Statistical Analysis Plan

Investigational Product:	ARO-APOC3
Protocol Title:	A Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Familial Chylomicronemia Syndrome
Study Number:	AROAPOC3-3001
Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA
Author:	[redacted] Arrowhead Pharmaceuticals, Inc.
Protocol Version:	Amendment 6.0
SAP Version:	Version 2.0
SAP Approval Date:	06MAY2024

Signature Page

Protocol Title:	A Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Familial Chylomicronemia Syndrome
Protocol Number:	AROAPOC3-3001
SAP Version/Date:	Version 2.0 / 06MAY2024

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

Signature	**Date**
[redacted] [redacted] Arrowhead Pharmaceuticals, Inc.	DocuSigned by: [redacted]
[redacted] [redacted] Arrowhead Pharmaceuticals, Inc.	DocuSigned by: [redacted]

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

Version Number	Date (DDMMYYYY)	Summary of Changes
v0.1 DRAFT	05MAY2021	
v0.2 DRAFT	01SEP2021	• The FAS is defined as all randomized subjects regardless of adherence to the treatment. • The primary efficacy endpoint is analyzed with non-parametric analysis method. MMRM and ANCOVA approaches are used as sensitivity analyses. • The missing primary efficacy endpoint will be imputed with pattern mixture model, which imputes missing data by having the missing data from subjects who do not adhere to therapy represented by the data from those subjects on the same arm that also did not adhere to therapy but had the measurement for the primary endpoint. Details are added in Appendix B. Tipping point method will be used as a sensitivity analysis. • Hypothesis testing procedure is specified. • Sample size calculation is updated with non-parametric method. • Unscheduled visit and early termination visit values are mapped to Analysis Windows. • Background TG therapy is added to baseline covariates and subgroups for the Sensitivity Analysis. • Incidence of acute pancreatitis is changed to a secondary endpoint. • Definition of TEAE is changed to further include AEs occurring up to 180 days after the last dose.
v0.3 DRAFT	01APR2022	• Missing PRO data will be imputed depends on the missing situation (section 8.3.2). Multiple imputation will be used as a supportive method. • In sequential testing, inferential conclusions about these efficacy endpoints will require statistical significance from both dose levels of the previous one to strongly control the family-wise overall type I error. Primary endpoint and key secondary endpoints will be tested sequentially. • In pattern-mixed model, if there are no or very few subjects in the same treatment arm who do not adhere to therapy and have Month 10 measurements, the treatment effect is considered washed out in ARO-APOC3

Version Number	Date (DDMMYYYY)	Summary of Changes
		arm. Baseline TG values from these patients (no intermediate measures will be used) and data from placebo group will be used to impute the missing Month 10 TG values for ARO-APOC3 arm; • For the placebo arm, missing Month 10 TG values will be imputed with multiple imputation assuming missing at random, including patient demographics, disease status, and baseline and post-baseline efficacy data, using observed data from all subjects in the placebo arm • Skewness of primary endpoint will be evaluated using Pearson's first or second coefficient of skewness. • Added ANCOVA model to analyze change from baseline at month 10 in fasting TG • Added robustness evaluation of Hodge Lehman estimate for primary endpoint • Two-way tipping point sensitivity analysis will be conducted • Analyses of secondary endpoints are updated. Same sensitivity analysis on primary endpoint will be applied to each to the secondary endpoints which will be sequentially tested. • Analyses of PRO endpoints from EORTC QLQ-C30, QLQ-PAN26 and EQ-5D-5L are added. Interested parameters are pain, nausea and vomiting, fatigue, emotional functioning, cognitive functioning, social functioning, role functioning, pancreatic pain, pancreatic digestive, pancreatic social activity from EORTC and index value and VAS from EQ-5D. These PRO endpoints will be analyzed separately using MMRM approach. PRO scaling and algorithms are added in Appendix C. • In addition to randomized period, extension period is added to this study. Primary analysis of this study will be based on data collected in randomized period. Final analysis will be based on complete database. Description of analysis for extension period and integrated analysis for long-term follow-up are provided.
v1.0 Final	26MAR2024	• Adding analysis of treatment-emergent adverse events of Arrowhead SMQ-

Version Number	Date (DDMMYYYY)	Summary of Changes
		Standardized MedDRA Query for Worsening of Glycemic Control and Local Injection Site Reaction. • Adding diabetes mellitus related analysis. • Updating the tipping point shift ranges.
V2.0 Final	06MAY2024	• Adding key secondary endpoint of "incidence of positively adjudicated events of acute pancreatitis (randomized period)" and which is listed as the 5th testing order in the sequence of hypothesis testing. • Adding the following other secondary endpoints: o Proportion of participants reaching TG of <880, and 1000 mg/dL at each scheduled assessment. o Proportion of participants achieving ≥40%, ≥70% reduction in fasting TG from baseline over time. • Adding the following other exploratory endpoints: o Area under the curve in fasting triglyceride from baseline to Month 12. o Incidence of positively, probably, or possibly adjudicated events of acute pancreatitis (either period). o Participant incidence of abdominal pain. o Time to the first positively adjudicated events of acute pancreatitis, and time to the first positively, probably, or possibly adjudicated events of acute pancreatitis. • Adding the analysis visits window for extension period. • Adding the definition of the study day in extension period. • Adding the data handling method if fasting APOC3 is below the limit of quantification. • Adding the definition of PK Analysis Set. • Adding the subgroup analysis of Region – Japan (Japan: Yes or No). • Updating the analyses of demographics, baseline characteristics and disease history.

Version Number	Date (DDMMYYYY)	Summary of Changes
		• Adding a sensitivity analysis of ANHECOVA for the primary endpoint. • Updating the definitions of glycemic status. • Updating the definitions of NODM. • Remove 'current statin therapy use' from the imputation model due to over 90% patients used statin from Phase 2 studies. • Updating the covariance structure used in the MMRM model for PRO endpoints analyses.

TABLE OF CONTENTS

List of Abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AECI	Adverse Event of Clinical Interest
ANCOVA	Analysis of Covariance
ANHECOVA	Analysis of Heterogenous Covariance
APOA-I or APOA1	Apolipoprotein A-I
APOA-V or APOA5	Apolipoprotein A-V
APOB	Apolipoprotein B
APOB-100	Apolipoprotein B 100
APOB-48	Apolipoprotein B 48
APOC2	Apolipoprotein C2
APOC3	Apolipoprotein C3
CECT	Contrast-Enhanced Computed Tomography
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DPP-4	Dipeptidyl Peptidase-4
DSC	Data Safety Committee
EORTC QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of Study
EQ-5D-5L	EuroQol 5-Dimension Instrument
FAS	Full Analysis Set
FCS	Familial Chylomicronemia Syndrome
HbA1c	Glycosylated Hemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR	Hazard Ratio
IP	Investigational Product

Abbreviation	Definition
IPD	Important Protocol Deviations
IWRS	Interactive Voice/Web Response System
K-M	Kaplan-Meier
LDL-C	Low-Density Lipoprotein Cholesterol
LFT	Liver Function Test
LIPD	Last IP Dose
LISR	Local Injection Site Reaction
LP(a)	Lipoprotein(a)
LS	Least Squares
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measure
MRI	Magnetic Resonance Imaging
NCA	Non-Compartmental Analysis
NLME	Nonlinear Mixed Effect
NODM	New Onset Diabetes Mellitus
non-HDL-C	Non-High Density Lipoprotein Cholesterol
PH	Proportional Hazards
PI	Product Investigator
PK	Pharmacokinetics
PT	Preferred Term
PPS	Per-Protocol Set
Q1	First Quartile
Q3	Third Quartile
Q3M	Once Every 3 Months
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean

Abbreviation	Definition
SGLT	Sodium-Glucose Transporter
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TG	Triglycerides
ULN	Upper Limit of Normal
VLDL-C	Very-Low-Density Lipoprotein Cholesterol

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined in the protocol for the double-blinded randomized period of study AROAPOC3-3001 dated 31AUG2023. The scope of this plan includes the planned final analyses to be included in the Clinical Study Report (CSR). The statistical analysis of open-label extension period will be provided in an addendum of the SAP on a later date.

2. STUDY OVERVIEW

2.1. Study Objectives

The primary objectives of the study are to evaluate the efficacy and safety of ARO-APOC3 in adults with familial chylomicronemia syndrome (FCS).

2.2. Study Design

2.2.1. Overview

This is a phase 3, multicenter, double-blinded, randomized, stratified, placebo-controlled study for ARO-APOC3 in subjects with FCS. This study contains 2 periods: randomized period and extension period. In randomized period, subjects who have met all inclusion/exclusion criteria will be randomized 2:1:2:1 to dose cohorts ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively. Each subject will receive SC injection of active treatment or placebo once every 3 months (Q3M) and total of 4 doses in 12 months.

Randomization will be stratified by level of triglycerides (TG) at Screening (≥2000 vs <2000 mg/dL).

Subjects who complete the randomized period will continue in a 2-part extension period, where all subjects will receive ARO-APOC3. In Part A of the extension period, subjects will remain blinded to their original treatment assignment and will initially receive open-label ARO-APOC3 at the dose corresponding to their study treatment dose in the randomized period. Thus, subjects who received ARO-APOC3 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (ie, ARO-APOC3 25 mg Q3M or 50 mg Q3M).

In Part B of the extension period, after the last subject completes the randomized period and a dose is selected, all subjects will switch to the selected dose of ARO-APOC3 Q3M until the last dose at Month 33. The timing of this switch may vary for each subject, based on when the subject entered Part A of the extension period and when the dose for Part B of the extension period is selected.

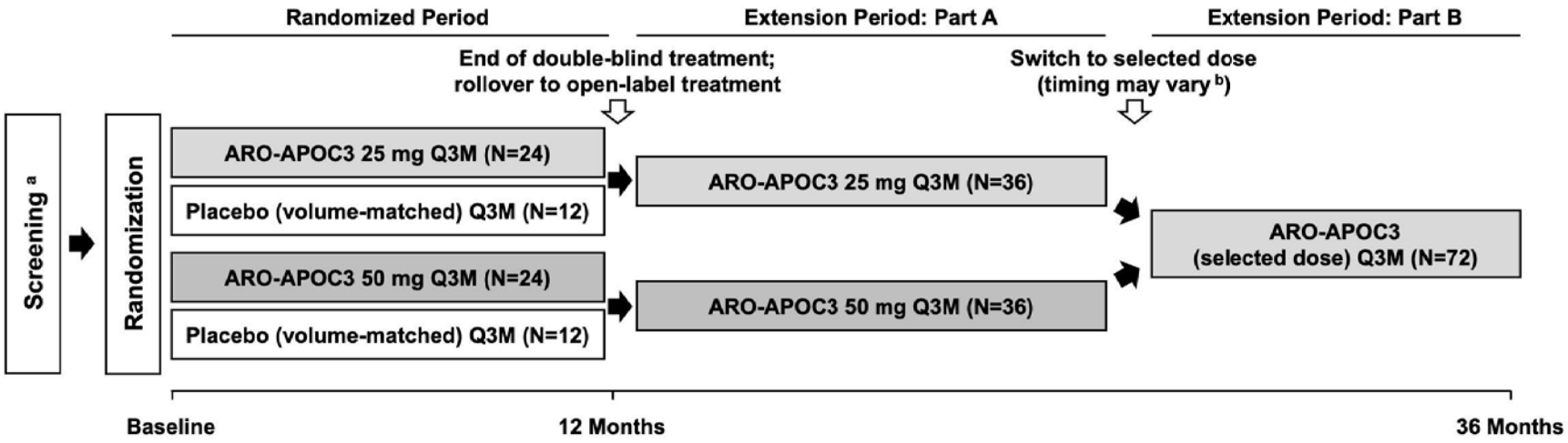
Central laboratory results of fasting serum TG and other lipid parameters (low-density lipoprotein cholesterol[LDL-C], total cholesterol, non-high density lipoprotein cholesterol[non-HDL-C], high-density lipoprotein cholesterol[HDL-C], very-low-density lipoprotein cholesterol[VLDL-C], apolipoprotein B 48[ApoB-48], lipoprotein(a)[LP(a)], apolipoprotein B 100[ApoB-100], total apolipoprotein B[ApoB], apolipoprotein C3[ApoC-III], apolipoprotein C2

[ApoC-II], apolipoprotein A-I[ApoA-I], and apolipoprotein A-V [ApoA-V]) will not be reported to the PI and will be blinded after Day 1. After Day 1, PIs should not perform local non-protocol testing of these analytes during a subject's study participation from the first dose of Investigational product (IP) until after the subject's Month 13 visit.

After completion of the Month 13 visit, through the Month 36/EOS Visit, the central laboratory will provide available lipid parameter results to the PI for each participant.

An independent Data Safety Committee (DSC) will review safety data after approximately 10 participants have received at least 1 dose of IP, and after half of the total number of participants planned for enrollment have received at least 1 dose of IP. DSC may also be asked by the study Sponsor to meet on an ad hoc basis to review safety data and make recommendations related to the study.

Figure 1: Study Schema



[a] Screening: review and stabilization of diet, medications, and laboratory values
[b] The duration of Parts A and B depend on when the participant entered Part A and when the dose was selected for Part B

Table 1: Schedule of Activities: Randomized Period

Study Visit	Screening	Randomized Period															
					Months												
					1	2	3		4	5	6	7	8	9	10	11	12
Study Day	Day -56 to -1	Day 1[a]	Day 2	Day 15 (±2 Days) (Japan Only)	Days (Each ±5 Days, Except at Day 91)												
					30	60	90[b]	91[c]	120	150	180[b]	210	240	270[b]	300	330	360[b,o]
Informed consent	X																
Dietary counseling / maintain diet	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Review with participant signs and symptoms of pancreatitis and when to seek medical care	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Eligibility criteria[d]	X	X															
Height and weight[e]	X	X					X				X			X			X
Vital signs (BP, temperature, respiratory rate, heart rate)	X	X		X			X				X			X			X
Demographics	X																
Medical history	X	X															
Physical examination (symptom directed after screening)	X	X		X			X				X			X			X
Single 12-Lead ECG[f]	X										X			X			X
Triplicate 12-Lead ECG[g]		X					X										
HBV/HCV serology screen	X																

Study Visit	Screening	Randomized Period														
					Months											
					1	2	3		4	5	6	7	8	9	10	11	12
Study Day	Day -56 to -1	Day 1[a]	Day 2	Day 15 (±2 Days) (Japan Only)	Days (Each ±5 Days, Except at Day 91)												
					30	60	90[b]	91[c]	120	150	180[b]	210	240	270[b]	300	330	360[b,o]
FSH (women not of childbearing potential to confirm postmenopausal status)	X																
Pregnancy test in women of childbearing potential (predose on dosing days)[h]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genotype (new sample or record from source documents, if available)[d]	X																
Clinical laboratory tests (predose on dosing days)[h]	X	X		X	X	X	X				X			X			X
Liver function tests (ALP, ALT, AST, total bilirubin), HbA1c, and CBC[i]					X	X	X		X	X	X	X	X	X	X	X	X
Lipid parameters (predose on dosing days)[j]	X	X			X	X	X		X	X	X	X	X	X	X[k]	X	X
Child-Pugh score (predose)	X[l]																
Anti-drug antibodies (predose on dosing days)		X			X		X				X			X			X
Full PK Subset[m]		X	X				X	X									

Study Visit	Screening	Randomized Period														
					Months											
					1	2	3		4	5	6	7	8	9	10	11	12
Study Day	Day -56 to -1	Day 1[a]	Day 2	Day 15 (±2 Days) (Japan Only)	Days (Each ±5 Days, Except at Day 91)												
					30	60	90[b]	91[c]	120	150	180[b]	210	240	270[b]	300	330	360[b,o]
Sparse PK Subset[n]		X					X										
IP administration (Vial or PFS)[o]		X					X				X			X			X[p]
Injection site assessment (all sites)[q]		X					X				X			X			X
2-hour postdose observation (Japan only)		X[r]					X[r]										
24-hour postdose follow-up (all sites)			X					X									
Diet assessment[s]		X					X				X			X			X
Quality of Life Assessment (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-PAN26)		X					X				X			X			X
Concomitant medications/ therapies	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; CBC=complete blood cell count; COVID=coronavirus disease; ECG=electrocardiogram; EORTC QLQ=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire;

EQ-5D-5L=EuroQol 5-dimension instrument; FSH=follicle-stimulating hormone; HbA1c= glycated hemoglobin HBV=hepatitis B virus; HCV=hepatitis C virus; IEC=Independent Ethics Committee; IP=investigational product; IRB=Institutional Review Board; PFS=prefilled syringe; PI=Principal Investigator; PK=pharmacokinetics; TG=triglyceride.

a. If a participant discontinues study participation early, then the Month 36 assessments (see Protocol Table 4) should be completed at the time of early discontinuation, if possible.
b. Assessments completed on dosing days are to be done predose, unless otherwise specified.
c. At Month 3, the 24-hour postdose visit will only occur for participants in the Full PK Subset at designated PK sites.
d. If required, sample for genotype analysis should be collected as soon as possible after informed consent is obtained. Review of medical history, concomitant medications, and diet assessment, as well as collection of laboratory samples for confirmation of all other eligibility criteria may occur up to 42 days (6 weeks) prior to Day 1. The sample used to confirm a qualifying baseline TG should be drawn after the site has confirmed the participant has maintained a stable diet for ≥4 weeks and stable background medications (see Protocol Table 5).
e. Height (cm) at screening visit only; weight (kg) at all indicated visits.
f. Single 12-lead ECG will be performed in the supine position after the participant has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.
g. Triplicate 12-lead ECG will be performed using validated ECG services equipment from a central facility approximately time-matched to whole blood PK collections for all participants. Triplicate measurements should be separated by approximately 1 minute with the patient in the supine or semi-supine position after resting comfortably for at least 5 minutes. At all timepoints, ECG assessments must be done prior to drawing the blood sample for PK assessments within 5 minutes prior to the PK blood collections at the 0.25 hour (15 min) postdose PK assessment, and within 10 minutes prior to all other PK collection times. For the prespecified “Full PK Subset”, the triplicate ECGs are to be collected at predose, and the PK assessments at 0.25, 1, 3, 6, and 24 hours postdose at Day 1 and Month 3 after study treatment administration (ARO-APOC3 or placebo). For the prespecified “Sparse PK Subset”, the triplicate ECGs are to be collected at predose and 2 hours postdose at Day 1 and Month 3 after study treatment administration (ARO-APOC3 or placebo).
h. Blood and urine samples will be collected at screening after obtaining informed consent. With prior written consent, a separate blood sample will be collected and stored for future research at Day 1 and Month 3. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, lab samples may be collected at alternative location (eg, home health [except in countries where this not allowed], local laboratory) using the central laboratory kit and shipped to the central laboratory for analysis. If central laboratory kit collection is not available, local laboratory safety testing may be permitted only in limited circumstances and only with prior Sponsor approval. Beginning on Day 1, at study visits with blood draws for clinical laboratory tests or lipid parameter measurements, participants will have fasted for at least 10 hours prior to blood draw unless otherwise specified. Samples collected on Month 1 and 2 will be analyzed for HbA1c only. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Protocol Appendix 3).
i. Any elevation in ALP, ALT, AST, or total bilirubin test results will be evaluated and followed as described in the consensus guidelines for suspected drug-induced liver injury during clinical trials (Protocol Appendix 2). HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Protocol Appendix 3). The CBC will be used to monitor platelet counts. If a participant does not enter the extension period, then continue monthly assessments of liver function tests and CBC for 12 months after the last dose of IP.
j. Whole blood for PD lipid analysis will be drawn after the site has confirmed the participant has maintained a stable diet for ≥4 weeks and stable background medications (see Protocol Table 5). Only TGs are required at screening. Lipid parameter testing must be done after the participant has fasted for ≥10 hours before collection at each study visit.
k. At Month 10, collect lipids twice, 2 to 7 days apart, for calculation of study endpoints. The second collection at Month 10 may be done through home health (except in countries where this is not allowed).
l. Child-Pugh score will be determined based upon standard of care clinical evaluations by the Investigator and predose Day 1 baseline laboratory values.
m. Full PK Subset: Whole blood for plasma PK samples will be drawn in approximately 36 participants (24 active and 12 placebo) enrolled at designated PK sites, including all participants enrolled at sites in Japan. PK collection time points (time window) are at predose, 0.25 hour (±5 minutes), 1 hour (±5 minutes), 3 hours (± 10 minutes), 6 hours (± 30 minutes), and 24 hours (± 1 hour) postdose at Day 1 and Month 3. For postdose samples that require next-day collection, participants may return to the clinical facility to have their blood drawn or they may opt to have their PK samples collected through home health (except in countries where this is not allowed).
n. Sparse PK Subset: Participants not in the Full PK Subset will have whole blood for plasma PK samples drawn predose and at 2 hours (± 10 minutes) postdose at Day 1 and Month 3 after study treatment administration (ARO-APOC3 or placebo).
o. Upon approval of global amendment 6 by the relevant regulatory authorities and IECs/IRBs, the PI (or appropriately trained and qualified clinical staff designated by the PI) will administer IP using a PFS to participants assigned to the 50 mg dose cohort (ARO-APOC3 50 mg or volume-matched placebo), once available at the study site. A PFS will not be introduced in the 25 mg dose cohort.

p. At Month 12, all participants will receive the first open-label dose of ARO-APOC3 at the dose corresponding to their study treatment dose in the randomized period. Thus, participants who received ARO-APOC3 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (ie, ARO-APOC3 25 mg Q3M or 50 mg Q3M).
q. For all participants, the injection site will be assessed for any signs of localized reaction after IP administration by the PI (or appropriately trained and qualified clinical staff designated by the PI).
r. The injection site will be assessed for any signs of localized reaction after administration. At these visits, participants enrolled in Japan will remain at the study site for 2 hours after completion of dosing, for observation and the following assessments: vital signs, triplicate 12-lead ECG and plasma PK sample at 1h (±5 minutes) post dose (as per the Full PK Subset collection schedule), and documentation of any adverse events. All participants enrolled in Japan will also have plasma PK samples and triplicate ECG monitoring through 6 hours after the first and second doses; see footnotes (g) and (m) for additional details.
s. Diet will be recorded on at least 3 of the past 5 days before the study visit.

Table 2: Schedule of Activities: Extension Period

	Extension Period									
	Months									
Study Visit	**13**	**14**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36/ EOS/ ET[a]**
	Days (Each ±5 Days)									
Study Day	**390**	**420**	**450[b]**	**540[b]**	**630[b]**	**720[b]**	**810[b]**	**900[b]**	**990[b]**	**1080**
Dietary counseling / maintain diet	X	X	X	X	X	X	X	X	X	X
Review with participant signs and symptoms of pancreatitis and when to seek medical care	X	X	X	X	X	X	X	X	X	X
Weight			X	X	X	X	X	X	X	X
Vital signs (BP, temperature, respiratory rate, heart rate)			X	X	X	X	X	X	X	X
Physical examination (symptom-directed)			X	X	X	X	X	X	X	X
Single 12-Lead ECG[c]			X	X	X	X	X	X	X	X
Pregnancy test in women of childbearing potential	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[d,e]	X	X	X	X	X	X	X	X	X	X
Liver function tests (ALP, ALT, AST, total bilirubin), HbA1c, and CBC[e]	X	X	X	X	X	X	X	X	X	X
Lipid parameters[f]	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies			X	X		X				X
IP administration (Vial or PFS) [g]			X	X	X	X	X	X	X	
Injection site assessment (all sites)[h]			X	X	X	X	X	X	X	
Diet assessment[i]										X
Quality of Life Assessment (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-PAN26)										X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain, or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; CBC=complete blood cell count; ECG=electrocardiogram; EORTC QLQ=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EOS=end of study;

EQ-5D-5L=EuroQol 5-dimension instrument; ET=early termination; IEC=Independent Ethics Committee; IP=investigational product; IRB=Institutional Review Board; PFS=prefilled syringe; PI=Principal Investigator.

a. If a participant discontinues study participation early, then the Month 36 assessments should be completed at the time of early discontinuation, if possible.
b. Assessments completed on dosing days are to be done predose, unless otherwise specified.
c. Single 12-lead ECG will be performed in the supine position after the participant has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.
d. In the event of logistical disruptions (eg, COVID-related) where a participant does not have direct access to the site, lab samples may be collected at alternative location (eg, home health [except in countries where this is not allowed], local laboratory) using the central laboratory kit and shipped to the central laboratory for analysis. If central laboratory kit collection is not available, local laboratory safety testing may be permitted only in limited circumstances and only with prior Sponsor approval. At study visits with blood draws for clinical laboratory tests or lipid parameter measurements, participants will have fasted for at least 10 hours prior to blood draw unless otherwise specified. Samples collected on Month 13 and 14 will be analyzed for HbA1c only.
e. Any elevation in ALP, ALT, AST, or total bilirubin test results will be evaluated and followed as described in the consensus guidelines for suspected drug-induced liver injury during clinical trials (Protocol Appendix 2). HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Protocol Appendix 3). The CBC will be used to monitor platelet counts.
f. Lipid parameter testing must be done after the participant has fasted for ≥10 hours before collection at each study visit.
g. Upon approval of global amendment 6 by the relevant regulatory authorities and IECs/IRBs, the PI (or appropriately trained and qualified clinical staff designated by the PI) will administer IP using the PFS to participants receiving the ARO-APOC3 50 mg dose, once available at the study site. A PFS will not be introduced in the 25 mg dose cohort.
h. For all participants, the injection site will be assessed for any signs of localized reaction after IP administration by the PI (or appropriately trained and qualified clinical staff designated by the PI).
i. Diet will be recorded on at least 3 of the past 5 days before the study visit.

2.2.2. Randomization and Blinding

Eligible participants will be allocated a unique randomization number, in accordance with the randomization schedule. Each participant will be randomly assigned 2:1:2:1 to the dose cohorts (ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively). Treatments will be administered per the randomized sequence generated by an Interactive Web Response System (IWRS). The allocation of active treatment or placebo will be performed using a block randomization algorithm. Randomization will be stratified by level of TG at screening (≥2000 mg/dL vs <2000 mg/dL).

Treatment assignment (active vs placebo) is blinded in the randomized period of this clinical study. Dose group assignment is not blinded, due to required injection volume differences dictated by the respective dose group. Therefore, participants will receive an injection of either active or placebo volume matched to the assigned dose group. During the extension period, subjects will receive open-label treatment, but blinding of the initial treatment assignment from the randomized period will be maintained. Randomized period will be unblinded after database lock.

Blinding of central laboratory results for TG and lipid assessments please refer to Protocol Section 11.1.

2.3. Study Endpoints

2.3.1. Primary Endpoint

Primary and secondary endpoints are for the randomized period only, except as noted. The primary endpoint in this study is as follows:

- Percent change from baseline at Month 10 in fasting TG

2.3.2. Primary Estimand

The primary estimand of interest is the difference in median percent change from baseline in fasting TG at Month 10 in FCS population, regardless of treatment compliance or other intercurrent events post-baseline. It is defined by the following attributes:

- The target population is adult FCS population as defined by the inclusion/exclusion criteria in protocol.
- The primary variable is fasting serum TG at month 10
- The intercurrent events includes noncompliance with treatment and use of prohibited medications. The occurrence of intercurrent events is considered irrelevant in defining treatment effect; the values of the endpoint will be used regardless of whether subject experiences an intercurrent event
- The population level summary measures difference in median percent change from baseline at month 10

2.3.3. Key Secondary Endpoints

Key secondary endpoints in this study are as follows:

- Percent change from baseline at Months 10 and 12 (averaged) in fasting TG
- Percent change from baseline at Month 10 in fasting APOC3
- Percent change from baseline at Month 12 in fasting APOC3
- Incidence of positively adjudicated events of acute pancreatitis during the randomized period

  Note: All AEs and SAEs reported by the Investigator during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the 2013 Atlanta definition meeting 2 of the following 3 criteria:

  1. Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
  2. Serum lipase activity (or amylase activity) ≥3 times the upper limit of normal (×ULN)
  3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography

2.3.4. Other Secondary Endpoints

Other secondary endpoints in this study are listed follows:

- Percent change from baseline at Month 10 in non-high density lipoprotein cholesterol (non-HDL-C) and HDL-C
- Percent change from baseline at Month 12 in fasting TG, non-HDL-C, and HDL-C
- Proportion of participants reaching TG of <500, 880, and 1000 mg/dL at each scheduled assessment
- Proportion of participants achieving ≥40%, ≥70% reduction in fasting TG from baseline over time
- Change and percent change from baseline at each scheduled assessment in fasting TG up to Month 12
- Participant incidence of treatment-emergent adverse events (TEAEs)

2.3.5. Exploratory Endpoints

The following exploratory endpoints are for both the randomized period and the extension period, except as noted:

- Change and percent change from baseline at each scheduled assessment in fasting lipid parameters (total cholesterol, LDL-C, HDL-C, non-HDL-C, VLDL-C, total APOB, APOB-48, LP[a], APOB-100, APOC2, APOC3, APOA1, and APOA5), with all values drawn after at least a 10-hour fast; LDL-C will be measured using ultracentrifugation methodology, preferentially, as well as Martin-Hopkins methodology
- Changes from baseline at each scheduled assessment in fasting serum blood glucose, glycosylated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide
- Area under the curve in fasting triglyceride from baseline to Month 12

- Incidence of positively, probably, or possibly adjudicated events of acute pancreatitis during the randomized period.

  Note: Probable pancreatitis and possible pancreatitis are defined as:

  Probable pancreatitis: a clinical diagnosis of pancreatitis with documentation of typical clinical features plus abnormal amylase/lipase (<3x upper limit of normal) and required:

  - Abdominal pain strongly consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back);
  - Typical supportive treatment for pancreatitis instigated (eg, nothing-by-mouth, intravenous fluids, prescription of analgesics [stronger than acetaminophen only]);
  - Amylase/ lipase levels that were elevated but <3X upper limit of normal;
  - Radiology investigations either not performed or not diagnostic; and
  - Discharge diagnosis of acute pancreatitis according to the attending physician with no alternative diagnosis proposed.

  Possible pancreatitis: documentation of typical clinical features of pancreatitis in a patient with known history of pancreatitis and required:

  - Previous medical diagnosis of acute pancreatitis, abdominal pain strongly consistent with acute pancreatitis (acute onset of a persistent, sever, epigastric pain often radiating to the back);
  - Typical supportive treatment for pancreatitis instigated (eg, nothing-by-mouth, intravenous fluids, prescription of analgesic [stronger than acetaminophen only]);
  - Serum amylase and lipase levels were either normal, not determined, or missing, radiology investigations not performed or not diagnostic; and
  - Discharge diagnosis of acute pancreatitis according to the physician with no alternative diagnosis made.
- Time to the first positively adjudicated events of acute pancreatitis
- Time to the first positively, probably, or possibly adjudicated events of acute pancreatitis
- Incidence of hospitalizations for abdominal pain
- Participant incidence of abdominal pain
- Participant incidence of emergent apheresis
- Population PK of ARO-APOC3, with assessment of the covariates of Country (Japan) and Race (Asian) for any significant effect on ARO-APOC3 PK (randomized period only)
- Incidence of anti-drug antibodies (ADA) to ARO-APOC3
- Change from baseline at each scheduled assessment in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 score

- Change from baseline at each scheduled assessment in EORTC QLQ-PAN26 score
- Change from baseline at each scheduled assessment in EuroQol 5-dimension instrument (EQ-5D-5L) score

3. STATISTICAL METHODOLOGY

3.1. General Considerations

3.1.1. Analysis Visits

Analysis Visits Window is defined based on scheduled target day. Within an analysis visit window, if a scheduled visit occurs, then the measurement from this scheduled visit will be used as the measurement for the visit window. If unscheduled visit occurs within a visit window, the measurement from the visit closest to the scheduled visit within the visit window will be used. If there are more than one measurement with equal distance to the scheduled measurement, the last one will be used. If no visits occur within a visit window, the measurement for this visit will be treated as missing. For early termination visit, it will be treated as analysis visit +1 if more than one visits are measured within one analysis visit window. The exception is that two closest lipid parameter records at Month 10 collected 48 hours apart will be used for endpoints. Otherwise, a nominal visit value(s) will be used.

Visit	Target Day	Analysis Window (Study Day)
Day 1	1	1
Month 1	30	(post Day 1, 45]
Month 2	60	(45, 75]
Month 3	90	(75, 105]
Month 4	120	(105, 135]
Month 5	150	(135, 165]
Month 6	180	(165, 195]
Month 7	210	(195, 225]
Month 8	240	(225, 255]
Month 9	270	(255, 285]
Month 10	300	(285, 315]
Month 11	330	(315, 345]
Month 12	360	(345, 375]
Month 13	390	(375, 405]
Month 14	420	(405, 435]
Month 15	450	(435, 465]
Month 18	540	(465, 585]

Month 21	630	(585, 675]
Month 24	720	(675, 765]
Month 27	810	(765, 855]
Month 30	900	(855, 945]
Month 33	990	(945, 1035]
Month 36	1080	(1035, 1125]

For the subjects experiencing acute pancreatitis during the randomized period and transitioned to the extension period, analysis visits window for the extension period is defined based on the study day in extension period.

Visit	**Target Day in extension period**	**Analysis Window (Study Day in extension period)**
Month 12	1	Extension Day 1
Month 13	30	(Post extension Day 1, 45]
Month 14	60	(45, 75]
Month 15	90	(75, 105]
Month 18	120	(105, 135]
Month 21	150	(135, 165]
Month 24	180	(165, 195]
Month 27	210	(195, 225]
Month 30	240	(225, 255]
Month 33	270	(255, 285]
Month 36	300	(285, 315]

3.1.2. Definitions

Enrollment Date

- Enrollment date is the same as randomization date.

Randomization Date

- The date a subject is randomized in the Interactive Voice/Web Response System (IWRS) as recorded on the eCRF.

Day 1

- For each subject, day 1 is defined as the first day that protocol-specified IP is administered to the subjects (placebo or active).

Study Day in the randomized period

- For each subject, and for a given date of interest, study day is defined as the number of days since Day 1: Study day = (date of interest – Day 1 date) + 1
- If the date of interest is prior to Day 1, Study day = (date of interest – Day 1 date), so that the day prior to Day 1 is study day -1.

Study Day in extension period

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

Last IP Date (LIPD)

- For each subject, the Last IP Date is defined as the date of the last administration of the IP.

End of Study (EOS) Date

- For each subject, the End of Study date is the date recorded on the EOS eCRF.

Study End Date

- The study end date is the last recorded EOS date of all randomized subjects.

Age

- Age will be the age in years as recorded on the Demographic eCRF.

Baseline Lipid and Lipid-related Parameters

- For TG, baseline is defined as the average of the last 2 non-missing values prior to the first dose or the last non-missing value prior to the first dose if only a single value is available;
- For other lipid related, lipoprotein and serum PD assessments, baseline is defined as the last non-missing predose value;
- For fasting APOC3, if the measured value at baseline visit is below the limit of quantification, then the baseline APOC3 will be missing, and this subject will not be included in the efficacy summary and analysis of APOC3.

Other Baseline Values

- For ECG, baseline is defined as the mean over all non-missing average value from each set of triplicates taken prior to the first dose.
- For all other variables, baseline is defined as the last non-missing value obtained prior to the first dose.

Initial On-therapy Baseline (integrated analysis of long-term follow-up)

- Initial on-therapy baseline is used in integrated analysis of long-term follow-up. For subjects who receive placebo in randomized period and receive active drug in extension period, the initial on-therapy baseline is defined as the first day that active IP is administered to the subjects. For participants who receive active drug in the randomized period, the initial on-therapy baseline is the value of last assessment prior to first dose of active IP in the randomized period.

IP Exposure Period in Months

- [min (LIPD + 90 days, EOS date) – Day 1 date + 1] / 365.25*12

Study Exposure in Months

- (EOS date – Day 1 date + 1) / 365.23*12

Treatment-Emergent Adverse Event (TEAE)

- Treatment-emergent adverse events are defined as adverse events occurring between the first dose of IP and EOS or 180 days after the last dose, whichever is later.

Adverse Event of Clinical Interest (AECI)

- Adverse events of clinical interest for this study include hypersensitivity/anaphylaxis, injection site reactions, and potential hepatotoxicity events. Details refer to Protocol Appendix 4.

New Onset Diabetes Mellitus (NODM)

- The New Onset Diabetes Mellitus (NODM) is defined as the subjects who did not have diabetes at baseline (i.e., non-diabetes), but develop postbaseline new onset diabetes mellitus, defined as having HbA1c ≥6.5% on two occasions postbaseline or that initiate diabetes medication.

Worsening of preexisting diabetes mellitus

- Worsening of preexisting diabetes mellitus is identified and evaluated for the subjects who have diabetes at baseline by the following:
    - Worsening of HbA1c that is considered clinically significant by the investigator to modify or change the anti-diabetic regimen.
    - New AEs related to hyperglycemia or complications of hyperglycemia.

3.1.3. Summary Statistics

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

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

In both randomized period and extension period, data will be analyzed by treatment groups of ARO-APOC3 25 mg, 50 mg and pooled placebo. In final analysis, integrated analysis of long-term follow-up will also be provided. Data collected on and after subjects receive active drug data will be summarized by received active drug.

3.1.4. Hypothesis Testing

For each dose of ARO-APOC3, the primary null hypothesis is that there is no difference in the median percent change from baseline in fasting TG at Month 10 between ARO-APOC3 and placebo, and the alternative hypothesis is that a median difference exists. Similarly, other null hypotheses for this study were no difference in the median percent change from baseline in

fasting ApoC3 at month 10, averaged fasting TG at Month 10 and Month 12 and fasting ApoC3 at month 12, respectively.

In order to control the family-wise Type I error at a 0.05 level, a fixed sequential testing procedure will be implemented in a hierarchical step-down manner. The hypothesis testing procedure from primary efficacy endpoint to key secondary endpoints will use a fixed-sequence stepping-down procedure. That is, only if the primary efficacy analysis of primary endpoint proves significantly in favor of active treatment groups will the secondary endpoints tested.

For secondary endpoints, hypotheses are also be tested in the same way following the specified order of fasting TG (averaged) at month 10 and month 12, fasting ApoC3 at month 10 and fasting ApoC3 at month 12. To strongly control the family-wise overall Type-I error, inferential conclusions about these efficacy endpoints will require statistical significance from both dose levels of the previous one.

Within each endpoint, there are two tests, ARO-APOC3 25 mg vs. placebo and ARO-APOC3 50 mg vs. placebo. When performing the efficacy analysis for an endpoint, the adjustment for multiplicity of testing two ARO-APOC3 treatment groups versus placebo will be carried out using Holm's step-down procedure. For incidence of positively adjudicated events of acute pancreatitis during the randomized period, ARO-APOC3 25 mg and 50 mg groups will be pooled together to be compared with placebo.

Sequence of Hypotheses Testing

Endpoints	Testing Order
Percent change from baseline at Month 10 in fasting TG (primary endpoint)	1
Percent change from baseline at Months 10 and 12 (averaged) in fasting TG	2
Percent change from baseline at Month 10 in fasting APOC3	3
Percent change from baseline at Month 12 in fasting APOC3	4
Incidence of positively adjudicated events of acute pancreatitis during the randomized period. ARO-APOC3 25 mg and 50 mg groups will be pooled together to be compared with placebo	5

For exploratory efficacy endpoints, nominal p-values and 95% confidence intervals (CIs) may be presented but should not be considered as confirmatory.

3.2. Analysis Sets

3.2.1. Full Analysis Set

Full Analysis Set (FAS) includes all randomized subjects regardless of adherence to the treatment. All efficacy analyses will be performed using the FAS. Subjects will be analyzed according to the treatment assigned at randomization.

3.2.2. Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who receive at least 1 dose of IP. All safety and tolerability analyses will be performed using this set. Subjects will be analyzed according to the treatment they actually receive.

3.2.3. Per-Protocol Analysis Set (PPS)

Per-Protocol analysis set include all randomized subjects who completed the study without major protocol deviations.

3.2.4. PRO Analysis Set

PRO analysis set includes all subjects who are randomized and have at least one PRO assessment. Subject in this analysis set will be analyzed according to their original treatment assignment, regardless of treatment received.

3.2.5. PK Analysis Set

PK analysis set include all FAS participants who have sufficient plasma concentration data to facilitate determination of PK parameters.

3.3. Covariates and Subgroups

3.3.1. Planned Covariates

Stratification factor

- TG at Screening (<2000 vs ≥2000 mg/dL)

Baseline Covariates

- Age (years)
- Sex (Female, Male)
- Race (White, Asian and other)
- BMI (kg/cm^2)
- Region (North America, Europe, other)
- LDL-C (mg/dL)
- Background TG lowering therapy (Yes, No)
- Genetic confirmation of FCS (Yes, No)

3.3.2. Subgroups

- TG at Screening category from IWRS (<2000 vs ≥2000 mg/dL)
- Age (<65, ≥65)
- Sex (Female, Male)
- Race (White, Asian, and other)
- BMI (<25 vs ≥ 25)
- Region (North America, Europe, other)
- Region – Japan (Japan: Yes or No)

- LDL-C (< baseline median, ≥ baseline median)
- Background TG lowering therapy (Yes, No)
- Genetic confirmation of FCS (Yes, No)

3.4. Subject Data and Study Conduct

3.4.1. Subject Disposition

The number and the percent of subjects who were screened, randomized, received IP, discontinued IP, discontinued randomized period, completed randomized period, discontinued extension period, completed extension period part A and completed extension period part B will be summarized.

Discontinuation will be tabulated separately by reason for IP, discontinue randomized period and discontinue extension period.

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

3.4.2. Protocol Deviations

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

Counts and percentages of subjects with important protocol deviations by deviation category during double-blinded randomization period will be summarized by treatment and in total based on all randomized subjects.

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

3.4.3. Demographics and Baseline Characteristics

All demographics and baseline data will be summarized using Full Analysis Set. It will be repeated on other analysis sets if the headcounts of the subjects are different.

Demographics data will include but not limit to:

- Age (in years), also categorized as <50, 50-<65, ≥65
- Sex (male, female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported, Unknown)
- Region (North America, Europe, Other)
- Region – Japan (Japan: Yes or No)

Baseline characteristics and disease history will include but not limit to:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (<25 kg/m^2 vs ≥25kg/m^2)

- Geometric mean TG at baseline (mg/dL)
- Geometric mean TG at baseline category (< 2000 mg/dL vs ≥ 2000mg/dL)
- TG at screening (mg/dL)
- TG at screening category from IWRS (< 2000 mg/dL vs ≥ 2000mg/dL)
- ApoC3 at baseline (ng/dL)
- LDL-C at baseline (mg/dL)
- LDL-C (< baseline median, ≥ baseline median)
- non-HDL-C at baseline (mg/dL)
- HDL-C at baseline (mg/dL)
- HbA1c at baseline (%)
- HbA1c at baseline category (<5.7%, 5.7-<6.5%, ≥6.5%)
- Diabetic medications use at baseline (Metformin/combo, Insulin, GLP1 receptor agonists, Dipeptidyl peptidase-4 [DPP-4] inhibitors, Sodium-glucose transporter [SGLT] 2 inhibitors, other, none)
- Genetic confirmation of FCS (Yes, No)
- Genetic confirmation of MCM (Yes, No)

3.4.4. Medical History

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

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

3.4.5. Concomitant Medications

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug (WHO DRUG) dictionary. Full Analysis Set will be used to summarize concomitant medication.

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

A list of all subjects experiencing an addition or change in lipid lowering therapies post-randomization during the double-blind portion of the trial will be provided. This listing will include dates administered.

A list of all subjects experiencing an addition or change in diabetic therapies post-randomization during the double-blind portion of the trial will be provided. This listing will include dates administered.

3.4.6. Investigational Product Exposure

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

- Duration of study follow-up in weeks (continuous)

- Duration of study follow-up (categorical): 0 to 3 months, >3 to 6 months, >6 to 9 months, >9 to 12 months, > 12 to 15 months, every 3 months up to end of extension period
- Total number of injections received (continuous)
- Number of injections received (category)
- Overall compliance (%)

3.5. Efficacy Analyses

The efficacy analysis will be performed based on the Full Analysis Set unless otherwise specified.

3.5.1. Primary Efficacy Endpoint

Primary Analysis

Due to the known distribution of TG and percent change from baseline in TG, normality assumption is usually difficult to satisfy. A nonparametric approach will be used as the primary analysis for the primary efficacy endpoint. As an extension to the Wilcoxon rank-sum test, the Hodges-Lehmann method will be used to estimate the median difference and its corresponding 95% CI for percent changes between ARO-APOC3 doses and placebo.

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

```
proc npar1way data = indata hl alpha=0.05;
     class trt01pn;
     var pchg;
run;
```

From the study design, during the randomized period, subjects who discontinue study drug prematurely will remain in the study. If a subject who has discontinued study drug fails to attend any follow-up appointments, reasonable efforts will be made in order to encourage the patient to complete the study visits.

A pattern-mixture model will be used as the primary imputation method as part of the primary analysis for the Month 10 percent change from baseline in fasting TGs. This imputation model will include factors such as patient demographics, disease status, and baseline TGs, as well as adherence to therapy. The imputation model will impute missing Month 10 TG values as follows:

- For subjects who do not adhere to therapy and who do not have Month 10 measurements, the missing data imputation method will use subjects in the same treatment arm who do not adhere to therapy and have Month 10 measurements; and
- If there are no or very few subjects in the same treatment arm who do not adhere to therapy and have Month 10 measurements, missing Month 10 TG values will be imputed as follows:
    - For the ARO-APOC3 treatment arms, the treatment effect is considered washed out. Baseline TG values from these patients (no intermediate measures will be used) and data from placebo group will be used to impute the missing Month 10 TG values; and

- For the placebo arm, missing Month 10 TG values will be imputed with multiple imputation assuming missing at random, including patient demographics, disease status, and baseline and post-baseline efficacy data, using observed data from all subjects in the placebo arm.

After the multiple imputation step, each imputed dataset will be analyzed by nonparametric Hodges-Lehmann method. The method provided by Rubin and a modified macro from Mogg and Mehrotra (2007) will be used to combine and derive treatment difference estimates, 95% confidence intervals and p-values for the imputation procedure.

Details of the primary imputation method is described in Appendix A.

Sensitivity Analyses

To evaluate the robustness of the analysis results, sensitivity analyses will be performed as following:

- The primary analysis will be performed using PPS without missing data imputation;
- The skewness of primary endpoint will be evaluated using Pearson's first coefficient of skewness. If the data have a weak mode or multiple mode, Person's second coefficient will be used to measure central tendency. Trimmed Hodge-Lehman statistic will be calculated to evaluate robustness.
- For primary endpoint, an analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG as a covariate will be performed using FAS instead of non-parametric analysis if normality assumption is not violated;
- For change from baseline at Month 10 in fasting TG, an analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG as a covariate will be performed using FAS if normality assumption is not violated;
- For change from baseline at Month 10 in fasting TG, an analysis of heterogenous covariance (ANHECOVA) as proposed in Ye et al (2022) will be performed using FAS if data permit;
- A mixed model for repeated measures (MMRM) model will be performed using FAS based on the missing at random (MAR) assumption;
- A tipping point analysis using FAS to investigate the robustness of departures from the MAR assumptions in the MI model in order to overturn conclusions from the primary analysis. A specified sequence of shift parameters that modify the imputed TG values will be applied. The specification is provided below.

To assess robustness of the Hodge-Lehman estimate, trimmed Hodge-Lehman statistic will be calculated based on ranked endpoint $(X_{(1)}, X_{(2)}, \ldots, X_{(n)})$. If distribution is negative skewed (mean is less than the mode), trimmed Hodge-Lehman statistic will be sequentially calculated after taking out $X_{(1)}$, $X_{(2)}$ up to $X_{(10)}$. If distribution is positive skewed (mean is greater than the mode), trimmed Hodge-Lehman statistic will be sequentially calculated after taking out $X_{(n)}, X_{(n-1)}$ to $X_{(n-10)}$. The Hodge-Lehman estimate based on all data and trimmed Hodge-Lehman statistic will be compared.

The Tipping Point Analysis will be conducted with following steps:

1. Missing values will be imputed using the MCMC method to achieve monotone missing data pattern. 100 datasets with monotone missing pattern will be generated. The variables to be used in the imputation model are treatment, early termination of IP status, baseline APOC3, baseline LDL-C, and observed TG values at each visit.

```
Proc mi data = indata out = mcmc nimpute = 100 seed = &seed;
  var trt01pn etipfl baseapoc3 baseldl base m1 m2 m3 m4 m5 m6 m7 m8 m9
m10 m11 m12;
  mcmc chain = multiple;
run;
```

2. For each of the datasets with monotone missing pattern, impute all visits under MAR assumption by using MONOTONE REG statement in PROC MI, then apply delta adjustment at each visit for both ARO-APOC3 group (shift parameter ST) and placebo group (shift parameter SP). Both positive and negative adjustments will be applied to show all possible combinations of shifts. The MNAR statement with the ADJUST option in PROC MI will be used to apply the shift parameter.
3. Each of the 100 completed datasets from the previous step will be analyzed using an MMRM analysis as described above.
4. The results of the 100 completed datasets will be combined for inference using PROC MIANALYZE.
5. Repeat Steps 1-4, with adjustment by different combination of shift parameters to the imputed TG values in both ARO-APCO3 and placebo groups. SP ranges from -500 mg/dL to 500 mg/dL of non-missing post-baseline TG values in placebo arm by 100 increase and ST ranges from -500 mg/dL to 500 mg/dL of non-missing post-baseline TG values in treatment arm by 100 increase as well.
6. The combinations of shift parameters that result in a reversed study conclusion (i.e., p-value increases from <0.05 to ≥ 0.05) will be flagged.

A pre-specified seed number of 4893155 will be used in all imputation procedures as described above. Alternative model specifications may be used based on the actual data if there is an issue in model convergence.

Covariate-Adjusted and Subgroup Analysis

The following analyses modified based on the primary analysis method will be performed as sensitivity analyses:

- Covariate-adjusted MMRM, one covariate at a time, using baseline covariates defined in Section 3.3.1. If a convergence issue occurs due to the number of participants at certain levels, then the covariate may be pooled or removed from the model.
- Subgroup analysis using subgroups defined in Section 3.3.2, with an added subgroup by treatment interaction term in MMRM. Depending on the distribution of baseline LDL-C and TG, subgroups of each may be re-defined.

3.5.2. Key Secondary Efficacy Endpoints

Primary Analysis

Percent change from baseline in key continuous secondary endpoints will be analyzed in a similar manner to the primary endpoint. Wilcoxon rank-sum test with the Hodges-Lehmann method will be used to test and evaluate the difference between treatment and placebo arms.

Sensitivity Analyses

For each key continuous secondary endpoint mentioned, following sensitivity analyses are planned:

- The Wilcoxon rank-sum test with the Hodges-Lehmann method will be performed using PPS without missing data imputation;
- An analysis of covariance (ANCOVA) model with treatment as a factor and baseline value as a covariate will be performed using FAS instead of non-parametric analysis if normality assumption is not violated;
- A mixed model for repeated measures (MMRM) model will be performed using FAS based on the MAR assumption;
- A tipping point analysis using FAS to investigate the robustness of departures from the MAR assumptions in the MI model in order to overturn conclusions from the primary analysis. A specified sequence of shift parameters that modify the imputed endpoint values will be applied. The specification refers to Section 3.5.1.

The key secondary endpoint of incidence of positively adjudicated events of acute pancreatitis during the randomized period, the pooled ARO-APOC3 25 mg and 50 mg groups and placebo will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline TG level category in FAS. The analysis will be repeated on PPS.

3.5.3. Other Secondary and Exploratory Endpoints

The test applied for secondary endpoints (except key secondary endpoints) and exploratory endpoints are considered exploratory, and descriptive statistics will be provided.

The continuous endpoints will be analyzed using an analysis of covariance (ANCOVA) model with the treatment group, and baseline TG level category as factors, and baseline value of the parameter as a covariate. Residuals will be analyzed for normality assumption of ANCOVA. If the assumption is violated, an analysis based on Hodges-Lehmann estimator will be performed.

The binary efficacy endpoints of proportion of subjects reaching TG levels of <500, 880 and 1000 mg/dL at each scheduled assessment will be analyzed using a logistic regression model with treatment group, and baseline TG level as a covariate. The endpoint of proportion of participants achieving ≥40%, ≥70% reduction in fasting TG from baseline over time and the other binary efficacy endpoints will be analyzed similarly.

The exploratory endpoint of time to the first positively adjudicated events of acute pancreatitis, and time to the first probably, or possibly adjudicated events of acute pancreatitis will be analyzed using Cox proportional hazards (PH) model with treatment and TG level category as factors. The hazard ratio (HR) and its 95% confidence interval and associated p-value will be provided. Kaplan-Meier (K-M) curves will be provided to provide a graphical description.

In rare cases, some efficacy lab parameters may have a value of 0 at baseline or at endpoint or both. If the lower limit of quantitation is available, then half of this limit will be used to impute

the value. If not, with values at 0, the primary imputation, which includes log-transformation of lab values at baseline and endpoint, will return an error. Under these circumstances, an extension to the existing pattern mixture model multiple imputation method with fully conditional specification methods will be applied to account for the observed data values of 0. This method is called the predictive mean matching method which uses a simulated regression model to impute values randomly from a set of observed values whose predicted values are close to the predicted value of the missing value.

3.6. Safety Analyses

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

3.6.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later will be used to code all events categorized as AEs to a system organ class and a preferred term. The severity of AEs will be graded following Common Terminology Criteria for Adverse Events (CTCAE) criteria and recorded on the eCRF.

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

Subject incidence of all TEAEs, TESAE, TEAEs related to IP, AECI, TEAEs leading to discontinuation of IP, and fatal adverse events will be tabulated by System Organ Class (SOC) and Preferred Term (PT) in alphabetical order.

Descriptive statistics summaries of subject incidence of TEAE, by SOC, PT, severity will be provided.

Summaries of treatment-emergent and serious adverse events by preferred term in any treatment arm will be provided in descending order of frequency.

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

Descriptive statistics summaries of subject incidence of TEAEs by SOC, PT and relationship to investigation product will be provided.

Descriptive statistics summary of subject incidence of TEAEs of Arrowhead SMQ-Standardized MedDRA Query for Worsening of Glycemic Control and Local Injection Site Reaction (LISR) by PT will be provided. A list of MedRA terms for the respective SMQ is referenced in Appendix D and Appendix E.

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

Subgroup analyses may be presented for TEAEs.

If any AE start date missing, the start date will be imputed following procedure in Appendix B. Tabulation of AEs related summaries will be based on imputed AE start dates if there any. Listing of AEs will only contain non-imputed AE start date.

3.6.2. Laboratory Tests Results

The glycemic status at baseline is defined as the following:

- Diabetes: Having HbA1c ≥6.5% at baseline;
- Prediabetes: Having HbA1c ≥5.7% and <6.5% at baseline;
- Normoglycemia: Having HbA1c <5.7% at baseline.

Based on the glycemic status at baseline, the frequency of subjects who meet the following criteria will be tabulated:

- Receiving diabetes medications at baseline;
- Excursions in HbA1c to ≥6.5% at any time post baseline (Not Applicable to diabetes at baseline);
- TEAEs indicating worsening of diabetes;
- New diabetes medication added;
- New onset of diabetes from medical review (Not Applicable to diabetes at baseline). This will be based on subjects with HbA1c <6.5% on day 1 or screening that are not receiving any diabetes medicines prior to treatment, who subsequently during the blinded period demonstrate a HbA1c ≥6.5%, confirmed with a second test and/or have a new diabetes drug therapy initiated.

The actual values and changes from baseline in HbA1c, fasting glucose, HOMA-IR and C-peptide from baseline over time will be summarized by treatment on overall subject and:

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

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

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

- HbA1c measurement >10% at any post-baseline visit;
- An increase from baseline with HbA1c >2% at any post-baseline visit;
- An increase from baseline with HbA1c >1% for at least 2 post-baseline visits in subjects with a baseline HbA1c >7.5%.

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

Lab shift tables for selected analytes of interest will be generated, following CTCAE criteria.

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

- CK > 5 × ULN
- CK > 10 × ULN
- ALT or AST > 3 × ULN
- ALT or AST > 5 × ULN
- Total bilirubin > 2 × ULN
- (ALT or AST > 3 × ULN) and (Total bilirubin > 2 × ULN or INR > 1.5)
- Creatinine > 2 mg/dL or 50% increase from baseline

3.6.3. Vital Signs and Physical Measurements

Systolic and diastolic blood pressure, heart rate and physical examination results will be summarized for each treatment group using descriptive statistics at each scheduled visit. Pregnancy and FSH test results will be listed.

3.6.4. 12-Lead Electrocardiograms

ECG assessments are performed in triplicate. The average of all available at each visit will be used for analysis. Observation within the following diagnosis or findings will be excluded from analysis: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.

PR, QRS, QT, QTc, and RR interval and their change from baseline will be summarized for each treatment group by scheduled visit. In each treatment group, subjects will be categorized and summarized per their maximum post-baseline absolute QCs interval using limits of 450 ms, 480 ms, and 500 ms. They will also be categorized per their maximum change from baseline QTc interval using limits of 30 ms and 60 ms.

3.7. Pharmacokinetic Analyses

For participants assigned to the “full PK” subgroup, including all participants in Japan, PK parameters from Non-Compartmental Analysis (NCA) will be generated when feasible. Analysis of variance (ANOVA) of primary ARO-APOC3 plasma exposures (C_{max} and AUC [dosenormalized if supported by data]) will be attempted to ascertain the degree of difference between Japanese and non-Japanese participants, and between Asian and non-Asian participants.

Population PK and PD analyses of ARO-APOC3 will be performed using Nonlinear Mixed Effect (NLME) methods and appropriate software (eg, Phoenix NLME or NONMEM). If there is sufficient diversity in demographics and other baseline characteristics in the study population, an attempt will be made to evaluate the baseline characteristics (eg, age, weight, sex, race, renal and hepatic function) as potential covariates of ARO-APOC3 PK and PD. This analysis will specifically evaluate the covariates of Country (Japan) and Race (Asian) for any potential

significant effect on ARO-APOC3 PK or PD. The PK and PD data collected in this study may be combined with those from study AROAPOC31001 to develop an integrated population PK and population PD model.

3.8. Immunogenicity Analysis

Immunogenicity will be assessed for anti-drug antibodies. Results will be described by frequency tables on subjects with presence of anti-drug antibodies, by time of assessment using Safety Analysis Set.

Summary statistics for changes from baseline in detected levels of anti-drug antibodies will be calculated and presented.

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

3.9. Patient-Reported Outcome Analyses

PRO endpoints of each domain of EORTC QLQ-C30, EORTC QLQ-PAN26 and EQ-5D-5L listed in Appendix C will be analyzed.

For each endpoint, descriptive statistics for recorded values and change from baseline will be displayed by using the PRO analysis set. Scoring of EORTC and EQ-5D-5L are provided in Appendix C.

Change from Baseline in the endpoints mentioned above will be compared between treatment groups and placebo using a mixed model for repeated measures (MMRM) under the assumption of missing at random.

The repeated measures are the change from baseline to end of randomized period (month 12). The model will include baseline, treatment (AROAPOC3 vs placebo), visit, and treatment-by-visit interaction and the stratification factors. The dependent variable of the model is the change from baseline at month 3, month 6, month 9 and month 12. The analysis visit is defined in Section 3.1.1. The random subject effects are not explicitly formulated in the model form but will be modeled as part of the within-subject error correlation structure. For this purpose, an unstructured covariance matrix (in SAS, type=UN) will be used. If the analysis using the unstructured covariance matrix fails to converge, additional covariance structure of compound symmetry, followed by heterogeneous compound symmetry will be tested. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If this still does not lead to convergence, the only basic statistics described below will be presented. Restricted maximum likelihood (REML) will be used to estimate the parameters in the model.

For this model, least squares mean (LS mean) and its standard errors, treatment difference in LS mean (AROAPOC3-placebo) and its 95% CI will be estimated for each timepoint.

Two imputation methods for missing assessments will be considered for PRO endpoints.

The primary imputation method is:

- If there are observations before and after the missing response, take the average value of the two neighboring response to obtain the imputed value.
- If there is no observation before the missing response, apply next observation carry backward. Missing baseline will not be imputed.

- If there is no observation after the missing response, apply the worst case scenario on the subject level.
- Baseline will not be used to impute missing post-baseline response

Multiple imputation will be used as a supportive imputation method. The interested PRO endpoints will be imputed separately. The imputation model includes the corresponding PRO assessments from baseline up to the visit when ≥30% subjects discontinue study.

4. SAMPLE SIZE DETERMINATION

A total of 72 subjects randomly assigned 2:1:2:1 to dose cohorts ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively, results in a 1:1 allocation for comparing each study treatment dose to pooled placebo. The study will have about 99% power to detect a statistically significant global or conjunctive difference in percentage change from baseline in TG between any active treatment group and pooled placebo using a 2-sided test and Holm's step down multiple comparison procedure, with a 2.5% level of significance for each test between ARO-APOC3 dose level vs. placebo. These estimates assume an average of 75% and 80% reduction from baseline in fasting TG at Month 10 in subjects receiving ARO-APOC3 25 mg and 50 mg, respectively, and 5% reduction in subjects receiving placebo. The SD is assumed to be 40% (Witztum 2019). The Wilcoxon (Mann-Whitney) rank-sum test is used with the assumption of $p_1=P(X<Y)$=0.108. The dropout rate is estimated to be 10-15%.

Of the 72 planned participants, approximately 12 will be recruited in Japan. The sample size for participants in Japan was selected based on a combination of target enrollment of 10% to 20% of the total study population in Japan and the anticipated availability of eligible participants in Japan.

5. PLANNED ANALYSES

5.1. Interim Analysis and Early Stopping Guides

No interim analysis is planned for this study.

An external independent DSC will formally review the accumulating data after approximately 10 participants have received at least 1 dose of IP, and after half of the total number of participants planned for enrollment have received at least 1 dose of IP. This group may also be asked by the study Sponsor to meet on an ad hoc basis to review safety data and make recommendations related to the study. Analyses for the DCS are provided by an independent biostatistical group, which is external to Arrowhead clinical trial study team.

5.2. Primary Analysis

The primary analysis is planned when all randomized subjects complete the randomized period or discontinue from study, whichever is earlier. Data collected in randomized period will be cleaned and all queries will be addressed. Cleaned data will be frozen prior to snapshot of

Primary Analysis. Any proposed amendments to the SAP, which cover randomized period, will only occur prior to database freeze.

5.3. Final Analysis

The final analysis is planned when all participants complete the extension period or discontinue from study, whichever is earlier. Final analysis is descriptive by nature. Same format as in Primary Analysis will be used to summarize data from complete database. In addition, integrated analysis of long-term follow-up will be provided. For integrated analysis, data collected on and after first dose of active treatment will be used. Initial on-therapy baseline values for subjects that received placebo in randomized period and enrolled in extension period will be used (see Section 3.1.2).

Database will be locked prior to Final Analysis. Data will be cleaned, and all queries will be addressed before database lock.

Any proposed amendments to the SAP, which cover extension period, will only occur prior to database lock.

6. CHANGE FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

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

7. PROGRAMMING SPECIFICATIONS

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

8. LITERATURE CITATIONS/REFERENCES

Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102-111.

Glynn R., Laird N., Rubin DB (1986). Selection Modeling Versus Mixture Modeling with Nonignorable Nonresponse. Drawing Inferences from Self-Selected Samples. pp 115-142.Hettmansperger, Thomas P., and Joseph W. McKean. Robust nonparametric statistical methods. CRC Press, 2010.

Holm, Sture. "A simple sequentially rejective multiple test procedure." Scandinavian journal of statistics (1979): 65-70.

Little, R.J.A (1993) Pattern-mixture models for multivariate incomplete data. Journal of the American Statistical Association, 88:125–134.Little, R. J. A., Yau, L. (1996) Intent-to-treat analysis for longitudinal studies with drop-outs. Biometrics, 52:471–483.

Mogg R, Mehrotra DV. Analysis of antiretroviral immunotherapy trials with potentially non-normal and incomplete longitudinal data. Stat Med. 2007 Feb 10;26(3):484-97.

Ratitch, Bohdana, Michael O'Kelly, and Robert Tosiello. "Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models." Pharmaceutical statistics 12.6 (2013): 337-347.

Robins, James M., and Naisyin Wang. "Inference for imputation estimators." Biometrika 87.1 (2000): 113-124.

Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, et al. Volanesorsen and triglyceride levels in familial chylomicronemia syndrome. N Engl J Med. 2019;381:531-542.

Ye, T., Shao, J., and Zhao, Q. (2022). Toward better practice of covariate adjustment in analyzing randomized clinical trials. J. Am. Stat. Assoc., To appear(0):1–13.

9. APPENDIX

9.1. Appendix A: Primary Analysis Imputation Method for Missing Month 10 TG with A Pattern Mixture Model

Pattern mixture model was first introduced by Glynn et al (1986) and Little (1993). Later Little and Yau (1996) suggested control-based pattern mixture models, which assume that after discontinuation, subjects on the experimental treatment who withdraw will tend to have efficacy close to subjects on the control treatment. The imputation model for this study will impute missing Month 10 fasting TG measurements as follows:

Scenario I:

For subjects who do not adhere to therapy and who do not have Month 10 fasting TG measurements, the missing data imputation method will use patients in the same treatment arm who do not adhere to therapy and have Month 10 fasting TG measurements.

Subjects without Month 10 fasting TG measurements and subjects with Month 10 fasting TG measurements but discontinue treatment prior to Month 10 will be selected. Missing Month 10 TG data will be imputed using PROC MI procedure with a multivariate imputation by fully conditional specification methods to create 100 datasets. In the imputation model, patient demographics (age, sex, ethnicity, baseline BMI), and baseline TG, LDL-C, ApoC-3 and other factors will be considered. The FCS statement will be used. This statement calls a multivariate imputation by fully conditional specification methods.

Sample SAS code is listed below:

```
proc mi data = datain out = imout1 minimum=0 nimpute = 100 seed = 98547;
  by trt01pn;
  var age sex ethnicity bmi baseapoc3 baseldl base m1 m2 m3 m4 m5 m6 m7 m8
m9 m10;
  class sex ethnicity;
  FCS; /* fully conditional specification method*/
  transform log(base) log(m1) log(m2) log(m3) log(m4) log(m5) log(m6)
log(m7) log(m8) log(m9) log(m10);
run;
```

Scenario II:

If there are no or very few patients in the same treatment arm who do not adhere to therapy and have Month 10 TG measurements, missing Month 10 TG measurements will be imputed as follows:

a. ARO-APOC3 treatment arms:

For each ARO-APOC3 arm, the treatment effect is considered washed out. Baseline TG values from these subjects (no intermediate measures will be used) and data from placebo group will be used to impute the missing Month 10 TG values; Missing Month 10 TG values will be imputed by using the method which was proposed by Ratitch et al (2013).

b. Placebo treatment arm:

For the placebo arm, missing Month 10 TG values will be imputed with multiple imputation assuming missing at random, including patient demographics, disease status, and baseline and post-baseline efficacy data from the observed data from all subjects in placebo arm. The SAS code is similar to the one specified in scenario I.

Scenario III:

For subjects who adhere to therapy (complete the 10-month efficacy treatment) but do not have Month 10 fasting TG measurements, the missing data will be imputed with multiple imputation method, and patients in the same treatment arm who adhere to therapy and have Month 10 fasting TG measurements will be used for the imputation.

If there are not enough observations to fit regression models for missing Month 10 values with a FCS regression method specified in Scenarios II (a and b) and III, a correlation test between baseline TG measurements and the covariates will be performed based on the Full Analysis Set. The covariate with the lowest absolute value of Spearman correlation coefficient will be removed from the model in Scenario II, while on the other hand, the one with the largest absolute value of that will be removed from the model in Scenario III. And then the analysis will be performed. If the model still does not fit, the variable with the next lowest value of Spearman correlation coefficient will be removed. This process will be repeated until the regression model fits successfully.

After imputation step, percentage change in TG will be calculated and each of the 100 multiply imputed datasets for FAS patients will be analyzed by either PROC NPAR1WAY procedure (primary) or PROC MIXED procedure (sensitivity). The estimate and standard error for treatment effect from the analysis will be analyzed by PROC MIANALYZE to obtain the overall estimate of treatment difference, as well as the confidence interval and p-value. The test statistics for making inference will be based on the method provided by Rubin and a modified macro from Mogg and Mehrotra (2007).

9.2. Appendix B: Handling of Missing and Incomplete Data

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

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

Adverse events (AEs):

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

Concomitant medications:

- Medications with missing or partial end dates will be assumed to be concomitant unless a partial end date documents it as ending prior to treatment.
- Start date:
    - If all year, month, and day are missing then use the subject's Day 1 date.
    - If year is available but day and month are missing, the day and month for the start date will be set to the 1st of January of the onset year.
    - If year and month are available but day is missing, the day will be set to the 1st of the month of the onset year.

Procedures:

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

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

9.3. Appendix C: Patient Report Outcome Instruments

In this study, there are 3 PRO measures: EQ-5D-5L, EORTC QLQ-C30 and QLQ-PAN26.

Question mapping for the PROs are outlined in the table below

EQ-5D-5L	
Mobility (MO)	1
Self-Care (SC)	2
Usual Activities (UA)	3
Pain Discomfort (PD)	4
Anxiety/Depression (AD)	5
Vertical VAS	6
EORTC QLQ-C30 (ver 3.0)	
Global Health Status/QoL	29,30
Functional scales	
Physical functioning	1-5
Role functioning	6,7
Emotional functioning	21,22,23,24
Cognitive functioning	20,25
Social functioning	26,27
Symptom scales/Items	
Fatigue	10,12,18
Nausea and vomiting	14,15
Pain	9,19
Dyspnoea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhoea	17
Financial difficulties	28
EORTC QLQ-PAN26	
Pancreatic Pain	31,33,34,35
Digestive	36,37
Altered bowel habit	46,47
Hepatic	44,45
Body image	48,49
Health care satisfaction	53,54
Sexuality	55,56

EQ-5D-5L Scoring

Question 1-5 of the EQ-5D-5L asked the subject to describe his present health stats on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each

question has 5 response choices, listed in order of increasing severity. The first response choice ("no problem") is coded as a 1; the last (contains "unable" or "extreme problem") is coded as a 5. In addition to the five variable representing these items, a string variable by concatenating the value for the five-dimension variables should be induced in the database. For example, if Mobility =2, Self-Care=1, Usual Activities =1, Pain/Discomfort=1, Anxiety/Depression=2, then string variable "Health State" would be "21112". The corresponding derived index value can be derived use following SAS code.

```
if mobility eq 1 then disut_mo=0;
else if mobility eq 2 then disut_mo=0.096;
else if mobility eq 3 then disut_mo=0.122;
else if mobility eq 4 then disut_mo=0.237;
else if mobility eq 5 then disut_mo=0.322;

if selfcare eq 1 then disut_sc=0;
else if selfcare eq 2 then disut_sc=0.089;
else if selfcare eq 3 then disut_sc=0.107;
else if selfcare eq 4 then disut_sc=0.220;
else if selfcare eq 5 then disut_sc=0.261;

if activity eq 1 then disut_ua=0;
else if activity eq 2 then disut_ua=0.068;
else if activity eq 3 then disut_ua=0.101;
else if activity eq 4 then disut_ua=0.255;
else if activity eq 5 then disut_ua=0.255;

if pain  eq 1 then disut_pd=0;
else if pain  eq 2 then disut_pd=0.060;
else if pain  eq 3 then disut_pd=0.098;
else if pain  eq 4 then disut_pd=0.318;
else if pain  eq 5 then disut_pd=0.414;

if anxiety eq 1 then disut_ad=0;
else if anxiety eq 2 then disut_ad=0.057;
else if anxiety eq 3 then disut_ad=0.123;
else if anxiety eq 4 then disut_ad=0.299;
else if anxiety eq 5 then disut_ad=0.321;

disut_total=disut_mo+disut_sc+disut_ua+disut_pd+disut_ad;
EQindex=1-disut_total;
```

EORTC QLQ-C30 Scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A higher score on the functional and global scales indicates better HRQoL, whereas for problems and symptoms higher scores indicate worse HRQoL (more problems and symptoms).

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score.

$$RawScore = RS = (I_{i1} + I_{i2} + \cdots + I_{in})/n$$

Where $i_1, i_2, \ldots, i_n$ are the items included in a scale, and $Q_1, Q_2, \ldots, Q_n$ are the corresponding scores of these items.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms

Linear transformation: Apply the linear transformation to 0-100 to obtain the score S

$$Functional\ scales: S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$
$$Symptom\ scales/items: S = \{(RS-1)/range\} \times 100$$
$$Global\ health\ status/QoL: S = \{(RS-1)/range\} \times 100$$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6.

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$EF\ score = \left\{1 - \frac{RawScore - 1}{3}\right\} \times 100$$

Fatigue

$$RawScore = \frac{Q_{10} + Q_{13} + Q_{18}}{3}$$
$$FA\ Score = \frac{RawScore - 1}{3} \times 100$$

The missing data may be classified as either missing items (one or more missing answers to questions within a questionnaire) or missing assessments (the whole questionnaire is missing for a patient). For missing items:

1. Check whether there are at least half of the items from the scale that have been answered.
2. If yes, use all the items that were completed, and apply the standard equations given on the previous pages for calculating the scale scores; ignore any items with missing values when making the calculations.
3. If No, set scale score to missing.
4. For single item measures, set score to missing (this applies to both EORTC and EQ5D-5L)

Missing assessments can be classified in terms of intermittent missing (ie, missing assessment (s) between two non-missing assessments) or monotone missing (ie. Missing all assessments after a certain time point possibility due to subject drop out or treatment discontinuation).

EORTC QLQ-PAN26 Scoring

The scoring for QLQ-PAN26 follows the similar procedure of QLQ-C30 as described above. The scoring of disease symptom scale and the of side effects of treatment Scale follows the same scoring of symptom scale in QLQ-C30.

9.4. Appendix D: List of Arrowhead SMQ-Standardized MedDRA Query for Worsening of Glycemic Control

Worsening of Glycemic Control:

Preferred Term	Preferred Term
Blood glucose increased	Impaired fasting glucose
Diabetes mellitus	Insulin resistance
Diabetes mellitus inadequate control	Insulin resistant diabetes
Diabetes with hyperosmolarity	Insulin-requiring type 2 diabetes mellitus
Diabetic ketosis	Ketoacidosis
Diabetic metabolic decompensation	Ketosis-prone diabetes mellitus
Glucose tolerance impaired	Type 2 diabetes mellitus
Glucose urine present	Blood glucose abnormal
Glycosuria	Blood glucose fluctuation
Glycosylated haemoglobin abnormal	Glucose tolerance decreased
Glycosylated haemoglobin increased	Glucose tolerance test abnormal
Hyperglycaemia	Hyperosmolar state
Hyperglycaemic crisis	Increased insulin requirement
Hyperglycaemic hyperosmolar nonketotic syndrome	Indeterminate glucose tolerance
Hyperglycaemic seizure	Insulin tolerance test abnormal
Hyperglycaemic unconsciousness	Metabolic acidosis

9.5. Appendix E: List of Arrowhead SMQ-Standardized MedDRA Query for Local Injection Site Reaction

Local Injection Site Reaction:

Preferred Term	Preferred Term
Injection site abscess	Injection site irritation
Injection site abscess sterile	Injection site ischaemia
Injection site atrophy	Injection site laceration
Injection site bruising	Injection site lymphadenopathy
Injection site calcification	Injection site macule
Injection site cellulitis	Injection site mass

Injection site cyst	Injection site necrosis
Injection site deformation	Injection site nerve damage
Injection site dermatitis	Injection site nodule
Injection site discharge	Injection site oedema
Injection site discolouration	Injection site pain
Injection site discomfort	Injection site pallor
Injection site dryness	Injection site panniculitis
Injection site dysaesthesia	Injection site papule
Injection site erosion	Injection site paraesthesia
Injection site erythema	Injection site photosensitivity reaction
Injection site exfoliation	Injection site plaque
Injection site extravasation	Injection site pruritus
Injection site fibrosis	Injection site rash
Injection site granuloma	Injection site reaction
Injection site haematoma	Injection site scab
Injection site haemorrhage	Injection site scar
Injection site hyperaesthesia	Injection site streaking
Injection site hypersensitivity	Injection site swelling
Injection site hypertrichosis	Injection site telangiectasia
Injection site hypertrophy	Injection site thrombosis
Injection site hypoaesthesia	Injection site ulcer
Injection site indentation	Injection site urticaria
Injection site induration	Injection site vasculitis
Injection site infection	Injection site vesicles
Injection site inflammation	Injection site warmth

DocuSign

Certificate Of Completion

Envelope Id: [redacted]
Status: Completed
Subject: Complete with DocuSign: AROAPOC3-3001 Statistical Analysis Plan v2.0.docx
Source Envelope:
Document Pages: 50
Signatures: 2
Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
[redacted]
EnvelopeId Stamping: Disabled
IP Address: [redacted]
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Record Tracking

Status: Original
5/6/2024 1:11:30 PM
Holder: [redacted]
[redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted]		Sent: 5/6/2024 1:12:58 PM Viewed: 5/6/2024 1:25:52 PM Signed: 5/6/2024 1:26:34 PM

Electronic Record and Signature Disclosure:
Accepted: 2/15/2024 7:40:46 AM
ID: 210bb0d8-92f6-4ddb-8afa-50143bf677f2

[redacted]		Sent: 5/6/2024 1:12:58 PM Viewed: 5/6/2024 1:13:17 PM Signed: 5/6/2024 1:13:47 PM

Electronic Record and Signature Disclosure:
[redacted]

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/6/2024 1:12:58 PM
Certified Delivered	Security Checked	5/6/2024 1:13:17 PM
Signing Complete	Security Checked	5/6/2024 1:13:47 PM
Completed	Security Checked	5/6/2024 1:26:34 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Arrowhead Pharmaceuticals, Inc. (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Arrowhead Pharmaceuticals, Inc.:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: [redacted]

To advise Arrowhead Pharmaceuticals, Inc. of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted] and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Arrowhead Pharmaceuticals, Inc.

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to [redacted] and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Arrowhead Pharmaceuticals, Inc.

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Arrowhead Pharmaceuticals, Inc. as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Arrowhead Pharmaceuticals, Inc. during the course of your relationship with Arrowhead Pharmaceuticals, Inc..