NOVOTECH
The Asia Pacific CRO

STATISTICAL ANALYSIS PLAN

A PHASE 1 SINGLE AND MULTIPLE DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMIC EFFECTS OF ARO-ANG3 IN ADULT HEALTHY VOLUNTEERS AND IN DYSLIPIDEMIC PATIENTS

Protocol No.: AROANG1001

Product Code: ARO-ANG3

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SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed by Novotech Inc., and has been approved for use on the AROANG1001 study:

Name	Title / Company	Signature	Date
Alan Herschtal	Principal Statistician, Biometrics, / Novotech	Electronically signed by: Jan Steyn Reason: I approve Date: Jul 16, 2021 12:37 GMT+10	16-Jul-2021

By my signature, I confirm that this SAP has been reviewed by Arrowhead Pharmaceuticals Inc., and has been approved for use on the AROANG1001 study:

Name	Title / Company	Signature	Date
Mei Dai	Associate Director, Clinical Pharmacology / Arrowhead	mei dai Electronically signed by: mei dai Reason: I have reviewed Date: Jul 16, 2021 14:42 EDT	16-Jul-2021
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1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data from AROANG1001 study.

This Statistical Analysis Plan (SAP) is an adjunct to the Arrowhead Pharmaceuticals protocol number AROANG1001 (Version 7.1, 15 Jan 2020). The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2. PROJECT OVERVIEW

2.1 Study Design

This is a phase 1 single and multiple dose-escalating study to evaluate the safety, tolerability, Pharmacokinetics and Pharmacodynamic Effects of ARO-ANG3 in Adult Healthy Volunteers and in Dyslipidemic Patients.

ARO-ANG3 is a drug candidate developed by Arrowhead Pharmaceuticals, Inc. to treat dyslipidemia. ARO-ANG3 is administered through subcutaneous injection.

This study will include the following cohorts, with the dose escalation schedule plotted as below. Dose escalation and start of new cohort are subject to Data Safety Committee (DSC) approval based on the evaluation of all available safety data.

- Cohorts 1, 2, 3 and 4: Healthy Volunteers (HV) with fasting TG>100mg/dL and fasting LDL-C >70mg/dL.

  Each of cohorts 1 – 4 cohort will recruit 10 healthy volunteers, with subjects randomized to receive placebo (4 subjects) or active ARO-ANG3 (6 subjects) in a double blinded fashion. The first two subjects in each cohort serve as sentinel subjects (one ARO-ANG3 and one placebo).
  Cohorts 1 – 4 will be single dosed as follows:
  - Cohort 1: 35 mg ARO-ANG3 or PBO, at Day 1
  - Cohort 2: 100 mg ARO-ANG3 or PBO, at Day 1
  - Cohort 3: 200 mg ARO-ANG3 or PBO, at Day 1
  - Cohort 4: 300 mg ARO-ANG3 or PBO, at Day 1
- Cohorts 2b, 3b and 4b: HV's.

  Each of cohorts 2b – 4b will recruit four (4) healthy volunteers in an open label fashion with all cohorts planned to receive multiple escalating doses of ARO-ANG3 at escalating dose levels of 100, 200, and 300 mg.
  Cohorts 2b – 4b will be multiple dosed as follows:
  - Cohort 2b: 100 mg ARO-ANG3, at Days 1 and 29
  - Cohort 3b: 200 mg ARO-ANG3, at Days 1 and 29
  - Cohort 4b: 300 mg ARO-ANG3, at Days 1 and 29
- Cohorts 5 with liver fat fraction of ≥ 10%:

  Cohort 5 will recruit 9 subjects (6 active and 3 PBO) in a double blinded fashion who have a liver fat fraction of ≥10% based on MRI-PDFF conducted at Screening.

- Cohorts 6: Patients on a stable statin regimen with LDL-C >70 mg/dL

  Cohort 6 will recruit 9 subjects (6 active and 3 PBO) in a double blinded fashion who are on a stable drug treatment regimen for elevated LDL-C including a statin for at least 6 months and with fasting Screening LDL-C > 70 mg/dL. All patients in cohort 6 will receive 200mg ARO-ANG3 or PBO, at Days 1 and 29

- 7, 7b and 7c: familial hypercholesterolemia.

  Cohort 7, 7b and 7c will each recruit up to 6 patients with a diagnosis of heterozygous or

homozygous familial hypercholesterolemia, defined as a documented positive genetic test OR Dutch Lipid Clinic Network Score ≥ 6 for NZ participants or ≥ 8 for all other participants, with LDL-C > 100 mg/dL (2.59 mmol/L) despite standard of care therapy OR with LDL-C > 70 mg/dL (1.81 mmol/L) while on a PCSK-9 inhibitor OR with LDL-C > 70 mg/dL (1.81 mmol/L) in the presence of documented atherosclerotic cardiovascular disease.
Cohorts 7, 7b and 7c will be multiple dosed as follows:

- Cohort 7: 200 mg ARO-ANG3, at Days 1 and 29
- Cohort 7b: 100 mg ARO-ANG3, at Days 1 and 29
- Cohort 7c: 300 mg ARO-ANG3, at Days 1 and 29

- Cohort 8: TGs ≥ 300 mg/dL (3.39 mmol/L)

  Cohort 8 is open-label with up to 6 patients with fasting serum triglycerides of at least 300 mg/dL (3.39 mmol/L). All subjects to receive 200 mg of ARO-ANG3 on Days 1, 29

- Cohort 9: an open-label extension (continued access) cohort into which patients from Cohorts 7, 7b and 7c may elect to enroll after completing the scheduled regimen of treatment under their original cohort.
  - 200 mg ARO-ANG3, at Days 113, 197, 281 and 365

Study part will be used in this SAP to describe the following:

- Healthy Volunteers (SAD)
  - Cohorts: 1, 2 ,3 and 4
- Healthy Volunteers (MAD)
  - Cohorts: 2b ,3b and 4b
- Disease Cohorts (MAD)
  - Cohort 5, 6, 7, 7b, 7c, 8 and 9

Dose Escalation Schedule

Single Dose Healthy Volunteers (double blind in cohorts 1, 2, 3, 4)			Multi-dose Patients (double blinded in cohorts 5, 6, open label in 2b, 3b, 4b, 7, 7b, 7c, 8)
Cohort*	Dose (Day 1)	Day 8 safety evaluation	Dose Regimen
Cohort 1**	35 mg		NA
Cohort 2**	100 mg		NA
Cohort 3**	200 mg		NA
Cohort 4**	300 mg		NA
			Cohort 5***: 200 mg or PBO dosed on Day 1, 29
			Cohort 6***:200 mg or PBO dosed on Day 1, 29
			Cohort 8***: 200 mg dosed on Day 1, 29
			Cohort 2b****: 100 mg dosed on Day 1, 29
			Cohort 3b****: 200 mg dosed on Day 1, 29
			Cohort 4b****: 300 mg dosed on Day 1, 29
			Cohort 7***: 200 mg dosed on Day 1, 29
			Cohort 7b****: 100 mg dosed on Day 1, 29
			Cohort 7c****: 300 mg dosed on Day 1, 29
			Cohort 9*****: 200 mg dosed on Days 113, 197, 281 and 365

* Cohorts 1, 2, 3 and 4 will use 2 sentinel subjects

**Dose escalation to the next highest dose level or to multiple dosing will occur after cumulative safety data through Day 8 for Cohorts 1, 2, 3, and 4 have been evaluated by the DSC

***Screening and enrolment into Cohorts 5, 6, 7 and 8 may not occur until an amended protocol justifying the dose to be used in these cohorts has been approved by the EC.

****No DSC vote is required to open these cohorts. These cohorts may enroll in parallel

***** Patients from Cohorts 7, 7b and 7c may elect to continue to receive up to four 200 mg doses administered approximately every 12 weeks. No DSC vote is required for patient to roll over into Cohort 9.

Participants who are withdrawn or discontinue prior to EOS for reasons other than an adverse event, may be replaced at Sponsor's discretion.

Cohorts 1 through 4 will enroll sequentially. Cohorts 5, 6, 7 and 8 may be opened by the DSC after review of cumulative safety data through Day 8 of Cohort 4 and only after approval by the HREC of an amended protocol updating safety information from Cohorts 1 through 4 which will include a rationale for the dose level to be used in Cohorts 5, 6, 7and 8 (See Section 4.8). These multi-dose patient cohorts may enroll in parallel after they are opened for enrollment by the Data Safety Committee (DSC) and after the amended protocol has been approved by the HREC. Screening for Cohorts 5, 6, 7 and 8 may begin after the described amended protocol has been approved by the EC.

Pharmacokinetic (PK) intensive sampling will be conducted for cohorts 1, 2, 3, 4, 2b, 3b and 4b on Day 1 (dosing day) at the time of 0 (pre-dose), 15 minutes, 0.5, 1, 2, 3, 6, 24 and 48 hours post-dose.

Additionally, PK intensive sampling will be conducted for cohorts 2b, 3b and 4b at the same time points relative to the Day 29 dose.

2.2 Objectives

2.2.1 Primary objective

To determine the incidence and frequency of adverse events possibly or probably related to treatment as a measure of the safety and tolerability of ARO-ANG3 using escalating single and multiple doses in healthy volunteers and multiple doses in dyslipidemic patients.

2.2.2 Secondary objectives

- To evaluate the single-dose and multi-dose pharmacokinetics of ARO-ANG3 in healthy volunteers.
- To determine the reduction in fasting serum ANGPTL3 from baseline in response to single and multiple doses of ARO-ANG3 as a measure of drug activity in healthy volunteers and in response to multiple doses of ARO-ANG3 in dyslipidemic patients (all values drawn after at least 8 hour fast).

2.2.3 Exploratory objectives

- To evaluate the effect of single or multiple doses of ARO-ANG3 on change from baseline in:
    - Fasting LDL-C
    - Total Cholesterol
    - non-HDL-C
    - HDL-C
    - VLDL-C
    - Triglycerides
    - Lp(a)
    - Total ApoB
    - apoB-48
    - apoB-100
    - apoC-III
    - apoC-II
    - apoA-V
    - lipoprotein lipase mass (if feasible)
    - CETP mass (if feasible)
    - apoA-I (all values drawn after at least 8 hour fast)
    - .
- To evaluate the effect of single or multiple doses of ARO-ANG3 on changes from baseline in BMI.
- To evaluate the effect of single or multiple doses of ARO-ANG3 on changes from baseline in fasting serum blood glucose, C-peptide, hemoglobin A1C, GTT and fasting serum insulin.

- To evaluate the effect of multiple doses of ARO-ANG3 on change from baseline liver fat content using Magnetic Resonance Imaging (using MRI-PDFF, Cohort 5 only).
- To evaluate the effect of multiple doses of ARO-ANG3 on change from baseline in post-prandial (post standardized high fat/high carbohydrate meal) serum TGs in specified cohorts.
- To evaluate excretion of ARO-ANG3 (full length and metabolites) and identify metabolites in plasma and urine in the multi-dose healthy volunteer cohorts (2b, 3b and 4b).

2.3 Study Endpoints

2.3.1 Primary Endpoints

- AEs/SAEs –
  - System Organ Class and Preferred Term;
  - Grade (mild, moderate or severe)
  - Causality (relationship to study treatment: Not Related, Possibly Related or Probably Related)
- Physical examinations –
  - Height
  - Weight
  - BMI
- Vital signs (Systolic/diastolic blood pressure, temperature, heart rate, respiratory rate)
- ECG measurements (using single 12-lead ECG)
- Injection Site Reactions (Mild, Moderate or Severe)
- Clinical laboratory tests (Biochemistry (including hemoglobin A1C), Hematology, Coagulation, Urinalysis, Microscopic urinalysis (if indicated), Serology, FSH, Drug and Alcohol use, Pregnancy, Lipid Parameters, Serum insulin levels, Serum glucose levels, Stool occult blood test)
- Concomitant medications/therapy, and
- Reasons for treatment discontinuation due to toxicity

2.3.2 Secondary Endpoints

<u>Plasma Pharmacokinetics (Cohorts 1, 2, 3, 4, 2b, 3b and 4b)</u>

- Blood samples will be collected for cohorts 1, 2, 3 and 4 at the time points of 0 (pre-dose), 15 min, 0.5, 1, 2, 3, 6, 9, 12, 18, 24 & 48 hours post-dose on Day 1. Blood samples will also be collected for cohorts 2b, 3b and 4b at the same time points relative to each of the dosing days (Days 1 and 29).

Urine pharmacokinetics (Cohorts 2b, 3b and 4b)

- Urine will be collected cumulatively from 0-6 hours and 6-24 hours post-dose for both doses (Day 1 and 29). In addition, spot collection will be performed on Days 1 (pre-dose), 8, 15, 22 and 29 (pre-dose). Urine creatinine will be measured on all urine samples (interval and spot collections), Metabolite ID will be performed on urine samples collected (pooled analysis).

Pharmacodynamics

- fasting serum ANGPTL3

2.3.3 Exploratory endpoints

Pharmacodynamics

- fasting LDL-C
- Total Cholesterol
- Fasting non-HDL-C
- Fasting HDL-C
- Fasting VLDL-C
- Fasting Triglycerides
- Fasting Lp(a)
- Fasting Total ApoB
- Fasting apoB-48
- Fasting apoB-100
- Fasting apoC-III
- Fasting apoC-II
- Fasting apoA-V
- lipoprotein lipase mass (if feasible)
- CETP mass (if feasible)
- Fasting apoA-I
- Hemoglobin A1c
- C-peptide
- fasting serum blood glucose
- C-peptide
- hemoglobin A1C
- GTT
- fasting serum insulin
- post-prandial Triglyceride (TG) Test
- liver fat content using Magnetic Resonance Imaging

Physical Exam

- BMI

2.4 Sample Size

2.5 This study represents a proof of principle study, and as such no formal sample size calculation was performed. Randomization

Eligible subjects in double-blind cohorts (cohorts 1, 2, 3, 4, 5 and 6) will be allocated a unique randomization number, in accordance with the randomization schedule. In each cohort, the first two subjects (sentinels) will be randomized separately to one active (ARO-ANG3) and one PBO. Each participant will be assigned to either active or PBO treatment. The allocation of active treatment or PBO will be performed using a block randomization algorithm.

All other cohorts (2b, 3b, 4b, 7, 7b, 7c, 8 and 9) are open label and participants in these cohorts will not be randomized.

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed according to the sponsor's representative (Novotech (Australia) Pty Ltd) Standard Operating Procedures (SOPs), which are written based on the principles of GCP.

All data collected on the eCRFs will be presented in the data listings and will be listed and sorted by participant number and visit, where applicable. All dates in listings will be presented in YYYY-MM-DD format. Summaries will be presented for the active drug patients in each cohort considered separately and for placebo patients pooled across cohorts, as well as overall (all active drug and placebo patients combined), as applicable.

Unless otherwise stated, the following basic descriptive statistics will be provided:

- Continuous variables: the number of non-missing values (N), mean, standard deviation (SD), median, minimum, maximum. For PK variables, the coefficient of variance (CV) the geometric mean, the geometric CV, and the number below the minimum level of quantification (n BLQ) will also be provided.
- Categorical variables: frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population with non-missing data, unless otherwise specified.

Baseline values will be defined as the last non-missing observation (pre-dose value closest to the first dose) for each participant prior to the dosing of study medication (i.e. start of injection on Day 1).

Medpace Research Labs (MRL) will be used as the preferred data source for calculations/analysis for the following PD markers: ANGPTL3, fasting LDL-C, Total Cholesterol, non-HDL-C, HDL-C, VLDL-C, Triglycerides, total apoB, apoB-48, apoB-100, apoC-III, apoA-I, apoC-II, apoA-V, lipoprotein lipase mass (if feasible), CETP mass (if feasible), Hemoglobin A1c and C-peptide.

If there is a repeat assessment, the repeat result would be used in the analysis table and the original result will only appear in listings. All repeat assessments captured in the Electronic Data Capture (EDC) system will be presented in the data listings.

Generally, no missing data will be imputed.

For continuous valued PD variables that have samples reported as BLOQ (post-baseline/day 1 visit), a nominal value of ½ LLOQ will be used for calculations. For samples reported as above the upper limit of quantitation, a nominal value equal to ULOQ will be used in calculations.

Continuously valued safety variables will be reported to the same precision as the source data. Derived variables will be reported using the same precision as the value(s) from which they were derived. For the reporting of descriptive statistics, the mean, median and SD will be reported to 1 decimal place more than the source data; the minimum and the maximum values will be presented to the same precision as the source data. Rounding is not allowed in the middle of calculations. It only takes place at the last step to report the final result. Post-dose time points/visits will be calculated relative to start time of injection on Day 1. Study day will be defined as the assessment date minus the dosing date +1.

Baseline demographic statistics will be tabulated (for categorical variables) and summarized (for continuously valued variables) by cohort for active drug patients, for placebo patients pooled and for all patients (active drug and placebo) considered collectively. Eligibility assessments at

baseline, including medical/surgical history data and physical examination data (including height and weight), will be listed for each participant.

3.1 Adverse event imputation rules

Adverse events will be flagged as treatment emergent using valid answers to the questions “For events that occurred on Day 1, did the event occur before start of study drug administration?” or “Did the event start before first dose of investigational product?” on the eCRF regardless of whether or not the AE onset date is complete. Adverse events that cannot be definitely determined as occurring prior to study drug administration will be counted as treatment emergent adverse events 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.

3.2 Concomitant medication imputation rules

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

Concomitant medication 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.

3.3 Procedure date imputation rules

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

4. ANALYSIS POPULATIONS

In this study, three analysis populations are defined: Safety Population, Pharmacokinetic Population, and Pharmacodynamic population. Data for Screen Failures will not be included in any summary tables, figures, or data listings. Subjects to be included in the defined (various) analysis populations will be decided upon at the blinded data review meeting prior to unblinding of double blinded cohorts. Unblinding of healthy volunteer cohorts may occur at Sponsor discretion on a cohort by cohort basis after all subjects in a cohort have completed their last planned on-site study visit (Day 113 End of Study). Study participants as well as sites will remain blinded. The same process will be applied to the open label cohorts even though there is no blinding for these cohorts.

Furthermore, any additional analysis populations not identified in the SAP will be identified in the final CSR as post hoc analyses. This may include additional study populations or subgroups of interest.

The number and percentage of subjects in each analysis population will be summarized.

Safety Population

All subjects who receive at least one dose of study treatment (ARO-ANG3 or PBO) will be included in the Safety Population. Subjects will be summarized according to the treatment they received.

All safety, treatment exposure, demographic and baseline characteristic data will be listed and summarized using the Safety Population.

Pharmacokinetic (PK) Population

Subjects who have received the active treatment (ARO-ANG3) and have adequate PK data to characterize PK profile will be included in the PK Population.

Subjects who prematurely discontinue from the study will be included in the Safety Population but may not be included in the PK Population if they do not have PK data to contribute to the analyses. Subjects with missing sample concentrations will be included in the PK analyses provided their PK parameters can be adequately characterized based upon the remaining data. Subjects who received placebo will be excluded from the PK population. The PK population will be used for the summaries of all PK data.

Subjects with protocol violations will be assessed on a participant-by-participant basis for inclusion in the PK Population.

Pharmacodynamic (PD) Population

Subjects who received at least one dose of study treatment (ARO-ANG3 or placebo) and had PD assessment from baseline and ≥1 assessment from post-baseline will be included in the PD population. Subjects will be summarized according to the treatment they received.

Subjects with protocol violations will be assessed on a participant-by-participant basis for inclusion in the PD Population. The determination of study populations will be made, prior to unblinding the PD data, at the blinded data review meeting before the final analyses. The PD population will be used for the summaries of all pharmacodynamic endpoints.

5. PARTICIPANT DISPOSITION

All subjects who provide informed consent and are randomized (Cohorts 1, 2, 3, 4, 5 and 6) or enrolled (Cohorts 2b, 3b, 4b, 7, 7b, 7c, 8 and 9) will be accounted for in this study. Participant disposition will be summarized using the Safety Population.

By-participant data listings for participant disposition will be generated, including informed consent date, randomization date/number (double blinded subjects), completion status, date of withdrawal and reason for withdrawal from the study, or date of screen failure and reason for screen failure if applicable.

The number of subjects randomized / enrolled, as well as the number and percentage of subjects completing the study and withdrawn from the study will be presented by study part and treatment group (dose level), for placebo patients pooled and overall. The reason for withdrawal will also be summarized for all subjects who do not complete the study.

6. PROTOCOL DEVIATIONS

Any protocol deviations will be presented for each participant in the by-participant data listings. Frequent deviations will be listed individually and rare ones will be combined as other or important deviations will be listed separately.

Prior to database lock, all protocol deviations will be reviewed by medical monitors and assigned a category (see below).

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the patient, investigator, or site staff. All deviations will be tracked and should be reported to IRBs in accordance with their reporting policy. Examples of deviations include, but are not limited to:

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

7. DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline body measurements will be summarized using the Safety Population.

7.1 Demographics

Demographic data, including age, gender, race, and physical examination data (weight, height and BMI), will be summarized by study part and treatment group (dose level) for active drug patients, for placebo patients pooled and overall. A by-participant data listing for demographic characteristics will be generated by cohort.

Baseline disease characteristics including serum ANGPTL3, fasting LDL-C, Total Cholesterol, non-HDL-C, HDL-C, VLDL-C, Triglycerides, Lp(a), total apoB, apoB-48, apoB-100, apoC-III Hemoglobin A1c, C-peptide and apoA-I will be summarized by study part and treatment group (dose level) for active drug patients, for placebo patients pooled and overall. A by-participant data listing for these characteristics will be generated.

7.2 Medical history

Past medical history will be coded using the Medical Dictionary for Regulatory Activities, MedDRA® with the latest available version. Medical history data, including the MedDRA codes, will be presented in the by-participant data listings.

7.3 Informed Consent and Eligibility

Informed consent date, and inclusion/exclusion eligibility criteria information, including any criteria not met, will be listed for each participant.

7.4 Pregnancy Test (Urine)

Child-bearing potential (yes/no), and if No, the reason (post menopause, surgically sterile, and other), and pregnancy test results will be included in the by-participant data listings. This includes the urine dipstick pregnancy test results assessed regularly at the scheduled study visits. Screening Follicle-Stimulating Hormone (FSH) will also be listed.

7.5 Serology Screen (Hepatitis/HIV)

Data for Hepatitis B, Hepatitis C and HIV assessment at screening will be listed for each participant.

7.6 Urine Drug Screen

Urine Drug Screen results at Screening will be listed for each participant.

7.7 Alcohol Breath Test

Alcohol Breath Test results at Screening will be listed for each participant to test for alcohol consumption.

8. TREATMENT EXPOSURE

Study drug administration results will be presented using the Safety Population. Study drugs include ARO-ANG3 and placebo.

Each single dose of either active drug (ARO-ANG3) or PBO (normal saline 0.9%), will be administered by subcutaneous injection. Injections will be made into the subcutaneous tissue at an appropriate site (e.g. abdomen, thigh, upper arm, etc.). The abdomen is the preferred site. Injection site is to be varied (no multiple injections into the same exact site. Alternating various locations on the abdomen is acceptable). Injection site location is to be recorded in the eCRF.

A by-participant data listing will be generated for study drug (ARO-ANG3 or Placebo) administrations. This listing will include study drug administration date, time, dose, and injection site. If study drug was not administered, the reason why the drug was not administered will be reported.

9. PHARMACOKINETICS (PK)

Pharmacokinetic Assessment:

As noted above, plasma PK samples are collected for cohorts 1, 2, 3, 4, 2b, 3b and 4b on Day 1 (dosing day) at the time of 0 (pre-dose), 15 minutes, 0.5, 1, 2, 3, 6, 9,12,18, 24 and 48 hours post-dose, and additionally for cohorts 2b, 3b and 4b at the same time points relative to the Day 29 dose.

Urine PK samples will be collected for cohorts 2b, 3b and 4b from 0-6 hours and from 6-24 hours post-dose for both doses (Days 1 and 29). Spot urine collection will take place on Days 1 (pre-dose), 8, 15, 22 and 29 (pre-dose).

9.1 Pharmacokinetic Parameters

Pharmacokinetic parameters for ARO-ANG3 will be calculated from the plasma concentration-time and urine excretion data using noncompartmental methods (Phoenix™ WinNonlin®, Version 8.1.0 or later, Princeton, NJ.) and actual sample collection times. The following Plasma and urine PK parameters for ARO-ANG3 will be reported on Day 1 for subjects in cohorts 1, 2, 3, 4, 2b, 3b and 4b, as well as on Day 29 for subjects in cohorts 2b, 3b and 4b, whenever data applicable:

Variable	**Definition**
Plasma PK parameters on Day 1 and Day 29	
AUC_{last}	The area under the plasma concentration-time curve, from time 0 (time of dosing) to the last time point with measurable analyte concentration.
$AUC_{0\text{-}24}$	Area under the plasma concentration-time curve, from time 0 to the 24-hour time point.
AUC_{inf}	Area under the plasma concentration-time curve extrapolated to infinite time
$AUC_{\%extrap}$	The extrapolated portion of AUC_{inf} calculated as: $AUC_{\%extrap} = 100 \times \frac{C_{last} / \lambda_z}{AUC_{inf}}$
C_{max}	Maximum observed PK concentration.
t_{max}	Time to reach C_{max}. If the maximum observed concentration value occurs at more than 1 time point, t_{max} is defined as the first time point with this value.
$t_{½}$	Terminal elimination half-life computed as: $t_{½} = \frac{\ln(2)}{\lambda_z}$ Where ln(2) is the natural logarithm of 2.
CL/F	Apparent total clearance of the drug from plasma calculated as: $CL / F = \frac{Dose}{AUC_{inf}}$
V_z/F	Apparent volume of distribution during the elimination phase calculated as: $V_z / F = \frac{Dose}{\lambda_z \cdot AUC_{inf}}$

Urine PK Parameters on Day 1 and Day 29	
$Ae_{0\text{-}24}$	Amount of unchanged drug excreted in the urine 0-24 hours postdose
$Fe_{0\text{-}24}$	Fraction excreted (or equivalently the percent of dose excreted) in the urine, calculated by 100 • (Ae, 0-24 h/ Dose).
CL_R	Renal clearance calculated as: $$CL_R = \frac{Ae_{0-24}}{AUC_{0-24}}$$

Additional PK parameters such as dose normalized C_{max} and AUCs, or BW normalized PK parameters may be estimated as appropriate.

The Sponsor will provide NCA analysis of plasma and urine PK data, details about the PK parameters calculation in Appendix A.

9.1.1 Non-Quantifiable Concentrations

All concentration values reported as no results (not collected or not determined) values will be treated as missing. For the calculation of concentration summaries, all concentrations below the quantifiable limit (BLQ) will be treated as 0, however, for estimating geometric mean and geometric CV% they will be treated as missing.

9.2 Biostatistical methods

9.2.1 Listings and Descriptive Summary Statistics – Plasma PK

ARO-ANG3 plasma concentrations will be listed by cohort, participant, dosing day (for cohorts 2b, 3b and 4b) and collection time. ARO-ANG3 concentrations will be summarized descriptively by study part, treatment group (dose level), dosing day and nominal sampling time for the PK Analysis Population, including n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV(%)], geometric mean (GM), geometric SD, geometric CV%.

The actual blood sampling dates and times relative to dosing time will be listed by study cohort, participant and nominal sampling time, with time deviation calculated, for all subjects with available plasma concentration data, including subjects receiving placebo or excluded from the PK Analysis Population.

Individual plasma concentration of ARO-ANG3 will be plotted on a linear and semi-log scales versus nominal time for each part/treatment. For each cohort, the spaghetti plots of individual plasma ARO-ANG3 on a linear and semi-log scales will also be presented.

Mean plasma PK concentration vs. nominal time will be plotted on both linear and semi-log scales for ARO-ANG3 by part and treatment. The mean concentration vs. nominal time may also be plotted by dose level across different populations if no significant difference between populations.

Plasma PK parameters for ARO-ANG3 will be listed by cohort and summarized by study part and treatment group (dose level) descriptively, including n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV(%)], geometric mean (GM), geometric SD, geometric CV%; For t_{max}, only n, minimum, median, and maximum will be reported. Diagnostic PK parameters listed in appendix A will be listed only. PK parameters may also be summarized as appropriate by dose level which included different populations.

Geometric CV% = 100*(exp(SD^2)-1)^0.5, where SD is the standard deviation of the log-transformed data.

Actual sampling times that are outside the sampling window (± 2 minutes for <6 hour timepoints; ± 5 minutes for the 8 - 48 hour timepoints;) will be listed and used for PK parameters calculation but will be excluded from summary of PK concentration.

9.2.2 Listings and Descriptive Summary Statistics – Urine PK

ARO-ANG3 urine concentrations/volume and PK parameters will be listed for each subject cohort, dosing day, and sampling time (for the case of spot collection) or time interval. ARO-ANG3 urine PK parameters will be summarized by study part, treatment (dose level) and dosing day using the PK Analysis Population.

Summary tabulations will display the number of observations, mean, SD, CV (%), median, minimum and maximum.

9.2.3 Pharmacokinetic Dose Proportionality

The dose proportionality of the Day 1 plasma PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}) for cohort 1-4, and cohort 2b, 3b, and 4b, will be investigated using the following power model,

$\ln(\text{PK parameter}) = \beta_0 + \beta_1 * \ln(\text{dose})$, where β_0 is the intercept and β_1 is the slope.

Each log-transformed PK parameter will be fit with a power model with a fixed effect term for log-transformed dose. For each PK parameter, the slope and associated 90% CI will be presented. A minimum of 3 values per dose cohort must be available for a given parameter to estimate dose proportionality with the power model.

The following is the example SAS code to be implemented:

```
PROC MIXED DATA=PKPARM;
      BY PARAMCD;
      MODEL LOGPK= LOGDOSE / SOLUTION CL;
      ESTIMATE "SLOPE" LOGDOSE 1 / ALPHA = 0.1 CL;
      ESTIMATE "INTERCEPT" INTERCEPT 1 / ALPHA = 0.1 CL;
      ODS OUTPUT SOLUTIONF =SOLNF;
      ODS OUTPUT ESTIMATES =ESTIMATE;
RUN;
```

Dose proportionality will be indicated if the 90%CIs for β all contain 1.

Plasma PK dose proportionality will also be assessed using the Day 29 PK parameters.

The dose proportionality may also be performed by dose level which included different population as appropriate.

10. SAFETY

Statistical methods for the safety analyses will be primarily descriptive in nature. Safety for each study part and treatment group (dose level) for active drug patients and for placebo patients pooled will be summarized separately.

Safety endpoints included in the analysis are AEs, injection site reactions, concomitant medications, clinical laboratory assessments, vital signs, physical examination, 12-lead ECG and reasons for treatment discontinuation. Safety endpoints will be analyzed using the Safety Population. Adverse Events, ISRs and Concomitant Medications are discussed in section 10 below. Laboratory Abnormalities, Pregnancies, Vital Signs, Physical Exam and ECGs are discussed later in their respective sections.

10.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®, the latest available version), and data will be summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percent of subjects reporting each AE will be summarized for each cohort and treatment group as well as overall. A participant with two or more AEs within the same level of summarization (i.e. SOC or PT) will be counted only once in that level. Percentages will be based on the number of subjects in the Safety Population within each dose level (cohort). The number of AEs reported will also be presented. A count of the total number of AEs for each cohort and treatment group, including multiple AEs per participant will also be provided.

Treatment-emergent AEs (TEAEs) are defined as pre-treatment existing conditions that worsen after study drug administration, or events that occur during the course of the study, during or after administration of study drug. Only TEAEs will be included in the AE summary tables, which will present data by cohort for active treatment patients and pooled for normal healthy volunteer cohort placebo subjects (cohorts 1, 2, 3 and 4) and patient cohort placebo subjects (cohorts 5 and 6). In the case of a missing AE start date or stop date, the most conservative approach will be followed, whereby an AE is classified as a TEAE unless it is not possible that the AE could be treatment emergent.

A table providing an overall summary of AEs will be produced. This will include the number of TEAEs; the number and percentage of subjects reporting at least one: TEAE, serious TEAE, grade 3 (severe) or higher TEAE, TEAE related to study treatment (possibly or probably related to ARO-ANG3), serious TEAE related to study treatment, grade 3 or higher TEAE related to the study drug and TEAE leading to drug or study withdrawal. TEAEs will also be tabulated by severity and by relationship to treatment.

For each cohort considered separately, additional AE tables will be generated as follows:

- TEAEs by SOC and PT in decreasing order of frequency
- TEAEs by PT in decreasing order of frequency
- TEAEs by Severity
- TEAEs by Relationship to Study Drug (ARO-ANG3)
- Treatment Emergent SAEs
- Study Drug (ARO-ANG3 or placebo) Related SAEs by SOC and PT
- TEAEs Leading to Study Drug or Study Withdrawal
- TEAEs occurring in >1 study participant in decreasing order of frequency

A by-participant AE data listing, including verbatim term, MedDRA (latest version) SOC and PT, severity, outcome and relationship to study treatment, will be provided. Separate listings will be generated for SAEs. AEs that started during the follow-up period will be flagged.

10.2 Adverse Events (AEs) at the Injection Site and Local Injection Site Reactions (LISR)

For purposes of data analysis, a local injection site reaction (LISR) is defined as an adverse reaction (usually immunologic) developing at the site of injection, lasting at least 48 hours, and is based on the specified MedDRA preferred terms provided below. For data analysis purposes AEs at the injection site with reported terms of bruising or hematoma will not be considered injection site reactions.

LISRs will only include events that start within 24 hours of the injection and persist for at least 48 hours from time of onset. Events for which it is not possible to determine whether the event duration was at least 48 hours (due to a partial start or end date or time) will be considered as LISRs.

Local Injection Site Reactions (LISR) will be reviewed based on description of symptoms, level of severity (mild, moderate or severe) and outcome of the reactions as well as other relevant data elements such as de/re-challenge, medical history, and possible confounding variables. Based on the review, the reactions will be specifically categorized and collated for the analysis.

The results will be summarized by cohort across all dose levels and percentages for the reported LISR by using the MedDRA coding system by System Organ Class (SOC), General disorders and administration site conditions and Preferred Terms that are associated with local injection site reactions.

The following MedDRA Preferred Terms 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 pain	Injection site erosion
Injection site oedema	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	

Those summaries will only include events that start within 24 hours of injection and persist for at least 48 hours from the onset of event. Events with onset within 24 hours of injection and missing resolution date will also be included in the summary.

The percentage of injections leading to local injection site reactions will be summarized using descriptive statistics.

The following calculation will be utilized to determine the percentage of injections leading to local injection site reactions for each participant:

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

The results of local injections site reactions will be provided in summary tabulation.

The same analysis applied to LISR's will be applied to all AE's at the injection site.

For the extension cohort (Cohort 9), an event that starts post the first dosing of Cohort 9, will be attributed to Cohort 9 only.

10.3 Concomitant medication

Concomitant medications and non-drug therapies will be coded using the World Health Organization Drug Dictionary (WHO-DD, the latest available version). Concomitant medications are medications taken at least once after the start of first study-drug administration. Medications stopped prior to the day of the start of first study-drug administration will not be considered concomitant medication. Prior medications will not be summarized, but they will be listed along with concomitant medications. Only concomitant medications will be summarized. Medications that started during the follow-up period will only be included in the follow-up concomitant summary table and will be flagged in the listing.

Individual data listings will be presented for each participant and summarized by WHO-DD Anatomical Therapeutic Chemical (ATC) anatomical group, and preferred term using frequency counts and percentages. Subjects who take the same medication more than once will be counted only once for that preferred term.

The number of concomitant medications reported, and the number and percentage of subjects reporting at least one concomitant medication will be presented per cohort. The number and percentage of patients reporting concomitant medications associated with each ATC anatomical group and preferred term will be reported by cohort.

For the extension cohort (Cohort 9), concomitant medications that are taken at least once after the first dosing of Cohort 9, will be attributed to Cohort 9. If the concomitant medication start date/time is before the first dosage given for Cohort 9, the concomitant medication will be assigned to the Cohort 9 as well as the previous cohort the participant was assigned to. Otherwise the concomitant medication will be assigned Cohort 9.

10.4 Laboratory (excluding PK/PD)

10.4.1 Definition of variables

Hematology Parameters

- Hemoglobin
- Red Blood Cell Count
- Hematocrit
- Mean Cell Volume (MCV)
- Mean Cell Hemoglobin (MCH)
- Mean Cell Hemoglobin Concentration (MCHC)
- Platelets
- White Blood Cell Count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Chemistry Parameters

- Sodium
- Potassium
- Chloride
- Bicarbonate

- Glucose
- Urea
- Creatinine (including calculated creatinine clearance)
- Creatine kinase
- Uric acid
- Phosphate
- Total calcium
- Anion gap
- Albumin
- Globulins
- Protein
- Total bilirubin
- Conjugated bilirubin
- Gamma glutamyl transferase (GGT)
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate transaminase (AST)
- Lactate dehydrogenase (LD)
- Lipase
- C-reactive protein
- Troponin I

Coagulation Parameters

- Partial Thromboplastin Time (PTT)
- Prothrombin Time (PT)
- INR
- Fibrinogen

*Urinalysis Parameters**

- Leukocytes
- Nitrites
- Urobilinogen
- Protein
- pH
- Blood
- Specific Gravity
- Ketone
- Bilirubin
- Glucose

*Microscopic urinalysis will be performed if indicated: White blood cells, red blood cells, epithelial cells, and bacteria.

Serology

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody screen

Serum insulin levels

- Insulin levels will be measured as per the Schedule of Assessments.

Serum glucose levels

- Blood glucose levels will be measured as per the Schedule of Assessments. Glucose level included in metabolic panel is acceptable.

FSH

Post-menopausal status will be confirmed by follicle-stimulating hormone (FSH) level consistent with post-menopausal state.

Drug and Alcohol Use Screen

The following will be tested for by a urine drug screen

- Benzodiazepines
- Amphetamines
- Barbiturates
- Methamphetamines
- Methadone
- Opiates
- Phencyclidine
- Cannabinoids
- MDMA
- Cocaine

An alcohol breath test will be done to test for alcohol consumption.

Pregnancy
Females of childbearing potential will have a urine pregnancy test.

Other

- Stool occult blood
- lipid metabolic genotype (drawn on all consenting subjects but analyzed only if scientifically warranted at sponsor discretion)

10.4.2 Biostatistical methods

All hematology, chemistry, coagulation and urinalysis parameters, as well as blood glucose levels and insulin levels will be summarized using descriptive statistics for each dose level (cohort) for all time points assessed, including change from baseline (last valid pre-dose value) for all post-dose assessments.

For specific laboratory values (ALT, AST, platelets, CK, ALP, T bilirubin, Creatinine, lipase, GGT) shift tables will be provided cross-tabulating the laboratory value grade at the baseline visit against the worst grade at any of the post-baseline visits. For this purpose, laboratory values will be graded according to the CTCAE criteria v5.

All remaining laboratory values will be compared to the normal range of the single local laboratory, and values that fall outside of the normal ranges will be flagged as: H (High) or L (Low) in the data listings. Results that were flagged as ‘LP’ will be reported as ‘L’ and results flagged as ‘HP’ will be reported as ‘H’. Shift tables from Day 1 (pre-dose) to all follow-up visits will be generated for each of these hematology, chemistry and coagulation laboratory parameters with values of Within Normal Limits (WNL), High, and Low used for the shift categories.

Early termination visit value will be kept as a nominal visit value, as well as mapped to the closest Study Visit using visit window. The closest value to the scheduled visit date will be used for the Scheduled Visits value in case of multiple records. The visit windows can be viewed in Appendix B of this SAP.

All laboratory data will be included in the by-participant data listings. Microscopic urinalysis will only be listed. Listings will be provided for both Central Laboratory readings and Local Laboratory readings separately.

Drug and Alcohol Use results will be listed. FSH and pregnancy test results will also be listed. Pregnancy test results will be summarized separately by time point.

The above methods will exclude cohort 9, as separate summary tables will be produced for cohort 9 for hematology, chemistry and coagulation parameters, considering the different assessment time points for these laboratory values for this cohort. Basic descriptive statistics will be provided for each time point and each laboratory parameter, considering both the actual values and the change from baseline.

10.5 Vital Signs

10.5.1 Definition of variables

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Pulse Rate (beats/min)
- Body Temperature (°C)
- Respiratory rate (breaths/minute)

10.5.2 Biostatistical methods

All vital sign parameters will be summarized using descriptive statistics for each dose level (cohort) for all time points assessed, including change from baseline (last valid pre-dose value) for all post-dose assessments. Pre-dosing vital signs on Day 1 will be used as baseline data. If the Day 1 pre-dose baseline value is missing, then the data from screening will be used as baseline data as appropriate.

Early termination visit value will be kept as a nominal visit value, as well as mapped to the closest Study Visit using visit window. The closest value to the scheduled visit date will be used for the Scheduled Visits value in case of multiple records. The visit windows can be viewed in Appendix B of this SAP.

All vital sign parameters will be listed per cohort for active drug subjects, for placebo subjects pooled across cohorts, as well as for all patients (active drug and placebo) considered collectively, for all time points assessed.

The above methods will exclude cohort 9, as a separate summary table of the vital signs will be produced for cohort 9, considering the different assessment time points for vital signs for this cohort. Basic descriptive statistics will be provided for each time point for each vital sign parameter, considering both the actual values and the change from baseline.

10.6 Physical examination

10.6.1 Definition of variables

The following body systems will be assessed:

- General Appearance
- HEENT (Head, Eyes, Ears, Nose and Throat)
- Cardiovascular
- Lungs
- Abdomen
- Lymph nodes
- Genitourinary
- Extremities
- Neurological
- Skin
- Musculoskeletal
- Other

Abnormal results of physical examinations will be categorized as follows:

- Abnormal NCS (Not Clinically Significant)
- Abnormal CS (Clinically Significant).

10.6.2 Biostatistical methods

Physical examination will be summarized by study visit and treatment cohort for active drug patients, for placebo patients pooled across cohorts, as well as for all patients (active drug and placebo) considered collectively. The frequency counts and percentages of subjects with different physical examination results and their clinical significance (for abnormal) will be summarized.

According to the schedule of assessments, a complete physical exam will be performed at Screening. Symptom-directed physical examinations will only be conducted at other visits as necessary. Only complete exams (screening) will be summarized.

Early termination visit value will be kept as a nominal visit value, as well as mapped to the closest Study Visit using visit window. The closest value to the scheduled visit date will be used for the Scheduled Visits value in case of multiple records. The visit windows can be viewed in Appendix B of this SAP.

By-participant data listings will be generated for all the physical examination data, including the Investigator assessment of clinical significance for abnormal findings, for all time points assessed.

10.7 12-lead ECG

10.7.1 Definition of variables

- Heart Rate (beats/min)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcF interval (msec)
- Overall interpretation of 12-lead ECG:
  - Normal
  - Abnormal NCS (Not Clinically Significant)
  - Abnormal CS (Clinically Significant)

10.7.2 Biostatistical methods

Descriptive statistics will be calculated for heart rate, PR interval, QRS interval, QT interval, and QTcF interval, including change from baseline (last valid pre-dose value on Day 1) for each dose level (cohort) for all time points assessed.

12-lead ECG measurements will be obtained at the scheduled time points after the participant is semi-supine for at least 3 minutes. Any abnormal ECGs will be repeated in triplicate, with each measurement approximately 1 minute apart. If triplicate ECG parameters are available, the average of the triplicate ECG parameters will be used. Unscheduled visits will be excluded from summary tables. However, the findings from the unscheduled visits will be listed.

In addition, the overall interpretation of 12-lead ECG results will be classified using frequency counts and percentages for the categories of Normal, Abnormal NCS and Abnormal CS for each treatment group for all time points assessed.

Early termination visit value will be kept as a nominal visit value, as well as mapped to the closest Study Visit using visit window. The closest value to the scheduled visit date will be used for the Scheduled Visits value in case of multiple records. The visit windows can be viewed in Appendix B of this SAP.

All ECG data will be presented in the by-participant data listings.

10.8 Pharmacodynamics

10.8.1 Definition of variables

- Fasting serum ANGPTL3
- LDL-C direct
- LDL-C (by PUC)
- Total Cholesterol
- non-HDL-C
- HDL-C
- VLDL-C
- Fasting triglycerides
- Lp(a)
- Total apoB
- apoB-100
- apoB-48
- apoC-III
- apoC-II
- apoA-I
- lipoprotein lipase mass (if feasible)
- CETP mass (if feasible)
- apoA-V
- Serum insulin
- Fasting glucose
- Hemoglobin A1c
- C-peptide

10.8.2 Biostatistical methods

Pharmacodynamic measurements (lipid values) at baseline (last valid pre-dose value) as well as their nadir value and change from baseline to nadir (absolute and percentage) will be summarized using descriptive statistics for each cohort considered separately for active drug patients, for placebo patients pooled across cohorts, as well as for all patients (active drug and placebo) considered collectively. All PD parameters above will be summarized using SI units as well as standard US units as required for IND submission.

For each laboratory parameter and Cohort, the nadir to be used is the value at the time point at which the average of the parameter value is lowest or highest from baseline across that Cohort, depending on the direction of the change. Early termination visit value will be kept as a nominal visit value, as well as mapped to the closest Study Visit using visit window. The closest value to the scheduled visit date will be used for the Scheduled Visits value in case of multiple records. The visit windows can be viewed in Appendix B of this SAP.

At each post-baseline assessment time point, (Day 8, Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99 and Day 113), as well as a nominal early termination visit, summary statistics of the pharmacodynamic measurements, their absolute change from baseline and their percentage change from baseline will be provided.

All PD parameter data will also be listed by participant.

For each of the pharmacodynamic measurements, paired t-tests will be used to estimate differences between baseline and each post-baseline time point for each treatment group, as well as the corresponding 95% CI and p-value.

Percent change from baseline in ANGPTL3 and other selected PD parameters (fasting LDL-C, Total Cholesterol, non-HDL-C, HDL-C, VLDL-C, Triglycerides, total apoB, apoB-48, apoB-100, and apoA-I) will be evaluated using a linear mixed model repeated measures (MMRM) approach. The repeated measures are the percentage change from baseline values measured at scheduled Week 2-16 study visits. The model will include fixed effects for treatment, week, treatment by week interaction, baseline value as a continuous covariate, and baseline by treatment interaction. Only cohorts that have placebo control participants will be analyzed using MMRM. Specifically, up to three separate MMRM models will be constructed, corresponding to the following three comparisons, each considered separately:

1. compare active drug participants from Cohorts 1, 2, 3 and 4 against pooled placebo participants from these 4 cohorts;
2. compare active drug participants from Cohort 5 against placebo participants from the same Cohort (participant to sufficient data being available);
3. compare active drug participants from Cohort 6 against placebo participants from the same Cohort (participant to sufficient data being available).

The analysis will be carried out using the SAS PROC MIXED procedure using an unstructured within-patient covariance structure and Kenward-Roger approximation to estimate the degrees of freedom for tests of fixed effects. In case of any convergence issues, additional covariance structures will be investigated, or the interaction term of treatment and week may be omitted from the model. Model-based estimates of least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals will be reported for each time point while p-values will be presented for the Week 16 time point only.

SAS code is provided below.

```
PROC MIXED DATA=XXX;
CLASS SUBJID TREATMENT VISIT;
MODEL PCTCHGBL=TREATMENT VISIT TREATMENT*VISIT BASE TREATMENT*BASE/
DDFM=KR;
REPEATED VISIT/SUBJECT=SUBJID TYPE=UN;
LSMEANS TREATMENT*VISIT/ALPHA=0.05 CL DIFF;
ESTIMATE "TRT DIFF AT WEEK 2" TREATMENT 1 -1 TREATMENT*WEEK 1 0 0 0 0 0
0 0  -1 0 0 0 0 0 0 0/CL;
RUN;
```

This summary table will exclude cohort 9, as a separate summary table of the pharmacodynamic measurements will be produced for cohort 9, considering the different assessment time points for the pharmacodynamic measurements for this cohort. Basic descriptive statistics will be provided for the nadir value, change between baseline and nadir value, both in absolute and relative terms. The value recorded at the last assessment prior to the original entry into the study under Cohort 7, 7b or 7c will be taken as the baseline value. Similarly, the nadir will be the lowest value recorded since the original entry into the study.

GTT and post-prandial triglyceride (PPTG) testing will be measured at time points outlined in the Schedule of Assessments. In Cohort 8, post-prandial TG evaluation is only to be completed in patients who are not at risk for post-prandial hypertriglyceridemia related abdominal pain or pancreatitis. GTT is optional in any patient with diabetes mellitus.

Change from baseline in glucose tolerance, insulin tolerance and % liver fat fraction from MRI-PDFF will be summarized by descriptive statistics.

For ANGPTL3, triglycerides and LDL-C, the proportion of participants achieving durable response will be summarized per cohort and overall. Durable response will be defined as achieving a laboratory parameter value below a pre-specified threshold at or before the Day 113 follow-up visit and maintaining it until the Day 113 follow-up visit. Results will be reported for three separate thresholds – 20% of baseline, 40% of baseline and 80% of baseline. The following four durable response categories will be considered.

- **Never Achieved Response** – Participants with no results meeting the response level at any timepoint up until and including Day 113.
- **Achieved and Maintained Response** – Participants who achieved the response level and maintained the response at every subsequent timepoint up until and including Day 113.
- **Achieved and Lost Response** - Participants who achieved the response level, however, at least one subsequent timepoint did not achieve the response. This includes participants that re-achieved the response at Day 113. Participants who were observed to lose the response but whose outcome at Day 113 is unknown due either to withdrawal/termination or due to the data being unavailable as a result of the data cut-off were also included.
- **Censored** - Participants who either have or have not achieved the response, but for whom the outcome at Day 113 is unknown either due to withdrawal/termination or due to the data being unavailable as a result of the data cut-off.

The proportion of participants achieving durable response will be further summarized per cohort and overall, at assessment visits prior to Day 113. For the purpose of this summary, the participant's durable response status will be considered to be in one of the following 3 categories at each assessment visit.

- **Below Response Threshold** –parameter value below the threshold of interest (20%, 40% or 80% of baseline) at the assessment visit under consideration.
- **Above Response Threshold** – above or at the threshold of interest (20%, 40% or 80% of baseline) at the assessment visit under consideration
- **Assessment Not Available** – parameter value was not available at the assessment visit under consideration.

11. IMMUNOGENICITY

For Cohorts 5, 6, 7, 7b, 7c and 8, blood samples for anti-drug antibodies testing will be collected at pre-dose, Day 57, and at the End of Study visit (Day 113) or at Early Termination as per Schedule of Assessments. Anti-drug antibodies will be analyzed using the Safety Population.

For continuous antibody measurement data, the observed assay value and change from baseline (last pre-dose value on Day 1) for each dose level (cohort) for all time points assessed will be summarized descriptively. In addition to other descriptive statistics, the summary statistics will also include geometric mean in the table. If categorical data (negative/positive) are reported for antibody measurement data, these values will be summarized as well by frequency counts and percentages.

All anti-drug antibodies measures will be presented in the by-participant data listings.

12. HANDLING OF MISSING DATA

Missing date/time imputation rules for AEs, concomitant medications and procedures are described in sections 3.1, 3.2 and 3.3 of this SAP.

The imputation rules for non-quantifiable PK concentration values are described in section 9.1.1 and 19.1 of this SAP.

13. CHANGES TO THE PLANNED ANALYSIS

Any changes to the analyses outlined in the approved SAP will be detailed in the Clinical Study Report (CSR).

14. INTERIM AND FINAL ANALYSIS

14.1 Dose Escalation, Data Safety Committee (DSC) Analyses

Dose escalation will require approval by the DSC based on all cumulative available safety data through Day 8 of the current cohort. Cohorts 2b-4b and 5-8 will be dosed on Day 1 and Day 29. DSC decisions will be based on all aggregate safety data available including all data available at least through Day 8 of the current cohort as shown in Figure 1. Dose escalation will proceed until all cohorts are fully enrolled or until the study is stopped or the DSC votes to not escalate to the next dose.

Blinding will be preserved to the extent possible for the HVs; however, treatment un-blinding may occur, at the PI's discretion, where deemed necessary for treatment of an AE or for a decision to be made regarding trial continuation.

A formal charter will be in place prior to study start and will establish the rules, meeting frequency and scope of responsibilities of the DSC.

14.2 Interim Analyses

Sponsor may request an interim descriptive analysis of the change from baseline in ANGPTL3, apoC-III and other measured lipid parameters any time after all HV subjects planned for enrollment in each cohort have received at least one dose of ARO-ANG3 or PBO. This interim analysis is for planning of future studies and will not impact the conduct of this study. Sponsor will remain blinded to all participant treatment assignments.

Sponsor may request an interim descriptive analysis of the change from baseline in ANGPTL3, apoC-III and other measured lipid parameters any time after all healthy volunteer participants planned for enrollment in each cohort have received at least one dose of ARO-ANG3 or Placebo. This interim analysis is for the planning of future studies and will not impact the conduct of this study.

An independent unblinded team comprising a Data Manager, Statistician and Statistical Programmers will perform analysis on the interim dataset. The Sponsor may be unblinded, however, the primary study team will remain blinded to all participant treatment assignments.

Interim Tables, Listings and Figures will be based on data available until the interim data cut-off date. The listings and summary tables produced for AEs will be based on analysis datasets meeting the following conditions:

All EDC AE data will be employed where the AE has been coded under MEDDRA.

AE's that were recorded in the screening period for participants that were not subsequently treated will not be included in the summary tables.

If the AE start date is incomplete, such as when the start day is unknown, the day will be imputed as the end of the month for the purposes of determining if the AE is treatment-emergent.

The listings, figures and summary tables for the safety and PD laboratory data will be based on data available until the interim data cut-off date from both the Central Safety and PD laboratories and will be based on analysis datasets meeting the following conditions:

No results from samples collected after the interim data cut-off date will be listed or summarized.

Primarily for the safety lab summaries, the central local laboratory data will be employed.

Medpace Research Labs (MRL) will be used as the preferred data source for calculations/analysis for the following PD markers: fasting direct LDL-C, LDL-C by PUC, Total Cholesterol, non-HDL-C, HDL-C, VLDL-C, Triglycerides, Total ApoB, apoB-48, apoB-100, apoC-III, apoA-I, apoC-II, apoA5, lipoprotein lipase mass, CETP mass. Where results are not available in the PD lab dataset for a sample, if possible, the results will be employed from the central lab dataset.

If necessary, data may be converted to accommodate a difference in reporting units between the primary laboratory data and substitute laboratory data.

Parameters with no data will not be reported.

All other interim outputs will be based on EDC data available until the interim data cut-off date.

14.3 Final Analysis (End of Study)

The end of study analysis will be based on the final version of the SAP.

15. SOFTWARE

The following software will be used to perform the statistical analyses: SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

16. TABLES

As indicated in the table of tables below, tables will be produced separately for healthy volunteer cohorts (Cohorts 1, 2, 3, 4, 5, 2b, 3b and 4b), and Patient Cohorts (Cohorts 6, 7, 7b, 7c, 8 and 9).

All tables that relate to parameters summarized in the baseline disease characteristics tables will be produced twice, once considering SI units and once considering US units. This includes the baseline disease characteristics tables themselves, as well as all PD measurement tables and all MMRM tables.

For brevity these tables do not appear in the list of tables below, but in the actual TFL's they will be included with a table number of a.2 where the table a.1 is the corresponding table in SI units.

No.	Title	Analysis Population	Include in interim analysis?
14.1	**Demographics and Other Baseline Characteristics**		
14.1.1.1	Participant Enrolment and Disposition, Healthy Volunteer Cohorts	Safety Population	X
14.1.1.2	Participant Enrolment and Disposition, Disease Cohorts	Safety Population	X
14.1.2.1	Demographics and Baseline Characteristics, Healthy Volunteer Cohorts	Safety Population	X
14.1.2.2	Demographics and Baseline Characteristics, Disease Cohorts	Safety Population	X
14.1.3.1	Pregnancy Test Results by Time Point, Healthy Volunteer Cohorts	Safety Population	X
14.1.3.2	Pregnancy Test Results by Time Point, Disease Cohorts	Safety Population	X
14.1.4.x.1	Baseline Pharmacodynamic Characteristics, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.1.4.x.2	Baseline Pharmacodynamic Characteristics, Disease Cohorts	Pharmacodynamic Population	X
14.2	**PK/PD**		
14.2.1.1	Plasma Concentrations of ARO-ANG3 (ng/mL) by Dose, Healthy Volunteer Cohorts	Pharmacokinetic Population	
14.2.2.1.1	Plasma Pharmacokinetic Parameters of ARO-ANG3, Healthy Volunteer Cohorts	Pharmacokinetic Population	

No.	Title	Analysis Population	Include in interim analysis?
14.2.2.1.1b	Dose-normalized Plasma ARO-ANG3 of C^{max} and AUCs by Sex, Healthy Volunteer Cohorts	Pharmacokinetic Population	
14.2.2.2.1	Urine Pharmacokinetic Parameters of ARO-ANG3, Healthy Volunteer Cohorts	Pharmacokinetic Population	
14.2.2.3.1	Analysis of Dose Proportionality for ARO-ANG3 using the Power Model, Healthy Volunteer Cohorts	Pharmacokinetic population	
14.2.3.2	Anti-drug Antibodies, Disease Cohorts	Safety Population	
14.2.4.1.x.1	Pharmacodynamic Measurements and Change Between Baseline and Nadir Values, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.1.x.2	Pharmacodynamic Measurements and Change Between Baseline and Nadir Values, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.2.x.1	Fasting serum ANGPTL3 - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.2.x.2	Fasting serum ANGPTL3 - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.3.x.1	LDL-C direct - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.3.x.2	LDL-C direct - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.4.x.1	LDL-C (by PUC) - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.4.x.2	LDL-C (by PUC) - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.5.x.1	Total Cholesterol - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.2.4.5.x.2	Total Cholesterol - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.6.x.1	non-HDL-C - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.6.x.2	non-HDL-C - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.7.x.1	HDL-C - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.7.x.2	HDL-C - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.8.x.1	VLDL-C - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.8.x.2	VLDL-C - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.9.x.1	Fasting triglycerides - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.9.x.2	Fasting triglycerides - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.10.x.1	Lp(a) - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	
14.2.4.10.x.2	Lp(a) - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	
14.2.4.11.x.1	Total apoB - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.11.x.2	Total apoB - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.12.x.1	apoB-100 - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.2.4.12.x.2	apoB-100 - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.13.x.1	apoB-48 - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.13.x.2	apoB-48 - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.14.x.1	apoC-III - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.14.x.2	apoC-III - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.15.x.1	apoC-II - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.15.x.2	apoC-II - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.16.x.1	lipoprotein lipase mass - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.16.x.2	lipoprotein lipase mass - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.17.x.1	CETP mass - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.17.x.2	CETP mass - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.18.x.1	apoA-V - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.18.x.2	apoA-V - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.2.4.19.x.1	Serum insulin - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.19.x.2	Serum insulin - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.20.x.1	Fasting glucose - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.20.x.2	Fasting glucose - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.21.x.1	Hemoglobin A1c - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.21.x.2	Hemoglobin A1c - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.22.x.1	C-peptide (ng/mL) - Absolute Values and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.22.x.2	C-peptide (ng/mL) - Absolute Values and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.23.x.3	Pharmacodynamic Parameters - Absolute Values and Change from Baseline, Cohort 9	Pharmacodynamic Population	X
14.2.4.24.1	Durable Response Categorization at Day 113, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.24.2	Durable Response Categorization at Day 113, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.25.1	Proportion of Participants with Durable Response, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.25.2	Proportion of Participants with Durable Response, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.26.x.1	MMRM Analysis of Serum ANGPTL3 up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.2.4.26.x.2	MMRM Analysis of Serum ANGPTL3 up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.27.x.1	MMRM Analysis of Serum ANGPTL3 at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.27.x.2	MMRM Analysis of Serum ANGPTL3 at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.28.x.1	MMRM Analysis of Serum LDL-C up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.28.x.2	MMRM Analysis of Serum LDL-C up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.29.x.1	MMRM Analysis of Serum LDL-C at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.29.x.2	MMRM Analysis of Serum LDL-C at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.30.x.1	MMRM Analysis of Serum Total Cholesterol up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.30.x.2	MMRM Analysis of Serum Total Cholesterol up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.31.x.1	MMRM Analysis of Serum Total Cholesterol at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.31.x.2	MMRM Analysis of Serum Total Cholesterol at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.32.x.1	MMRM Analysis of Serum non-HDL-C up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.32.x.2	MMRM Analysis of Serum non-HDL-C up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.2.4.33.x.1	MMRM Analysis of Serum non-HDL-C at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.33.x.2	MMRM Analysis of Serum non-HDL-C at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.34.x.1	MMRM Analysis of Serum HDL-C up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.34.x.2	MMRM Analysis of Serum HDL-C up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.35.x.1	MMRM Analysis of Serum HDL-C at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.35.x.2	MMRM Analysis of Serum HDL-C at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.36.x.1	MMRM Analysis of Serum VLDL-C up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.36.x.2	MMRM Analysis of Serum VLDL-C up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.37.x.1	MMRM Analysis of Serum VLDL-C at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.37.x.2	MMRM Analysis of Serum VLDL-C at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.38.x.1	MMRM Analysis of Serum Triglycerides up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.38.x.2	MMRM Analysis of Serum Triglycerides up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.39.x.1	MMRM Analysis of Serum Triglycerides at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.2.4.39.x.2	MMRM Analysis of Serum Triglycerides at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.40.x.1	MMRM Analysis of Serum apoB up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.40.x.2	MMRM Analysis of Serum apoB up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.41.x.1	MMRM Analysis of Serum apoB at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.41.x.2	MMRM Analysis of Serum apoB at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.42.x.1	MMRM Analysis of Serum apoB-48 up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.42.x.2	MMRM Analysis of Serum apoB-48 up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.43.x.1	MMRM Analysis of Serum apoB-48 at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.43.x.2	MMRM Analysis of Serum apoB-48 at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.44.x.1	MMRM Analysis of Serum apoB-100 up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.44.x.2	MMRM Analysis of Serum apoB-100 up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.45.x.1	MMRM Analysis of Serum apoB-100 at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.45.x.2	MMRM Analysis of Serum apoB-100 at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.2.4.46.x.1	MMRM Analysis of Serum apoA-I up to Day 99 and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.46.x.2	MMRM Analysis of Serum apoA-I up to Day 99 and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.47.x.1	MMRM Analysis of Serum apoA-I at Day 113 (EOS) and Change from Baseline, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.47.x.2	MMRM Analysis of Serum apoA-I at Day 113 (EOS) and Change from Baseline, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.48.1	Glucose Tolerance Test and Change Between Baseline and Day 85 Values, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.48.2	Glucose Tolerance Test and Change Between Baseline and Day 85 Values, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.49.1	Post Prandial Triglycerides Test (PPTG) Results, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
14.2.4.49.2	Post Prandial Triglycerides Test (PPTG) Results, Disease Cohorts	Pharmacodynamic Population	X
14.2.4.50.1	Percentage Fat Fraction on MRI-PDFF	Pharmacodynamic Population	X
14.3	**Safety**		
14.3.1.1	Concomitant Medications and Non-Drug Therapies, Healthy Volunteer Cohorts	Safety Population	X
14.3.1.2	Concomitant Medications and Non-Drug Therapies, Disease Cohorts	Safety Population	X
14.3.3	**Adverse Events**		
14.3.3.1.1	Overall Summary of Treatment Emergent Adverse Events, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.1.2	Overall Summary of Treatment Emergent Adverse Events, Disease Cohorts	Safety Population	X
14.3.3.2.1	Treatment Emergent Adverse Events by System Organ Class and Preferred	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
	Term in Descending Order of Frequency, Healthy Volunteer Cohorts		
14.3.3.2.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term in Descending Order of Frequency, Disease Cohorts	Safety Population	X
14.3.3.3.1	Treatment Emergent Adverse Events by System Organ Class and Preferred Term in Decreasing Order of Frequency, Cohorts Pooled by Dose	Safety Population	X
14.3.3.4.1	Treatment Emergent Adverse Events in Descending Order of Frequency by Preferred Term, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.4.2	Treatment Emergent Adverse Events in Descending Order of Frequency by Preferred Term, Disease Cohorts	Safety Population	X
14.3.3.5.1	Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in Descending Order of Frequency, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.5.2	Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in Descending Order of Frequency, Disease Cohorts	Safety Population	X
14.3.3.6.1	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and by Severity, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.6.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and by Severity, Disease Cohorts	Safety Population	X
14.3.3.7.1	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and by Relationship to Study Drug Healthy Volunteer Cohorts	Safety Population	X
14.3.3.7.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and by Relationship to Study Drug, Disease Cohorts	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.3.3.8.1	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term in Descending Order of Frequency, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.8.2	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term in Descending Order of Frequency, Disease Cohorts	Safety Population	X
14.3.3.9.1	Serious Study Drug Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.9.2	Serious Study Drug Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term, Disease Cohorts	Safety Population	X
14.3.3.10.1	Treatment Emergent Adverse Events Leading to Study Drug or Study Withdrawal, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.10.2	Treatment Emergent Adverse Events Leading to Study Drug or Study Withdrawal, Disease Cohorts	Safety Population	X
14.3.3.11.1	Treatment Emergent Adverse Events Occurring in >1 Study Participant in Descending Order of Frequency by Preferred Term, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.11.2	Treatment Emergent Adverse Events Occurring in >1 Study Participant in Descending Order of Frequency by Preferred Term, Disease Cohorts	Safety Population	X
14.3.3.12.1	Injections Leading to Adverse Events at the Injection Site by System Organ Class and Preferred Term, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.12.2	Injections Leading to Adverse Events at the Injection Site by System Organ Class and Preferred Term, Disease Cohorts	Safety Population	X
14.3.3.13.1	Injections Leading to Adverse Events at the Injection Site by System Organ	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
	Class and Preferred Term and by Severity, Healthy Volunteer Cohorts		
14.3.3.13.2	Injections Leading to Adverse Events at the Injection Site by System Organ Class and Preferred Term and by Severity, Disease Cohorts	Safety Population	X
14.3.3.14.1	Treatment Emergent Adverse Events Related to Local Injection Site Reactions	Safety Population	X
14.3.3.14.2	Treatment Emergent Adverse Events Related to Local Injection Site Reactions	Safety Population	X
14.3.3.15.1	Treatment Emergent Adverse Events Related to Local Injection Site Reactions	Safety Population	X
14.3.3.15.2	Treatment Emergent Adverse Events Related to Local Injection Site Reactions	Safety Population	X
14.3.3.16.1	Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term, Healthy Volunteer Cohorts	Safety Population	X
14.3.3.16.2	Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term, Disease Cohorts	Safety Population	X
14.3.4.1.1	Laboratory - Hematology: Summary and Change from Baseline, Healthy Volunteer Cohorts,	Safety Population	X
14.3.4.1.2	Laboratory - Hematology: Summary and Change from Baseline, Disease Cohorts	Safety Population	X
14.3.4.1.3	Laboratory - Haematology for extension Cohort 9	Safety Population	X
14.3.4.2.1	Laboratory - Chemistry: Summary and Change from Baseline, Healthy Volunteer Cohorts	Safety Population	X
14.3.4.2.2	Laboratory - Chemistry: Summary and Change from Baseline, Disease Cohorts	Safety Population	X
14.3.4.2.3	Laboratory - Chemistry for extension Cohort 9	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
14.3.4.3.1	Laboratory - Coagulation: Summary and Change from Baseline, Healthy Volunteer Cohorts	Safety Population	X
14.3.4.3.2	Laboratory - Coagulation: Summary and Change from Baseline, Disease Cohorts	Safety Population	X
14.3.4.3.3	Laboratory - Coagulation for extension Cohort 9	Safety Population	X
14.3.4.4.1	Laboratory - Urinalysis: Summary and Change from Baseline, Healthy Volunteer Cohorts	Safety Population	X
14.3.4.4.2	Laboratory - Urinalysis: Summary and Change from Baseline, Disease Cohorts	Safety Population	X
14.3.4.5.1	Haematology Shifts from Baseline, Healthy Volunteer Cohorts	Safety Population	X
14.3.4.5.2	Haematology Shifts from Baseline, Disease Cohorts	Safety Population	X
14.3.4.6.1	Biochemistry Shifts from Baseline, Healthy Volunteer Cohorts	Safety Population	X
14.3.4.6.2	Biochemistry Shifts from Baseline, Disease Cohorts	Safety Population	X
14.3.4.7.1	Coagulation Shifts from Baseline, Healthy Volunteer Cohorts	Safety Population	X
14.3.4.7.2	Coagulation Shifts from Baseline, Disease Cohorts	Safety Population	X
14.3.4.8.1	Shift from Baseline Grade to Worst Post-Baseline Grade, Healthy Volunteer Cohorts	Safety Population	X
14.3.4.8.2	Shift from Baseline Grade to Worst Post-Baseline Grade, Disease Cohorts	Safety Population	X
14.3.5/6/7	**Other Safety**		
14.3.5.1	Vital Signs, Healthy Volunteer Cohorts	Safety Population	
14.3.5.2	Vital Signs, Disease Cohorts	Safety Population	
14.3.5.3	Vital Signs for extension Cohort 9	Safety Population	

No.	Title	Analysis Population	Include in interim analysis?
14.3.6.1	Physical Examination, Healthy Volunteer Cohorts	Safety Population	
14.3.6.2	Physical Examination, Disease Cohorts	Safety Population	
14.3.7.1.1	ECG Values, Healthy Volunteer Cohorts	Safety Population	
14.3.7.1.2	ECG Values, Disease Cohorts	Safety Population	
14.3.7.2.1	ECG Findings, Overall Interpretation, Healthy Volunteer Cohorts	Safety Population	
14.3.7.2.2	ECG Findings, Overall Interpretation, Disease Cohorts	Safety Population	

Table to be produced with US Units and SI units separately (*x = 1 for SI units and x = 2 for US units*).

17. LISTINGS

As indicated in the table of listings below, listings will be produced separately for healthy volunteer cohorts (Cohorts 1, 2, 3, 4, 5, 2b, 3b, and 4b), and Patient Cohorts (Cohorts 6, 7, 7b, 7c, 8 and 9).
All listings that relate to parameters summarized in the baseline disease characteristics tables (will be produced twice, once considering SI units and once considering US units. The numbering convention used for these additional US unit listings will be the same as that used for the tables, as stated in section 16.

No.	Title	Analysis Population	Include in interim analysis?
16.2.1	**Participant Disposition**		
16.2.1.1.1	Listing of Enrolment, Healthy Volunteer Cohorts	Safety Population	X
16.2.1.1.2	Listing of Enrolment, Disease Cohorts	Safety Population	X
16.2.1.2.1	Listing of Screen Failures, Healthy Volunteer Cohorts	Screening Population	X
16.2.1.2.2	Listing of Screen Failures, Disease Cohorts	Screening Population	X
16.2.1.3.1	Listing of Patient Eligibility, Healthy Volunteer Cohorts	Safety Population	X
16.2.1.3.2	Listing of Patient Eligibility, Disease Cohorts	Safety Population	X
16.2.2.1.1	Listing of Protocol Deviations, Healthy Volunteer Cohorts	Safety Population	X
16.2.2.1.2	Listing of Protocol Deviations, Disease Cohorts	Safety Population	X
16.2.3.1.1	Listing of Disposition, Healthy Volunteer Cohorts	Safety Population	X
16.2.3.1.2	Listing of Disposition, Disease Cohorts	Safety Population	X
16.2.3.2.1	Listing of Randomization, Healthy Volunteer Cohorts	Safety Population	X
16.2.3.2.2	Listing of Randomization, Disease Cohorts	Safety Population	X
16.2.4	**Demographic and Other Baseline Data**		
16.2.4.1.1	Listing of Demographics, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.1.2	Listing of Demographics, Disease Cohorts	Safety Population	X
16.2.4.2.1	Listing of Medical History, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.2.2	Listing of Medical History, Disease Cohorts	Safety Population	X
16.2.4.3.1	Listing of Follicle-Stimulating Hormone (FSH) Results, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.3.2	Listing of Follicle-Stimulating Hormone (FSH) Results, Disease Cohorts	Safety Population	X
16.2.4.4.1	Listing of Child-bearing Potential and Pregnancy Test Results, Healthy Volunteer Cohorts	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
16.2.4.4.2	Listing of Child-bearing Potential and Pregnancy Test Results, Disease Cohorts	Safety Population	X
16.2.4.5.1	Listing of Serology Screen, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.5.2	Listing of Serology Screen, Disease Cohorts	Safety Population	X
16.2.4.6.1	Listing of Drug Screen, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.6.2	Listing of Drug Screen, Disease Cohorts	Safety Population	X
16.2.4.7.1	Listing of Alcohol Screen, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.7.2	Listing of Alcohol Screen, Disease Cohorts	Safety Population	X
16.2.4.8.1	Listing of Lipid Metabolic Genotype Test Results, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.8.2	Listing of Lipid Metabolic Genotype Tests, Disease Cohorts	Safety Population	X
16.2.4.9.1	Listing of Log of Lipid Collection, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.9.2	Listing of Log of Lipid Collection, Disease Cohorts	Safety Population	X
16.2.4.10.x.1	Listing of Baseline Disease Characteristics, Healthy Volunteer Cohorts	Safety Population	X
16.2.4.10.x.2	Listing of Baseline Disease Characteristics, Disease Cohorts	Safety Population	X
16.2.4.11.1	Listing of Genes Tested for Mutations Associated with Dyslipidemia, Healthy volunteer Cohorts	Safety Population	X
16.2.4.11.2	Listing of Genes Tested for Mutations Associated with Dyslipidemia, Disease Cohorts	Safety Population	X
16.2.5	**Treatment Administration**		
16.2.5.1.1	Listing of Study Drug Administrations, Healthy Volunteer Cohorts	Safety Population	X
16.2.5.1.2	Listing of Study Drug Administrations, Disease Cohorts	Safety Population	X
16.2.5.2.1	Listing of Concomitant/Prior Medications and Non-Drug Therapies, Healthy Volunteer Cohorts	Safety Population	X
16.2.5.2.2	Listing of Concomitant/Prior Medications and Non-Drug Therapies, Disease Cohorts	Safety Population	X
16.2.6	**PK/PD**		
16.2.6.1.1	Listing of Individual ARO-ANG3 Plasma Concentrations, Single Dosed Healthy Volunteer Cohorts	Pharmacokinetic Population	

No.	Title	Analysis Population	Include in interim analysis?
16.2.6.2.1	Listing of Individual ARO-ANG3 Plasma Concentrations, Multiple Dosed Healthy Volunteer Cohorts	Pharmacokinetic Population	
16.2.6.3.1	Listing of Individual ARO-ANG3 Urine Concentration (ng/mL), Healthy Volunteer Cohorts	Pharmacokinetic Population	
16.2.6.4.1	Listing of Individual ARO-ANG3 Plasma Pharmacokinetic Parameters, Healthy Volunteer Cohorts	Pharmacokinetic Population	
16.2.6.5.1	Listing of Individual ARO-ANG3 Urine Pharmacokinetic Parameters, Healthy Volunteer Cohorts	Pharmacokinetic Population	
16.2.6.6.2	Listing of Anti-drug Antibodies, Disease Cohorts	Safety Population	X
16.2.6.7.1	Listing of Glucose Tolerance Test (GTT) Adherence, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
16.2.6.7.2	Listing of Glucose Tolerance Test (GTT) Adherence, Disease Cohorts	Pharmacodynamic Population	X
16.2.6.8.1	Listing of Glucose Tolerance Test (GTT) and Change Between Baseline and Day 85 Values, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
16.2.6.8.2	Listing of Glucose Tolerance Test (GTT) and Change Between Baseline and Day 85 Values, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
16.2.6.9.1	Listing of Post-Prandial Triglyceride (TG) Adherence, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
16.2.6.9.2	Listing of Post-Prandial Triglyceride (TG) Adherence, Disease Cohorts	Pharmacodynamic Population	X
16.2.6.10.1	Listing of Post-Prandial Triglyceride (TG) Test Results and Change Between Baseline and Day 85 Values, Healthy Volunteer Cohorts	Pharmacodynamic Population	X
16.2.6.10.2	Listing of post-prandial triglyceride (TG) Test results and Change Between Baseline and Day 85 Values, Disease Cohorts	Pharmacodynamic Population	X
16.2.6.11.x.1	Listing of Pharmacodynamic Parameters, Healthy Volunteer Cohorts	Safety Population	X
16.2.6.11.x.2	Listing of Pharmacodynamic Parameters, Disease Cohorts	Safety Population	X
16.2.6.12.1	Listing of Serum Insulin, Healthy Volunteer Cohorts	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
16.2.6.12.2	Listing of Serum Insulin, Disease Cohorts	Safety Population	X
16.2.6.13.2	Listing of Percentage Liver Fat Fraction on MRI-PDFF	Safety Population	X
16.2.7	**Adverse Events**		
16.2.7.1.1	Listing of Adverse Events, Healthy Volunteer Cohorts	Safety Population	X
16.2.7.1.2	Listing of Adverse Events, Disease Cohorts	Safety Population	X
16.2.7.2.1	Listing of Serious Adverse Events, Healthy Volunteer Cohorts	Safety Population	X
16.2.7.2.2	Listing of Serious Adverse Events, Disease Cohorts	Safety Population	X
16.2.7.3.1	Listing of Adverse Events Leading to Study Drug Withdrawn or Study Withdrawn, Healthy Volunteer Cohorts	Safety Population	X
16.2.7.3.2	Listing of Adverse Events Leading to Study Drug Withdrawn or Study Withdrawn, Disease Cohorts	Safety Population	X
16.2.7.4.1	Listing of Adverse Events at the Injection Site, Healthy Volunteer Cohorts	Safety Population	X
16.2.7.4.2	Listing of Adverse Events at Injection Site, Disease Cohorts	Safety Population	X
16.2.7.5.1	Listing of Adverse Events Related to Local Injection Site Reactions, Healthy Volunteer Cohorts	Safety Population	X
16.2.7.5.2	Listing of Local Injection Site Reactions, Disease Cohorts	Safety Population	X
16.2.7.6.1	Listing of Adverse Events Leading to Death, Healthy Volunteer Cohorts	Safety Population	X
16.2.7.6.2	Listing of Adverse Events Leading to Death, Disease Cohorts	Safety Population	X
16.2.8	**Laboratory Parameters**		
16.2.8.1.y.1	Listing of Hematology – Central Laboratory, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.1.y.2	Listing of Hematology – Central Laboratory, Disease Cohorts	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
16.2.8.2.y.1	Listing of Hematology – Central Laboratory, Clinically Significant Values, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.2.y.2	Listing of Hematology – Central Laboratory, Clinically Significant Values, Disease Cohorts	Safety Population	X
16.2.8.3.y.1	Listing of Biochemistry – Central Laboratory, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.3.y.2	Listing of Biochemistry – Central Laboratory, Disease Cohorts	Safety Population	X
16.2.8.4.y.1	Listing of Biochemistry – Central Laboratory, Clinically Significant Values, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.4.y.2	Listing of Biochemistry – Central Laboratory, Clinically Significant Values, Disease Cohorts	Safety Population	X
16.2.8.5.y.1	Listing of Coagulation – Central Laboratory, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.5.y.2	Listing of Coagulation – Central Laboratory, Disease Cohorts	Safety Population	X
16.2.8.6.y.1	Listing of Coagulation – Central Laboratory, Clinically Significant Values, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.6.y.2	Listing of Coagulation – Central Laboratory, Clinically Significant Values, Disease Cohorts	Safety Population	X
16.2.8.7.y.1	Listing of Urinalysis – Central Laboratory, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.7.y.2	Listing of Urinalysis – Central Laboratory, Disease Cohorts	Safety Population	X
16.2.8.8.y.1	Listing of Urinalysis – Central Laboratory, Clinically Significant Values, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.8.y.2	Listing of Urinalysis – Central Laboratory, Clinically Significant Values, Disease Cohorts	Safety Population	X
16.2.8.9.y.1	Listing of Microscopic Urinalysis – Central Laboratory, Healthy Volunteer Cohorts	Safety Population	X

No.	Title	Analysis Population	Include in interim analysis?
16.2.8.9.y.2	Listing of Microscopic Urinalysis – Central Laboratory, Disease Cohorts	Safety Population	X
16.2.8.10.y.1	Listing of Microscopic Urinalysis – Central Laboratory, Clinically Significant Values, Healthy Volunteer Cohorts	Safety Population	X
16.2.8.10.y.2	Listing of Microscopic Urinalysis – Central Laboratory, Clinically Significant Values, Disease Cohorts	Safety Population	X
16.2.9/10/11	**Other Safety**		
16.2.9.1	Listing of Vital Signs, Healthy Volunteer Cohorts	Safety Population	X
16.2.9.2	Listing of Vital Signs, Disease Cohorts	Safety Population	X
16.2.10.1	Listing of Physical Examination, Healthy Volunteer Cohorts	Safety Population	X
16.2.10.2	Listing of Physical Examination, Disease Cohorts	Safety Population	X
16.2.11.1.1	Listing of ECG Values, Healthy Volunteer Cohorts	Safety Population	X
16.2.11.1.2	Listing of ECG Values, Disease Cohorts	Safety Population	X
16.2.11.2.1	Listing of ECG Clinically Significant Values, Healthy Volunteer Cohorts	Safety Population	X
16.2.11.2.2	Listing of ECG Clinically Significant Values, Disease Cohorts	Safety Population	X
16.2.11.3.1	Listing of ECG Findings, Disease Cohorts	Safety Population	X
16.2.11.3.2	Listing of ECG Findings, Disease Cohorts	Safety Population	X

Listing to be produced with US Units and SI units separately (x = 1 for SI units and x = 2 for US units)
Listing to be produced for central and local laboratories separately (*y = 1 for Central and y = 2 for Local laboratories*).

18. FIGURES

PK Figures will be produced for HV cohorts 1, 2, 3, 4, 2b, 3b and 4b. PD and Safety figures will be produced for all cohorts.
All figures that relate to parameters summarized in the baseline disease characteristics tables will be produced twice, once considering SI units and once considering US units. The numbering convention used for these additional US unit figures will be the same as that used for the tables, as stated in section 16.

No.	Title	Analysis Population	Include in interim analysis?
14.2.1.1.1a	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Linear Scale): SAD	PK	
14.2.1.1.1b	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Semi-logarithmic Scale): SAD	PK	
14.2.1.2.1a	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Linear Scale): MAD Day 1	PK	
14.2.1.2.1b	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Semi-logarithmic Scale): MAD Day 1	PK	
14.2.1.3.1a	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Linear Scale): MAD Day 29	PK	
14.2.1.3.1b	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Semi-logarithmic Scale): MAD Day 29	PK	
14.2.1.4.1a	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Linear Scale): SAD and MAD Day 1	PK	
14.2.1.4.1b	Mean (+/-SD) Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Dose (Semi-logarithmic Scale): SAD and MAD Day 1	PK	
14.2.2.1.1a	Spaghetti Plot of Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Treatment (Linear Scale): SAD	PK	
14.2.2.1.1b	Spaghetti Plot of Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Treatment (Semilogarithmic Scale) : SAD	PK	
14.2.2.2.1a	Spaghetti Plot of Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Treatment (Linear Scale): MAD Day 1	PK	
14.2.2.2.1b	Spaghetti Plot of Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Treatment (Semilogarithmic Scale) : MAD Day 1	PK	
14.2.2.3.1a	Spaghetti Plot of Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by Treatment (Linear Scale): MAD Day 29	PK	
14.2.2.3.1b	Spaghetti Plot of Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time by	PK	

No.	Title	Analysis Population	Include in interim analysis?
	Treatment (Semilogarithmic Scale) : MAD Day 29		
14.2.3.1.1a	Individual Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time (Linear Scale): SAD	PK	
14.2.3.1.1b	Individual Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time (Semi-logarithmic Scale): SAD	PK	
14.2.3.2.1a	Individual Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time (Linear Scale) : MAD Day 1	PK	
14.2.3.2.1b	Individual Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time (Semi-logarithmic Scale): MAD Day 1	PK	
14.2.3.3.1a	Individual Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time (Linear Scale): MAD Day 29	PK	
14.2.3.3.1b	Individual Plasma Concentrations of ARO-ANG3 for healthy volunteers versus Time (Semi-logarithmic Scale): MAD Day 29	PK	
14.2.4.1.1	Linear Regression Plot of ARO-ANG3 Parameters for healthy volunteers: SAD	PK	
14.2.4.2.1	Linear Regression Plot of ARO-ANG3 Parameters for healthy volunteers: MAD Day 1	PK	
14.2.4.3.1	Linear Regression Plot of ARO-ANG3 Parameters for healthy volunteers: SAD and MAD Day 29	PK	
14.2.4.4.1	Linear Regression Plot of ARO-ANG3 Parameters for healthy volunteers: SAD and MAD Day 1	PK	
14.2.5.1.1	Box Plots of Dose Normalized Plasma ARO-ANG3 Parameters for healthy volunteers by Gender: SAD.	PK	
14.2.5.2.1	Box Plots of Dose Normalized Plasma ARO-ANG3 Parameters for healthy volunteers by Gender: MAD Day 1	PK	
14.2.5.3.1	Box Plots of Dose Normalized Plasma ARO-ANG3 Parameters for healthy volunteers by Gender: MAD Day 29	PK	
14.2.5.4.1	Box Plots of Dose Normalized Plasma ARO-ANG3 Parameters for healthy volunteers by Gender: MAD and SAD Day 1	PK	
14.3.1.1.x.1	Mean (+/-SD) Plasma Concentrations of Triglycerides versus Time by Dose	PD	X
14.3.1.2.x.1	Mean (+/-SD) Plasma Concentrations of LDL-C versus Time by Dose	PD	X
14.3.1.3.x.1	Mean (+/-SD) Plasma Concentrations of HDL-C versus Time by Dose	PD	X
14.3.1.4.x.1	Mean (+/-SD) Plasma Concentrations of non-HDL versus Time by Dose	PD	
14.3.1.5.x.1	Mean (+/-SD) Plasma Concentrations of ANGPTL3 versus Time by Dose	PD	X

No.	Title	Analysis Population	Include in interim analysis?
14.3.1.6.x.1	Mean (+/-SD) Percentage Reduction from Baseline in Plasma Concentrations of Triglycerides versus Time by Dose	PD	
14.3.1.7.x.1	Mean (+/-SD) Percentage Increase from Baseline in Plasma Concentrations of HDL-C versus Time by Dose	PD	
14.3.1.8.x.1	Mean (+/-SD) Percentage Reduction from Baseline in Plasma Concentrations of non-HDL-C versus Time by Dose	PD	
14.3.1.9.x.1	Mean (+/-SD) Percentage Reduction from Baseline in Plasma Concentrations of ARO-ANG versus Time by Dose	PD	
14.4.1.1.1	eDISH plot for healthy volunteer cohorts (active and placebo) for peak post-dose Total bilirubin vs ALT	Safety	X
14.4.1.1.2	eDISH plot for disease cohorts (active v placebo) EOS Total bilirubin vs ALT	Safety	X
14.4.1.2.1	eDISH plot for healthy volunteer cohorts (active and placebo) EOS Total bilirubin vs ALT	Safety	X
14.4.1.2.2	eDISH plot for disease cohorts (active and placebo) for peak post-dose Total bilirubin vs ALT.	Safety	X
14.4.2.1	Mean ALT over time, active and placebo cohorts	Safety	X
14.4.2.2	Mean AST over time, active and placebo cohorts	Safety	X
14.4.2.3	Mean Creatinine over time, active and placebo cohorts	Safety	X
14.4.2.4	Mean Lipase over time, active and placebo cohorts	Safety	X
14.4.2.5	Mean Total bilirubin over time, active and placebo cohorts	Safety	X

Figures to be produced with US Units and SI units separately (x = 1 for SI units and x = 2 for US units)

19. APPENDIX A NONCOMPARTMENTAL PHARMACOKINETIC ANALYSIS

19.1 Handling Missing or Non-Quantifiable Data

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

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

For Urine PK parameters calculation and summary, all BLQ will be set to zero.

19.2 Pharmacokinetic Parameter Calculation

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

Pharmacokinetic analysis will be carried out where possible using actual blood sampling times postdose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time. Cmax and tmax will be obtained directly from the concentration-time profiles. For multiple peaks, the highest postdose concentration will be reported as Cmax. In the case that multiple peaks are of equal magnitude, the earliest tmax will be reported.
AUC will be estimated using the linear trapezoidal rule for increasing concentrations and the log-trapezoidal rule for decreasing concentrations (i.e., “linear up / log down” trapezoidal rule in Phoenix WinNonlin). The total AUCinf was calculated as AUClast + Ct/λz. The apparent clearance (CL/F) was estimated as Dose/AUCinf, and the terminal-phase volume of distribution (Vz/F) was estimated as Dose/[AUCinf*λz].

19.2.1 Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant (λz) will only be calculated when a reliable estimate can be obtained using at least 3 data points, not including Cmax, and the adjusted coefficient for determination of exponential fit (R2-adj) of the regression line is ≥0.75. Parameters requiring λz for their calculation (eg, AUCinf, t1/2, CL, and Vz) will only be calculated if the R2-adj value of the regression line is ≥0.75.

The following regression-related diagnostic PK parameters will be determined, when possible.

Parameter	Units	Definition
λz	1/h	apparent terminal elimination rate constant
λz N	NA	number of data points included in the log-linear regression
λz Span Ratio	NA	time period over which λz was determined as a ratio of t1/2
R2-adj	NA	adjusted coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λz (ie, the difference between λz Upper and λz Lower) should be ≥2 half-lives. If the λz Span Ratio is <2, the robustness of the t1/2 values will be discussed in the PK report.

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

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

If the extrapolated area is >20%, AUCinf (and derived parameters) will be flagged and excluded from the summary statistics and statistical analysis.

19.3 Treatment of Outliers in Pharmacokinetic Analysis

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

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

20. APPENDIX B EARLY TERMINATION ANALYSIS WINDOWS

The early termination visit value will be mapped to the closest scheduled visit within the specified analysis windows below:

Visit	**Analysis Window (Study Day)**
Day 1	[1, 2)
Day 3	[2, 6)
Day 8	[6, 12)
Day 15	[12, 19)
Day 22	[19, 26)
Day 29	[26, 36)
Day 43	[36, 50)
Day 57	[50, 64)
Day 71	[64, 78)
Day 85	[78, 92)
Day 99	[92, 106)
Day 113	[106, EOS]

21. REFERENCES

1) Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000;17(10): 1278–1283.

AROANG1001_Phase 1_SAP_V9.0_Final_14Jul 2021

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