) Visit assessments. Subjects in the Extension Treatment Period will complete study visits as specified in the Protocol schedule of assessments (SOA) and will be dosed quarterly (once every 12 weeks [Q12W]). Initially, subjects will receive the same dose level received during the 36-week Treatment Period. However, dose levels in the Extension Treatment Period may be consolidated to a single dose level based on sponsor decision after an interim analysis of safety and efficacy data at Week 24 of the 36-week Treatment Period. The interim analysis will be conducted once the data is available for a majority of enrolled subjects. Once a single dose has been selected by the sponsor, all subjects will be transitioned to the selected dose level.

Study Schema:



2.2.2. Randomization

This is an open-label clinical study. Subjects will be randomized by the interactive web response system (IWRS) in a 1:1 ratio into ARO-ANG3 200 mg or 300 mg dose groups.

2.2.3. Sample Size Determination

This is an exploratory study to investigate the low-density lipoprotein cholesterol (LDL-C) reduction capability of 200 mg and 300 mg ARO-ANG3 in subjects with HoFH. The sample size of up to approximately 20 subjects is based on clinical considerations. Based on the drug effect results from the hyperlipidemia population in the Phase 1/2a study AROANG1001, with this sample size, the study should be able to demonstrate clinically meaningful LDL-C reduction capability of ARO-ANG3 in HoFH patients.

2.3. Study Endpoints

2.3.1. Primary Endpoint

The primary endpoint is percent change from baseline to Week 24 in fasting calculated LDL-C and LDL-C using preparative ultracentrifugation (PUC).

2.3.2. Secondary Endpoints

The following secondary endpoints will be evaluated:

- Percent and absolute change from baseline in fasting LDL-C (using PUC) at each scheduled assessment;
- Percent and absolute change from baseline in fasting calculated LDL-C at each scheduled assessment;
- Percent and absolute change from baseline in fasting angiopoietin-like protein 3 (ANGPTL3) at each scheduled assessment;
- Percent and absolute change from baseline in fasting total ApoB at each scheduled assessment;
- Percent and absolute change from baseline in fasting high-density lipoprotein cholesterol (HDL-C) at each scheduled assessment;
- Percent and absolute change from baseline in fasting non-high-density lipoprotein cholesterol (non-HDL-C) at each scheduled assessment;
- Percent and absolute change from baseline in fasting very-low-density lipoprotein cholesterol (VLDL-C) at each scheduled assessment;
- Percent and absolute change from baseline in fasting total cholesterol (TC) at each scheduled assessment;
- Percent and absolute change from baseline in fasting triglyceride (TG) at each scheduled assessment;
- Subject incidence of treatment-emergent adverse events (TEAEs);
- Subject incidence of anti-drug antibodies (ADAs) to ARO-ANG3 at each scheduled assessment;
- Proportion of subjects who met US apheresis eligibility criteria of LDL-C $\geqslant$300 mg/dL (see US [National Lipid Association] Lipid Apheresis Criteria) at Week 24;
- Proportion of subjects who meet European Union (EU) apheresis eligibility criteria (see German Apheresis Working Group) at Week 24

The following secondary endpoints will be evaluated in the 24-month optional Extension Treatment Period:

- Percent and absolute change from baseline in fasting calculated LDL-C and fasting LDL-C (using PUC), fasting ANGPTL3, fasting total ApoB, fasting HDL-C, fasting non-HDL-C, fasting VLDL-C, fasting TC, and fasting TG at each scheduled assessment

- Subject incidence of ADAs to ARO-ANG3 at each scheduled assessment

- Subject incidence of TEAEs

2.3.3. Exploratory Endpoints

The following exploratory endpoints are defined in this study:

- Change from baseline in other fasting lipid parameters at each scheduled assessment in the 36-week Treatment Period as well as over time during the Extension Treatment Period (LDL/HDL ratio, ApoB-48, lipoprotein [LP][a], ApoB-100, Apolipoprotein C ApoC-III, ApoC-II, ApoA-I, and ApoA-V)

- Plasma PK concentrations of ARO-ANG3 at each scheduled assessment

3. STATISTICAL METHODOLOGY

3.1. General 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-ANG3 200 mg, 300 mg and overall.

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 the fasting TG value collected during the Screening period. If only one value is available, then this value will be used. For other lipid related parameters, 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 or discontinuation as recorded in the electronic case report form (eCRF).

End of study (EOS)

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

3.1.3. Analysis Visit Window

No analysis visit window will be defined for this study. All efficacy and safety endpoints will be analyzed according to the nominal visits (i.e. assigned visit).

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 "Event started prior to first dose?" 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.

3.2. Analysis Populations

The following study populations are defined in this study:

3.2.1. Full Analysis Set (FAS)

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

3.2.2. 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.

3.2.3. Pharmacokinetic (PK) Analysis set

All participants who receive at least 1 dose of IP and have at least one measurable PK concentration.

3.3. Subject Data and Study Conduct

3.3.1. Subject Disposition

Participant disposition will be summarized as the number and percentage of patients who were screened, failed screening (together with reason for screen failure), randomized, completed treatment at Week-36 treatment period, completed treatment at 24-Month extension treatment period, completed study at Week-36 treatment period, completed study at 24-Month extension treatment period, discontinued the treatment at Week-36 treatment period and discontinued the treatment at 24-Month extension treatment period (together with the reasons for discontinuation), discontinued the study at Week-36 treatment period and discontinued the study at 24-Month extension treatment period (together with the reasons for discontinuation), and in each analysis population by each ARO-ANG3 200 mg, 300 mg and overall in the FAS and the Safety Analysis Set.

Disposition will be listed by treatment and participant.

3.3.2. Protocol Deviations

Protocol deviation listing will be presented by participant.

3.3.3. Demographic and Baseline Characteristics

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

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 Pacific Islander, White, Unknown, Other.
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown

Baseline Characteristics

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- BMI group: <25 kg/m^2, ≥25 kg/m^2
- LDL-C (using Friedewald formula, Martin-Hopkins methodology and Ultracentrifugation) at baseline (mg/dL)
- ANGPTL3 at baseline (ng/mL)
- total ApoB at baseline (mg/dL)
- HDL-C at baseline (mg/dL)
- non-HDL-C at baseline (mg/dL)
- VLDL-C (Calculated and Ultracentrifugation) at baseline (mg/dL)
- TC at baseline (mg/dL)
- Geometric Mean TG at baseline (mg/dL)
- Lp (a) at baseline (nmol/L)
- Concomitant proprotein convertase subtilisin kexin type-9 (PCSK9) Inhibitor Use (Yes, No)
- Concomitant Statin Use: high intensity, moderate intensity, low intensity, none
- Regular Use of Alcohol (Yes, No)

- Regular Use of Tobacco (Yes, No)

3.3.4. Medical History

Medical history (MH) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher. Medical Histories will be summarized in the FAS using system organ class (SOC) and preferred term (PT).

Listings of all reported medical history will be provided.

3.3.5. Prior and Concomitant Medications

Prior and Concomitant Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version B3 Global September 2021 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-ANG3 200 mg, 300 mg and overall in the Safety Analysis Set.

The data will be listed by participant.

3.3.6. 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 during 36-Week Treatment Period , the number of doses receiving during the 24-Month Extension Treatment Period and the total number of doses receiving during the study will be summarized by treatment arm and overall in the Safety Analysis Set.

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

3.4. Efficacy Analyses

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

3.4.1. Primary Efficacy Outcome Analysis

Baseline values, actual change, and percent change from baseline in LDL-C (using Friedewald formula, Martin-Hopkins methodology and PUC) at Week 24 will be summarized with descriptive statistics by treatment group and overall.

Waterfall plots of percent change from baseline to Week 24 will be provided.

3.4.2. Secondary Efficacy Outcome Analyses

Baseline values, as well as the actual change and percent change from baseline at each visit will be summarized with descriptive statistics by treatment group and overall in the 36-Week Treatment Period and over time during the 24-month Extension Treatment Period for the following continuous secondary efficacy endpoints:

- Percent and absolute change from baseline in fasting LDL-C (using PUC) at each scheduled assessment;
- Percent and absolute change from baseline in fasting calculated LDL-C at each scheduled assessment;
- Percent and absolute change from baseline in fasting ANGPTL3 at each scheduled assessment;
- Percent and absolute change from baseline in fasting total ApoB at each scheduled assessment;
- Percent and absolute change from baseline in fasting HDL-C at each scheduled assessment;
- Percent and absolute change from baseline in fasting non-HDL-C at each scheduled assessment;
- Percent and absolute change from baseline in fasting VLDL-C at each scheduled assessment;
- Percent and absolute change from baseline in fasting TC at each scheduled assessment;
- Percent and absolute change from baseline in fasting TG at each scheduled assessment.

The mean percent change (+/-SD) will also be plotted by visit.

The number and percentage of subjects who meet eligibility criteria at Week 24 will be summarized by treatment for the following secondary endpoints:

- Proportion of subjects who met US apheresis eligibility criteria of LDL-C ≥300 mg/dL (see US [National Lipid Association] Lipid Apheresis Criteria) at Week 24

- Proportion of subjects who meet European Union (EU) apheresis eligibility criteria (see German Apheresis Working Group) at Week 24

    - A patient with primary cardiovascular disease (CVD) prevention is considered as meeting German apheresis eligibility criteria if LDL-C >160 mg/dL

    - A patient with secondary CVD prevention is considered as meeting German apheresis eligibility criteria if LDL-C >120 mg/dL

3.4.3. Exploratory Efficacy Outcome Analyses

The following continuous exploratory efficacy endpoints will be analyzed in a similar manner to the continuous secondary endpoints in the 36-Week Treatment Period and over time through 24-month Extension Treatment Period:

- Change from baseline in other fasting lipid parameters at each scheduled assessment in the 36-week Treatment Period as well as over time during the Extension Treatment Period (LDL/HDL ratio, ApoB-48, lipoprotein [LP][a], ApoB-100, ApoC-III, ApoC-II, ApoA-I, and ApoA-V)

The mean percent change (+/-SD) will also be plotted by visit.

3.4.4. Efficacy Analysis on Subgroups of Participants

Summary statistics will be presented for the primary efficacy endpoint of LDL-C using Friedewald formula in each subgroup by each treatment arm and total.

Prespecified subgroup analyses will be based on:

- Concomitant PCSK9 Inhibitor Use (Yes, No)

- 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

3.5. Safety Analyses

Safety analyses will be summarized by treatment arm and overall in the Safety Analysis Set.

3.5.1. Adverse Events

AE terms will be coded using the MedDRA dictionary version 24.0 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.

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. Serious adverse events (SAEs), TEAEs related to study drug, TEAEs leading to study drug discontinuation, and injection site reactions (ISR) will also be listed separately.

An overall AE summary will be present by the number and percent of patients with the following:

- All TEAEs
- Serious TEAEs
- Study drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Study drug-related TEAEs leading to study drug discontinuation
- TEAEs leading to death
- ISR

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

- All TEAEs
- Serious TEAEs

- Study drug-related TEAEs
- TEAEs leading to study drug discontinuation
- 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.

Injection site reactions (ISR)

The number and percentage of participants reporting ISRs, as well as the number of ISRs will be summarized by PT and maximum severity grade.

3.5.2. 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 will be presented by each ARO-ANG3 200 mg and 300 mg for each assessment time point, beginning with the Screening visit.

Counts and percentages of subjects with any post-baseline observation that is below the lower limit of normal (<LLN) or above the upper limit of normal (>ULN) will be summarized for each hematology and chemistry parameter by treatment group and total.

Shifts from baseline to worst post-baseline value will be presented for specified lab tests (Alanine aminotransferase [ALT], Aspartate aminotransferase [AST], creatine kinase [CK], total bilirubin) by treatment group and total.

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

- ALT or 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

3.5.3. Vital Signs

Vitals Signs results (weight, 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.

3.5.4. 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.

3.5.5. Physical Examination

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

3.5.6. Other Safety Analyses

Substance use:

Substance use results collected at Screening will be listed.

3.6. 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. Also, the titer values will be summarized descriptively for each time point by treatment if data available.

3.7. PK Analyses

For the 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 the 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-ANG3 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.

3.8. Interim Analysis

An interim analysis is planned for this study after a majority of participants complete the Week 24 visit. Safety data and selected PD data, will be reviewed in aggregate by treatment groups.

4. CHANGES FROM PROTOCOL-SPECIFIED STATISTIC ALANALYSES

No changes have been issued or planned.

5. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 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.