ARO-APOC3
PROTOCOL AROAPOC3-2003
PROTOCOL DATED 25-SEP-2024

Amendment 3	**Version Date: 25-SEP-2024**
Amendment 2	**Version Date: 22-NOV-2022**
Amendment 1	**Version Date: 12-JAN-2022**
Original Protocol:	**22-NOV-2021**

A PHASE 2 OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF ARO-APOC3 IN ADULTS WITH DYSLIPIDEMIA

Investigational Product:	ARO-APOC3
Study Phase	2b
Indications:	Dyslipidemia
IND Number:	144947
EU CT Number:	2024-511331-96-00
Study Sponsor:	Arrowhead Pharmaceuticals, Inc. 177 East Colorado Boulevard, Suite 700 Pasadena, CA 91105 USA

INVESTIGATOR'S AGREEMENT

By my signature below, I attest to the following:

- I have received and read the Investigator's Brochure for ARO-APOC3. I have carefully read the AROAPOC3-2003 study protocol.
- I agree to conduct the study according to the protocol and in accordance with the principles of the International Council on Harmonisation (ICH) E6 Good Clinical Practice guidelines and all applicable laws, regulations, and requirements.
- I understand that any changes to the protocol must be approved by the sponsor, Arrowhead Pharmaceuticals, Inc. and the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) and, in certain cases, the US Food and Drug Administration (FDA) or other applicable regulatory agencies, before they may be implemented.
- I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Study Emergency Contact	Sponsor Medical Monitor Contact	Sponsor Global Safety Officer
IQVIA Biotech Medical Monitoring +1.614.362.7101* *Regional contact information will be provided in the site manual.	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company: Arrowhead Pharmaceuticals, Inc.		
Name of Investigational Product: ARO-APOC-3 Injection (also referred to as ARO-APOC3)		
Name of Active Ingredient: ARO-APOC3 (ADS-005)		
Protocol Number: AROAPOC3-2003, Amendment 3	**Phase:** 2b	**Countries:** Australia, Canada, Germany, Hungary, Netherlands, New Zealand, Poland, and the United States of America
Title of Study: A Phase 2 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of ARO-APOC3 in Adults With Dyslipidemia		
Background: Dyslipidemia is defined as an imbalance in plasma lipids (eg, cholesterol, low-density lipoprotein cholesterol [LDL-C], triglycerides [TG], and/or high-density lipoprotein cholesterol [HDL-C]) that includes severely high hypertriglyceridemia (SHTG) and mixed dyslipidemia (MD), two conditions that are associated with clinical complications. SHTG is characterized by marked elevations in TG levels, which can lead to acute pancreatitis, as well as an increased risk of cardiovascular disease and atherosclerosis (Hegele 2014; Scherer 2014). MD is defined as the presence of high LDL-C combined with at least one other lipid abnormality (ie, high LDL-C with either low HDL-C and/or high TG) and is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) (Kersten 2017). The prevalence of SHTG in adults in the US is approximately 1.7%, based on the National Health and Nutrition Examination Survey (NHANEs) database (2001-2006) of individuals with TG levels between 500 and 2000 mg/dL (5.65 to 22.6 mmol/L) (Christian 2011; Laufs 2020), while the prevalence of MD in adults in the US is approximately 21% (42.0 M). Currently, the therapeutic options that can adequately treat SHTG and MD are limited, and additional treatments options are needed. ApoC3 is an 8.8 kilodalton (kDa) protein component of triglyceride-rich lipoproteins (TRLs), such as very-low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol, chylomicrons, HDL-C, and remnant particle lipoproteins. ApoC3 is synthesized predominantly in hepatocytes. It inhibits the hydrolysis of TG on TRLs at the muscle and adipose tissue capillary level through inhibition of lipoprotein lipase (LPL) and delays clearance of lipoprotein remnants by the liver by inhibiting hepatocyte receptor-mediated uptake. ApoC3 functions as a key regulator of fasting and postprandial plasma TG levels. ARO-APOC3 is a synthetic, double-stranded, hepatocyte-targeted RNA interference (RNAi) trigger designed to specifically silence messenger RNA (mRNA) transcripts from the *APOC3* gene using an RNAi mechanism. Given the important role of ApoC3 in serum TG level modulation and its primary source of synthesis in hepatocytes, reduction of ApoC3 through a hepatocyte-targeted RNAi strategy is likely to reduce circulating TG by preventing ApoC3-mediated inhibition of LPL, thus allowing enhanced peripheral LPL activity. Additionally, ApoC3 silencing is expected to remove the steric blockade of ApoC3 at the hepatocyte, leading to enhanced clearance of TRLs from circulation by the liver.		
Objectives: The primary objective of the study is to evaluate the safety and efficacy of long-term treatment with ARO-APOC3 in adults with dyslipidemia.		

Endpoints:

Primary:

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

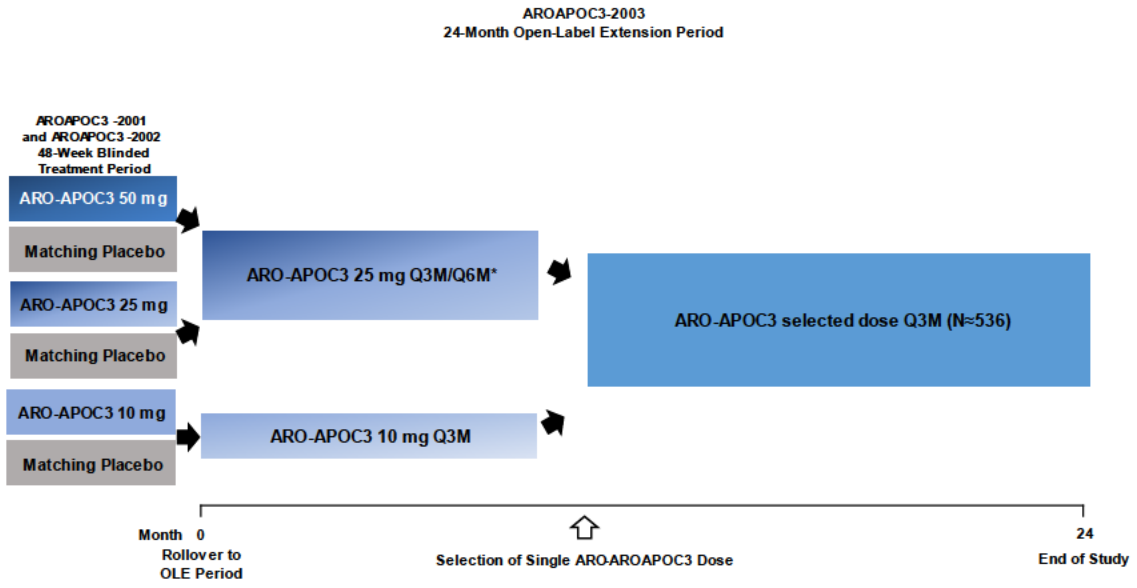
Secondary:

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

Exploratory:

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

Study Design:



Note: Subjects assigned to receive the 50 mg ARO-APOC3 dose or placebo in the parent studies (AROAPOC3-2001 and AROAPOC3-2002) were transitioned to receive the 25 mg dose. The dosing frequency remained the same until the single dose selection by the sponsor at which point all subjects transition to Q3M.

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

Methodology:

This study is conducted in adult subjects with dyslipidema. Enrolled subjects are counseled to remain on stable background medications and on the specified diet throughout the study, as recommended by the Investigator in accordance with local standard of care.

All eligible subjects enrolling from either AROAPOC3-2001 or AROAPOC3-2002 studies receive open-label ARO-APOC3, administered subcutaneously (SC). Participants previously assigned to receive either 10 mg ARO-APOC3, 25 mg ARO-APOC3, or placebo in the "parent study" (AROAPOC3-2001 or AROAPOC3-2002) receive ARO-APOC3 at the corresponding dose level in this open-label extension (OLE) study. However, participants who were previously assigned to receive 50 mg ARO-APOC3 or placebo in the parent study, receive the 25 mg dose upon enrollment into this OLE study. Any participants in the 50-mg dose group previously enrolled in this OLE prior to discontinuation of the 50 mg dose are transitioned to 25 mg ARO-APOC3 at their next dosing visit. All dosing groups are administered ARO-APOC3 either every 3 months (Q3M) or every 6 months (Q6M), consistent with their assigned dosing schedule in the parent study. To enroll in this OLE study, each subject must complete the 48-week study treatment period in the respective randomized, double-blind, placebo-controlled parent study (AROAPOC3-2001 or AROAPOC3-2002).

After the last subject in the parent study reaches the Month 12/end of study (EOS) visit of the parent study and a single dose has been selected, all subjects in this OLE study receive open-label treatment with the selected ARO-APOC3 dose and Q3M regimen.

This OLE study is not powered for statistical analysis. All eligible subjects completing the blinded 12-month treatment period from the parent study have the option to be enrolled into this study.

Number of Subjects (Planned): Up to approximately 536 subjects from studies AROAPOC3-2001 and AROAPOC3-2002 who have met all protocol eligibility criteria will enroll in this OLE study. No formal power analysis is conducted for sample size considerations.

Diagnosis and Main Criteria for Inclusion:

The study will enroll adults, ≥18 years of age, with dyslipidemia who have completed the 48-week Treatment Period in the parent studies (AROAPOC3-2001 and AROAPOC3-2002).

Subject Inclusion Criteria

To be eligible for enrollment, subjects must meet all the following inclusion criteria:

1. Adults ≥18 years of age who are nonpregnant, nonlactating, and do not plan to become pregnant during the study
2. Able and willing to provide written informed consent prior to the performance of any study specific procedures
3. Completed the 48-week study treatment period in the parent study

Subject Exclusion Criteria

A potential subject will be excluded from the study if any of the following criteria apply:

1. Subject was permanently discontinued from ARO-APOC3 in the parent study due to:
   a. Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), or
   b. Elevated HbA1c (see Appendix 4).
2. Any new condition or worsening of existing condition (eg, renal, hematologic, gastrointestinal, endocrine, cardiovascular, pulmonary, immunologic, psychiatric) or any other situation that, in the Investigator's judgment, would make the subject unsuitable for enrollment, could interfere with the subject participating in or completing the study, would make it difficult to comply with protocol requirements, or put the subject at additional safety risk
3. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)

Investigational Product, Dosage, and Mode of Administration:

The test formulation is active ARO-APOC3 administered SC. The active pharmaceutical ingredient contained in ARO-APOC3 is a synthetic, double-stranded, small interfering RNA oligonucleotides (siRNA) duplex conjugated to an N-acetyl galactosamine (NAG) targeting ligand to facilitate hepatocyte delivery.

Dosage information: ARO-APOC3 on Day 1, then Q3M (or Q6M if assigned to the 50 mg dose group in study AROAPOC3-2002): initial dosage, 10 mg or 25 mg as assigned in the parent study. Participants who were previously assigned to receive 50 mg ARO-APOC3 or placebo in the parent study will be assigned to the 25 mg dose group (Q3M or Q6M) upon enrollment into this OLE study (see Methodology).

Following the final data analysis in the parent studies, a single dose is selected and all active subjects are transitioned to the selected dose for the duration of the study.

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

- The 50 mg dosing group was discontinued.
- If assigned to the 50 mg dose group, the subject was transitioned to the 25 mg dose group at the next dosing visit as long as HbA1c discontinuation criteria (refer to Appendix 4) have not been met.
- Discontinuation criteria were added for subjects with elevated HbA1c during the OLE (see Appendix 4).

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

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

ARO-APOC3 is administered under investigator supervision at the clinical study site. ARO-APOC3 is initially supplied in vial form until a prefilled syringe (PFS) is available (see Section 9). Upon required regulatory and ethical approvals, ARO-APOC3 self-administration by subjects at the clinical study site and under direct supervision of the investigator or designated staff may be permitted.

Duration of Treatment:

The duration of the OLE study is approximately 2 years. All subjects receive ARO-APOC3 during this OLE study.

Reference Therapy, Dosage and Mode of Administration:

Not applicable

Criteria for Evaluation:

Safety: Subject incidence of TEAEs.

Efficacy: Change from baseline in TG, HDL-C, non-HDL-C, fasting total ApoB, fasting LDL-C, total cholesterol, LDL/HDL ratio, VLDL-C, and lipoprotein(a) (Lp[a]).

Pharmacodynamics: Change from baseline in ApoC-III, ApoB-48, ApoB-100, ApoC-II, ApoA-I, and ApoA-V

Immunogenicity: Incidence and titers of anti-drug antibodies against ARO-APOC3

Statistical Considerations:

Descriptive summaries will be provided for safety and efficacy assessments, as applicable. All data in this OLE study will be summarized as an overall treatment group.

For efficacy endpoints, change and/or percent change from baseline or response rate over time will be summarized. Baseline will be defined as the baseline from the parent study. The change or percent change from the measurements at enrollment of this OLE study will also be explored.

Treatment-emergent AEs will be summarized using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). The incidence of AEs, SAEs, related AEs, related SAEs, and AEs leading to discontinuation will be summarized by SOC, PT, and severity. All AEs will also be presented in listings. The duration of AEs will be determined and included in listings along with the action taken and outcome. The incidence of laboratory abnormalities will be assessed using descriptive summary statistics. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Abnormal physical examination findings will be summarized by time point and presented in listings.

Electrocardiogram parameters, changes from baseline, and qualitative assessments will be summarized.

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

Descriptive summaries will be provided for the following pharmacodynamic (PD) parameters: ApoC-III, ApoB-48, ApoB-100, ApoC-II, ApoA-I, and ApoA-V.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study protocol.

Table 2: Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (same as SGPT)
AP	acute pancreatitis
API	active pharmaceutical ingredient
ApoA-I	apolipoprotein A-I
ApoA-V or ApoA5	apolipoprotein A-V
ApoB	apolipoprotein B
ApoB-48	apolipoprotein B 48
ApoB-100	apolipoprotein B 100
ApoC-II or ApoC2	apolipoprotein C-II
ApoC-III or ApoC3	apolipoprotein C-III
ARO	Arrowhead Pharmaceuticals, Inc.
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase (same as SGOT)
CECT	contrast-enhanced computed tomography
CM	chylomicronemia
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
Da	Dalton
DSC	Data Safety Committee
ECG	electrocardiogram
eCRF	electronic case report forms
EOS	end of study
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation

Abbreviation	Definition
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HTG	hypertriglyceridemia
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFCC	International Federation of Clinical Chemistry
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IWRS	interactive web response system
kDa	kilodalton
LDL-C	low-density lipoprotein cholesterol
LISR	local injection site reactions
Lp(a)	lipoprotein(a)
LPL	lipoprotein lipase
MD	mixed dyslipidemia
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
NAG	N-acetyl galactosamine
NHANEs	National Health and Nutrition Examination Survey
NHV	normal healthy volunteer
NOAEL	no-observed-adverse-effect level
OLE	open-label extension
OTC	over-the-counter
PD	pharmacodynamic
PFS	prefilled syringe
PK	pharmacokinetic

Abbreviation	Definition
PT	Preferred Term
Q3M	once every 3 months
Q6M	once every 6 months
Q12W	once every 12 weeks
Q24W	once every 24 weeks
RBC	red blood cell
RISC	RNA-induced silencing complex
RNAi	RNA interference
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SHTG	severely high hypertriglyceridemia
siRNA	small interfering RNA oligonucleotides
SOA	Schedule of Assessments
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TG	triglyceride
TRL	triglyceride-rich lipoprotein
ULN	upper limit of normal
VLDL-C	very-low-density lipoprotein cholesterol

4. INTRODUCTION

4.1. Overview of Dyslipidemia

Dyslipidemia is defined as an imbalance in plasma lipids (eg, cholesterol, low-density lipoprotein cholesterol [LDL-C], triglycerides [TG], and/or high-density lipoprotein cholesterol [HDL-C]) that includes severely high hypertriglyceridemia (SHTG) and mixed dyslipidemia (MD), two conditions that are associated with clinical complications. SHTG is characterized by marked elevations in TG levels, which can lead to acute pancreatitis, as well as an increased risk of cardiovascular disease and atherosclerosis (Hegele 2014; Scherer 2014). MD is defined as the presence of high LDL-C combined with at least one other lipid abnormality (ie, high LDL-C with either low HDL-C and/or high TG) and is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) (Kersten 2017). The prevalence of SHTG in adults in the US is approximately 1.7%, based on the National Health and Nutrition Examination Survey (NHANEs) database (2001-2006) of individuals with TG levels between 500 and 2000 mg/dL (5.65 to 22.6 mmol/L) (Christian 2011; Laufs 2020), while the prevalence of MD in adults in the US is approximately 21% (42.0 M). Currently, the therapeutic options that can adequately treat SHTG and MD are limited, and additional treatments options are needed.

4.2. Overview of ARO-APOC3 Development

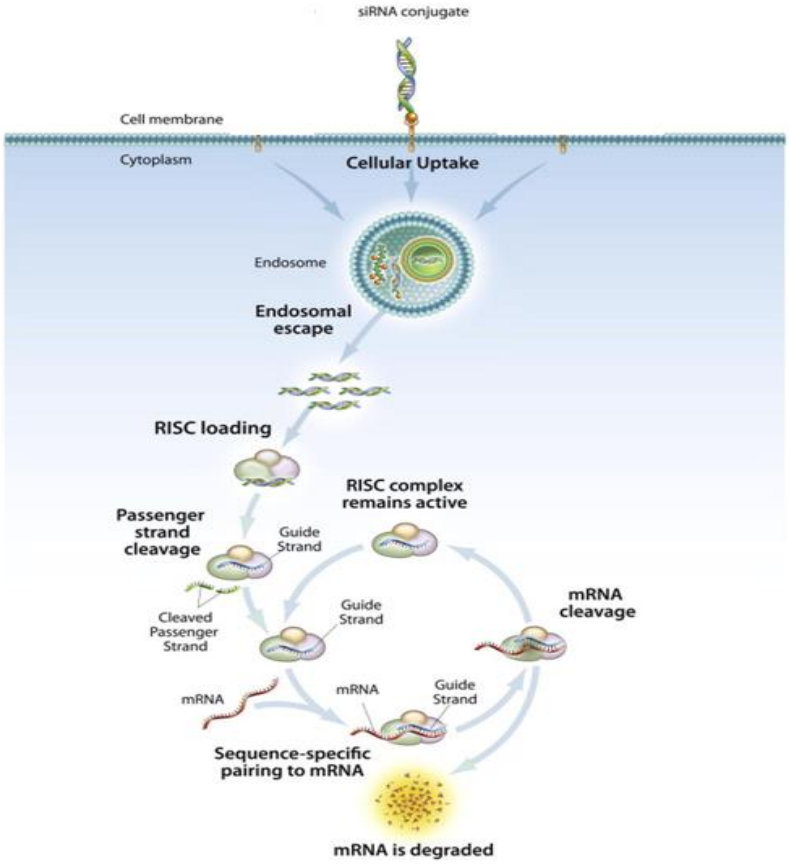
A brief overview of existing information on ARO-APOC3 is provided below; a comprehensive review of available data is contained in the Investigator's Brochure (IB) provided by the sponsor, which should be reviewed prior to initiating the study.

4.2.1. Mechanism of ARO-APOC3 Action and Therapeutic Rationale

ARO-APOC3 works through a mechanism of RNA interference (RNAi). RNAi-based therapeutics have the potential to silence the expression of any specific target gene. RNAi is a naturally occurring phenomenon by which small interfering RNA oligonucleotides (siRNAs) trigger a sequence-specific down-regulation of gene expression. RNAi triggers refer to synthetic oligonucleotides designed to target for silencing specific gene expression (Fire 1998). The RNAi trigger is a short, double-stranded siRNA conjugated to a hepatocyte-targeted N-acetyl galactosamine (NAG) targeting moiety, acting as a ligand for the highly expressed, hepatocyte-specific asialoglycoprotein receptor. Available nonclinical and clinical pharmacokinetics (PK) data show rapid absorption and clearance of all NAG conjugated triggers from the blood stream within 24 to 48 hours post-subcutaneous (SC) administration.
ARO-APOC3 is a synthetic, double-stranded, hepatocyte-targeted RNAi trigger designed to specifically silence messenger RNA (mRNA) transcripts from the *APOC3* gene using an RNAi mechanism. Preclinical distribution studies show that ARO-APOC3 is primarily distributed to the liver, where the trigger molecule is taken up by hepatocytes via receptor-mediated endocytosis. Introduction of the double-stranded RNAi trigger into the cytoplasm of hepatocytes results in its association with the protein components of the RNA-induced silencing complex (RISC), resulting in "on-target," highly sequence-specific degradation of mRNA complementary to the antisense strand of the RNAi trigger. Active RISC is a multiple turnover enzyme complex; therefore, incorporation of a single RNAi trigger into RISC can result in the degradation of many mRNA molecules and, subsequently, prolonged reduction of the expression of the corresponding

protein. The persistence of pharmacologic activity significantly beyond the period of plasma exposure is due in part to this unique RNAi mechanism in which a small amount of guide strand can persist and be active within RISC in the cytoplasm of target cells for extended periods of time.

Figure 1: siRNA Mechanism of Action



Abbreviations: mRNA=messenger ribonucleic acid; RISC=RNA-induced silencing complex; siRNA=small interfering RNA oligonucleotides.

Silencing of hepatic *APOC3* using ARO-APOC3 is expected to lower serum TG by preventing ApoC3-mediated inhibition of lipoprotein lipase (LPL), thus allowing enhanced peripheral LPL activity. Additionally, *APOC3* silencing is expected to remove the steric blockade of ApoC3 at the hepatocyte, leading to enhanced clearance of triglyceride-rich lipoproteins (TRLs) from circulation.

4.2.2. Preclinical Studies

The sponsor is conducting a comprehensive preclinical program to support the SC administration of ARO-APOC3. Studies of potential clinical significance and relevance to this protocol are summarized below.

Additional details regarding preclinical pharmacology, PK, and toxicology results are provided in the IB.

- Preclinical pharmacology of ADS-005, the active pharmaceutical ingredient (API) in ARO-APOC3, shows that ADS-005 treatment in transgenic mice (TgAPOC3) resulted in dose-dependent reduction of hepatic APOC3 mRNA levels, which correlated with reduced serum APOC3 of >90%. Reductions in serum APOC3 were associated with reductions in serum lipids (maximum mean reduction of 91% in TG, 45% in total cholesterol, and 64% in LDL-C).
- Similar reductions in serum APOC3 were also observed after ADS-005 doses in a diet induced dyslipidemic rhesus monkey model. ADS-005 has been well tolerated in rats and in nonhuman primate toxicology studies.
- Results of non-Good Laboratory Practice (GLP) in vitro toxicology studies indicate there is minimal potential for induction of the innate immune system, no potential for complement activation, mitochondrial toxicity/cytotoxicity, or platelet aggregation in human whole blood associated with ADS-005 exposure at concentrations up to 250 μg/mL, which far exceeds the blood concentrations anticipated at the doses to be used clinically.
- ADS-005 was shown to be nongenotoxic and had no adverse effects on the central nervous, respiratory, or cardiovascular systems as demonstrated by the results of the International Council for Harmonisation (ICH)-recommended battery of genetic toxicity and safety pharmacology studies.
- Multiple-dose GLP toxicity studies with SC administration of ADS-005 in rats (limited cross reactivity) and cynomolgus monkeys (full cross reactivity) demonstrated that ADS-005 was well tolerated for 24 and 37 weeks of dosing, respectively, and the no-observed-adverse-effect levels (NOAELs) were 15 mg/kg in rats and 180 mg/kg in cynomolgus monkeys.
- In both rat and cynomolgus monkey studies, the prominent histopathologic findings were consistent with those described for other SC-administered NAG-siRNA drugs, such as microscopic findings identified in the liver and kidneys consistent with hepatic targeting and renal clearance and evidence of Kupffer cell mediated uptake of the drug in rats.
- Reproductive toxicology studies with SC administration of ADS-005 were conducted under a fertility and early embryo-fetal development study design in rats (Q1W in males; Q3D in females through Gestation Day 6) and an embryo-fetal development study design in rats and rabbits. Fertility parameters evaluated in rats (percent motile sperm, sperm density, spermatid density, sperm morphology, ovarian or uterine alterations) were unaffected by doses of ADS-005 as high as 50 mg/kg administered either once every 3 days or once weekly. ADS-005 induced embryo-fetal developmental toxicity at doses ≥15 mg/kg/day (QD 12 days) in rats, the lowest dose evaluated, while doses ≤180 mg/kg/day (QD 13 days) were well tolerated in rabbits. In a follow-up single dose embryo-fetal development study in rats, ADS-005 was not developmentally toxic at ≤50 mg/kg when administered once at the beginning of the organogenesis period. As the ADS-005 drug will be administered once every 12 weeks (Q12W) in the current clinical study, the ≤50 mg/kg NOAEL in the single dose rat study is considered to more accurately predict human risk than the

exaggerated daily dosing utilized in the original rat embryo-fetal study. Therefore, the 50 mg/kg/day in the rat studies represents the lowest NOAEL in the reproductive and developmental toxicity testing completed to date and offers a 60-fold margin of safety based on dose in comparison to the planned maximum clinical dose of 50 mg/60 kg patient (0.83 mg/kg) to be employed in this study.

4.2.3. Clinical Studies

The Sponsor is conducting a comprehensive program of clinical studies investigating ARO-APOC3 as a potential therapeutic candidate for the treatment of SHTG and MD.

4.2.3.1. Phase 1 Study AROAPOC31001

The Sponsor has completed a Phase 1, single and multiple dose-escalating study (AROAPOC31001) to evaluate the safety, tolerability, PK, and pharmacodynamic (PD) effects of ARO-APOC3 in adult healthy volunteers as well as in patients with HTG. Interim results from Study AROAPOC31001 show that in healthy volunteers, treatment with ARO-APOC3 reduces hepatic production of APOC3 via RNAi, leading to reductions in serum TG, LDL-C, and apolipoprotein B (APOB), and increases in HDL-C. Doses of 10, 25, 50, and 100 mg all demonstrated durable PD activity lasting beyond Month 3. Aside from mild and transient local injection site reactions (LISRs), and transient and self-limited alanine aminotransferase (ALT) elevations, single and repeat doses of ARO-APOC3 were well tolerated in healthy volunteers, and the safety profile based on Phase 1 data warranted additional later-stage clinical evaluation. Preliminary data from participants with chylomicronemia also demonstrated substantial reductions in APOC3 and TG levels with repeat doses (at baseline and on Day 29) of ARO-APOC3 25 mg and 50 mg. Additional information regarding results of Study AROAPOC31001 can be found in the IB.

Results from the Phase 1 study provided information for the design of randomized, double-blind, placebo controlled Phase 2 studies in participants with SHTG (AROAPOC3 2001) or MD (AROAPOC3-2002), and an open label extension study for participants from either of those studies (AROAPOC3-2003). Results from the Phase 1 study also provided information justifying the dosing levels and interval as well as other design aspects.

4.2.3.2. Phase 2b Study AROAPOC3-2001 (SHASTA-2) in Subjects with Severe Hypertriglyceridemia

The AROAPOC3-2001 (SHASTA-2) study was a Phase 2b, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ARO-APOC3 in adults with SHTG. A total of 226 subjects were treated with at least 1 of 2 planned doses of study treatment (ARO-APOC3 or placebo). Evaluation of key PD parameters showed that all doses of ARO-APOC3 (10 mg, 25 mg, and 50 mg) provided robust and sustained efficacy over 24 weeks compared with placebo. At Week 24, ARO-APOC3 significantly decreased mean serum APOC3 levels by 69% to 78% ($P<0.0001$). ARO-APOC3 significantly decreased median serum TGs by 75% to 80% ($P<0.0001$) at Week 24. Importantly, >90% of subjects in the 25 and 50 mg dose groups achieved TGs <500 mg/dL (<5.65 mmol/L) as early as Week 4 that were sustained through Week 24, and between 50% to 72% achieved normalization of TGs (<150 mg/dL [<1.69 mmol/L]) from Week 4 through Week 24.

As of 13 October 2023, treatment-emergent adverse events (TEAEs) were reported in 43 out of 54 subjects in the ARO-APOC3 10 mg cohort, 36 out of 55 subjects in the ARO-APOC3 25 mg cohort, and 49 out of 56 subjects in the ARO-APOC3 50 mg cohort versus 43 out of 61 subjects in the pooled placebo cohort.

Treatment-emergent SAEs were reported in 4 out of 54 subjects in the ARO-APOC3 10 mg cohort, 2 out of 55 subjects in the ARO-APOC3 25 mg cohort, and 7 out of 56 subjects in the ARO-APOC3 50 mg cohort versus 10 out of 61 subjects in the pooled placebo cohort. No SAE was considered to be related to study drug by the Investigator and no subject discontinued study drug due to an SAE. There were no SAEs with outcome of death reported.

An increase in HbA1c levels was observed in ARO-APOC3 cohorts in subjects who had preexisting diabetes at baseline. In subgroup analyses, increases in HbA1c changes were most notable in a subset of subjects receiving the 50 mg dose of ARO-APOC3.

4.2.3.3. Phase 2b Study AROAPOC3-2002 (MUIR) in Subjects with Mixed Dyslipidemia

The AROAPOC3-2002 (MUIR) study is a completed Phase 2b, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ARO-APOC3 in adults with mixed lipidemia. A total of 353 subjects were treated with at least 1 of 2 planned doses of study treatment (ARO-APOC3 or placebo).

Evaluation of key PD parameters showed that all doses of ARO-APOC3 provided robust and sustained efficacy over 24 weeks compared with placebo. For those cohorts receiving their second dose at Week 12, ARO-APOC3 significantly decreased mean serum APOC3 levels by 59% to 80% ($P<0.0001$) at Week 24. For those subjects dosed at Day 1 and Week 12, median serum TGs were significantly decreased by 46% to 64% ($P<0.0001$) at Week 24 compared to placebo.

As of 19 September 2023, TEAEs were reported in 46 out of 67 subjects in the ARO-APOC3 10 mg cohort, 45 out of 67 subjects in the ARO-APOC3 25 mg cohort, 47 out of 66 subjects in the ARO-APOC3 50 mg Q12W cohort, and 49 out of 66 subjects in the ARO-APOC3 50 mg once every 24 weeks (Q24W) cohort versus 55 out of 87 subjects in the pooled placebo cohort.

Treatment-emergent serious adverse events (SAEs) were reported in 2 out of 67 subjects in the ARO-APOC3 10 mg cohort, 5 out of 67 subjects in the ARO-APOC3 25 mg cohort, 7 out of 66 subjects in the ARO-APOC3 50 mg Q12W cohort, and 5 out of 66 subjects in the ARO-APOC3 50 mg Q24W cohort versus 5 out of 87 subjects in the pooled placebo cohort. There was 1 SAE of lacunar infarction reported as possibly related to study treatment and considered not related by the sponsor. There were 4 SAEs with outcome of death reported and all were considered not related to the study treatment. There was 1 subject in the ARO-APOC3 50 mg Q12W cohort with study drug discontinuation due to a treatment-emergent SAE of myocardial infarction which was considered not related to the study treatment.

An increase in HbA1c levels was observed in ARO-APOC3 cohorts in subjects who had preexisting diabetes at baseline. In subgroup analyses, increases in HbA1c changes were most notable in a subset of subjects receiving the 50 mg dose Q12W of ARO-APOC3.

Additional details can be found in the IB.

4.3. Potential Risks of Study Participation

Potential risks of study participation include the following:

- **Embryo-Fetal**: When administered daily during the period of organogenesis, ADS-005 induced embryo-fetal developmental toxicity at doses ≥15 mg/kg/day in rats, while doses ≤180 mg/kg/day were well tolerated in rabbits. However, daily dosing of ADS-005 is of questionable relevance to potential human exposure as the anticipated dose administration in humans is quarterly (Q12W). In a follow-up rat embryo-fetal developmental toxicity study, ADS-005 was not developmentally toxic at ≤50 mg/kg when administered once during organogenesis, which is considered to more accurately reflect the potential human exposure, implicating daily dosing as the cause of the observed developmental toxicity observed in the original study. However, out of a high degree of caution, eligible subjects enrolled in this study, both male and female (including partners), must agree to use 2 highly effective forms of contraception during the study or agree to abstinence (acceptable only if this method is in alignment with the normal lifestyle of the subject).
- **Liver Function**: ARO-APOC3 targets the liver. siRNA literature has described ALT changes associated with off-target effects of the siRNA seed region on microRNAs in the hepatocyte (Janas 2018). The siRNA sequence of the ARO-APOC3 sense and antisense molecules have been screened for potential mRNA and microRNA homology, and sequences with homology were excluded from consideration. Thus, risk for off-target effects have been actively minimized by design. In the AROAPOC31001 study, transient mild to moderate elevations in ALT were occasionally seen (refer to the IB for details) without accompanying elevation in international normalized ratio (INR) or total bilirubin. To mitigate this risk, the proposed study protocol has built in stopping rules for ALT and aspartate aminotransaminase (AST) elevation. Blood samples will be drawn as specified in the Schedule of Assessments (SOA) (Table 3) to evaluate liver injury and liver function.
- **Local Injection Site Reactions (LISRs)**: Other SC-administered modified siRNA drug candidates evaluated in clinical studies have been associated with mild to moderate LISRs (eg, pain, erythema) (Appendix 1). Generally, mild injection site AEs were reported in AROAPOC31001. LISRs were reported in the completed Phase 2 studies (AROAPOC3-2001 and AROAPOC3-2002). All of these AEs were mild in severity and resolved with no intervention and no action taken with the study drug. No other subjects reported LISRs. In this study, steps will be taken to minimize LISRs such as rotating injection sites and allowing the ARO-APOC3 solution to come to room temperature prior to injection.

  To minimize the risk of LISRs, Clinical Trial Site staff are instructed to follow the guidance below when administering SC injections of study drugs:

  - Follow best practices for SC administration.
  - Stabilize medication at room temperature.
  - Assess injection sites before administration.

- Rotate injection sites to avoid developing lumps or nodules or absorption issues.
- Apply a cold compress or ice pack if needed before and after the injection.
- Hydrate the subject.
- Use good hand hygiene.

If a study subject experiences a LISR:

- Monitor the subject for any signs of adverse reactions, such as redness, swelling, pain, or itching at the injection site. If any reactions occur, assess their severity and provide appropriate care.
- Documentation and follow-up: Document the site of injection, the exact timing of the study drug administration, and any adverse reactions in the eCRF. Follow up with the patient to ensure that any LISRs are resolved. Record onset of each LISR, resolution state, and time.
- Adverse events, including LISRs, are reported according to MedDRA Terms and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 (Section 12.6.1) (NIH 2017).

Note: For SC administration, moderate LISRs are reactions with erythema, induration, swelling >5 cm, or associated with pain >24 hours that interfere with daily activity and require the use of non-narcotic pain management (FDA 2007).

By following the guidelines, best practices, and suggestions provided above, study staff can help minimize the risk of LISRs when administering SC study drugs, thereby ensuring the safety and comfort of clinical trial patients.

- **Glycemic Control:** The completed Phase 2 ARO-APOC3 clinical trials indicated an increase in serum glycated hemoglobin (HbA1c) in the ARO-APOC3 treatment group versus the placebo group. The increased HbA1c values were observed in a small group of subjects who had preexisting diabetes at baseline, particularly in a subset of subjects in the highest (50 mg) ARO-APOC3 dose group.

  To mitigate the risk of worsening glycemic control, investigators are encouraged to evaluate diabetes status, conduct frequent measurement of glycemic status, and adjust diabetes treatment according to local clinical practice and diabetes care institutional guidelines.

  In addition, any subject with worsening diabetic control may return for an unscheduled visit for evaluation of HbA1c prior to the next planned dose to confirm continued treatment eligibility.

  For those subjects who, despite diabetes treatment adjustments, remain with elevated HbA1c above protocol pre-established level, a number of study drug discontinuation criteria have been established (Appendix 4).

Routine monitoring of HbA1c and fasting glucose concentrations will be assessed as part of the clinical laboratory panels to monitor glycemic control, as specified in the SOA (Table 3).

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

- To evaluate the safety and efficacy of long-term treatment with ARO-APOC3 in adults with dyslipidemia.

5.2. Endpoints

5.2.1. Primary Endpoint

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

5.2.2. Secondary Endpoints

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

5.2.3. Exploratory Endpoints

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

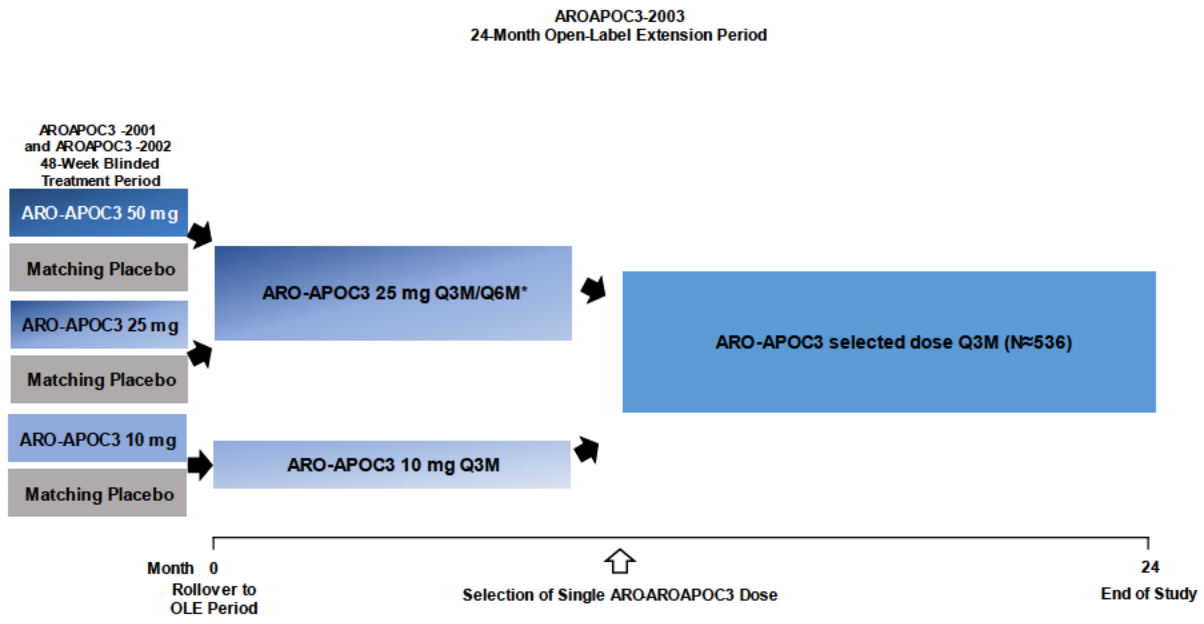
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is an open-label extension (OLE) Phase 2b clinical study. Subjects who have signed an Ethics Committee (EC)/Institutional Review Board (IRB) approved informed consent form (ICF) may be enrolled after completing either AROAPOC3-2001 or AROAPOC3-2002 (parent studies). Subjects must continue to maintain a stable diet and stable lipid-lowering therapy in accordance with local standard of care, as well as other background medications taken during the parent study (see Section 8.1), throughout the duration of the 24-month OLE period (refer to Table 3).

All eligible subjects from the AROAPOC3-2001 and AROAPOC3-2002 studies receive ARO-APOC3, administered open-label upon enrollment in this OLE study. Subjects previously assigned to 10 mg ARO-APOC3, 25 mg ARO-APOC3, or placebo Q3M in the parent study receive ARO-APOC3 at the same frequency in this OLE study. Subjects previously assigned to 50 mg ARO-APOC3 or placebo Q3M or 50 mg ARO-APOC3 or placebo Q6M in the parent study, transition to 25 mg ARO-APOC3 in this OLE at the same frequency in this OLE study. Any participants in the 50 mg dose group (Q3M or Q6M) enrolled in this OLE prior to the discontinuation of the 50 mg dose cohort (Amendment 2, dated 22 November 2022) transition to ARO-APOC3 25 mg Q3M or Q6M. After the last subject in the parent study reaches the Month 12/end of study (EOS) visit of the parent study and a single dose has been selected, all subjects in this OLE study transition to the selected ARO-APOC3 dosing regimen (refer to Figure 2).

Figure 2: Study Schema



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

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

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

- The 50 mg dosing group was discontinued.
- If assigned to the 50 mg dose group, a subject transitioned to the 25 mg dose group at the next dosing visit as long as HbA1c discontinuation criteria (see Appendix 4) have not been met.
- Discontinuation criteria were added for subjects with elevated HbA1c during the OLE (see Appendix 4).

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

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

Table 3: Schedule of Assessments

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

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

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

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

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

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

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

6.1.1. Informed Consent

It is the responsibility of the Investigator (or medically qualified designee) to obtain a written informed consent from everyone participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Investigator (or medically qualified designee) must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the Investigator or by Arrowhead Pharmaceuticals, Inc.

For this study, each eligible subject will be required to provide written informed consent before participation in the study.

All eligible subjects will have the study explained by the Investigator or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomforts, risks, and benefits in taking part, as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each subject will acknowledge receipt of this information by giving written informed consent for participation in the study. The subject will be given a copy of the signed ICF to retain.

6.1.2. Enrollment

Subjects who have completed 48-week treatment period in the parent study, have provided written informed consent, and meet all eligibility criteria outlined in Section 7.1 and Section 7.2 will be eligible to enroll in this study. The Day 1 enrollment visit will be completed within 30 days of completing the parent study.

Individuals who do not meet the enrollment criteria for participation in this study (screen failure) may not be rescreened.

6.1.3. Treatment Period

The Treatment Period in this open-label study will be 24 months.

Eligible subjects will complete Day 1 assessments and receive open-label ARO-APOC3 at the same dose as assigned in the parent study within 30 days of completing the parent study (refer to SOA, Table 3).

All subjects will return to the site for monthly study visits for the first 3 months for follow-up. Thereafter, subjects will return to the site approximately every 90 days as outlined in the SOA (Table 3).

Subjects previously assigned to 50 mg ARO-APOC3 or placebo Q3M or 50 mg ARO-APOC3 or placebo Q6M in the parent study transition to 25 mg ARO-APOC3 in this OLE at the same frequency in this OLE study. Subjects assigned to the 10 or 25 mg ARO-APOC3 Q3M dosing groups in the parent study are administered ARO-APOC3 SC Q3M consistent with their respectively assigned dose level in the parent study. With the selection of a single dose all subjects transition to the 25 mg Q3M regimen.

6.1.4. Adverse Event Monitoring

Safety assessments will include AEs and SAEs, physical examinations, vital sign measurements (blood pressure, heart rate, temperature, pulse oximetry, and respiratory rate), electrocardiograms (ECGs), clinical laboratory tests, concomitant medications/therapy, and reasons for treatment discontinuation. Safety assessments will be performed at specified time points and prior to study completion.

The AE/SAE reporting period for an enrolled subject begins when the subject provides informed consent. Treatment-emergent AEs and treatment-emergent SAEs are defined as those that occur following study drug administration or are a preexisting condition exacerbated by study drug. The TEAE reporting period begins after the first dose and extends until the EOS visit is complete.

All SAEs that occur during the AE reporting period, in addition to reporting via electronic case report forms (eCRFs), must also be reported to the sponsor via the SAE report form immediately after being notified, regardless of the relationship of the SAE to study treatment. All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. If the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product (IP), the Investigator will promptly notify the sponsor. Laboratory or diagnostic (eg, ECG) abnormalities will be reported as AEs if considered clinically significant by the Investigator. Laboratory or diagnostic assessment abnormalities not reported as AEs are not to be reported as clinically significant in the study database.

6.1.5. Early Termination

If a subject discontinues from the study prematurely, every reasonable effort will be made to perform the Early Termination Visit within 30 days of the decision to terminate a subject's study participation. The reason for Early Termination will be documented in source documents and eCRF. Procedures as outlined in the SOA (Table 3) will be completed. Subjects who discontinue ARO-APOC3 due to SAE will be encouraged to remain available for follow-up for medical monitoring until resolution.

6.2. Number of Subjects

Up to 536 subjects completing the AROAPOC3-2001 or AROAPOC3-2002 parent studies may be enrolled in this study.

6.3. Treatment Assignment

Subjects entering this study will be assigned a unique 14-character alpha-numeric study identifier.

6.4. Dose Adjustment Criteria

6.4.1. Safety Criteria for Adjustment or Stopping Doses

A decision to pause/suspend or permanently discontinue dosing in an individual subject **may** be indicated based on any of the following:

- Any confirmed pregnancy in the study will lead to permanent discontinuation of ARO-APOC3 dosing for that subject; or
- A need for apheresis or other emergent interventions indicated to lower TG; or
- Acute pancreatitis; or
- In subjects with normal (per central laboratory reference range) AST or ALT on Day 1, treatment-emergent elevations >3× ULN at least possibly related to IP, per study Investigator, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 3 for specific guidelines regarding treatment discontinuation or interruption for subjects with any of the below findings:
  - AST or ALT >5× ULN will lead to permanent discontinuation of IP dosing of that subject per Appendix 3. The subject will remain on study follow-up visits until EOS as per the SOA (refer to Table 3).
  - AST or ALT >3× ULN with a total bilirubin >2× ULN
  - AST or ALT >3× ULN with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
  - AST or ALT >3× ULN with a treatment-emergent INR >1.5 (must be confirmed on repeat) and which is not explained by another plausible cause.

Some subjects enrolling into this study may have baseline elevations in transaminases. In subjects with elevated (per central laboratory reference range) AST or ALT on Day 1, treatment-emergent elevations >2× baseline or ≥300 U/L (whichever occurs first) at least possibly related to IP per study Investigator, as specified below, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 3 for specific guidelines regarding treatment discontinuation or interruption for subjects with any of the below findings:

- AST or ALT >3× baseline or ≥300 U/L (whichever occurs first)
- AST or ALT >2× baseline or ≥300 U/L (whichever occurs first) with the new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
- AST or ALT >2× baseline or ≥300 U/L with a total bilirubin >2× ULN
- AST or ALT >2× baseline or ≥300 U/L or with a treatment-emergent INR >1.5 (must be confirmed on repeat) and which is not explained by another plausible cause

Treatment modification guidelines for subjects with elevated AST or ALT are provided in Appendix 3.

For any subject experiencing an acute pancreatitis, their next dose of ARO-APOC3 should be postponed until they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor.

6.4.2. Study Drug Discontinuation Criteria for Increased HbA1c

Regarding HbA1c study drug discontinuation criteria, participants should discontinue IP if they meet the following criteria (refer to Appendix 4):

- HbA1c measurement >10% (or 86 mmol/mol International Federation of Clinical Chemistry [IFCC] units) at the last visit prior to the next dose; or
- An increase from baseline HbA1c >2% (or >17 mmol/mol IFCC units) at the last visit prior to the next dose; or
- In participants with a baseline HbA1c >7.5% (or >58 mmol/mol IFCC units), an increase in HbA1c from baseline >1% (or >8.6 mmol/mol IFCC units) at repeat study visits with the last one being the visit prior to the next dose.

Participants who discontinue IP due to HbA1c elevations will be followed for 6 months after their last dose per the SOA (Table 3).

6.5. Criteria for Study Termination

The sponsor reserves the right to discontinue the study at any time. The circumstances under which the study may be terminated include:

- Discontinuation of the study is in the interest of the health of study subjects;
- Continuation of the clinical study no longer serves a scientific purpose.

Reasons will be provided in the event of this happening. The Investigator reserves the right to discontinue the study for safety reasons at any time in collaboration with the sponsor.

6.6. Rationale for Study Design

This is a 24-month, Phase 2, OLE study, open only to subjects that have completed the parent study (ie, AROAPOC3-2001 or AROAPOC3-2002). The primary objective of the study is to evaluate the long-term safety and efficacy of ARO-APOC3 in subjects with dyslipidemia. All active subjects in this study will be transitioned to a single dose once the final safety and efficacy data analyses are complete in the parent study and once a single dose is selected for later-stage studies.

Subjects enrolling into this study will have the option to remain on the same stable background medications (including statins and other lipid-lowering therapies) taken during the parent study, or, if medically indicated, to modify their background therapies prior to Day 1. During the study, subjects should remain on a stable regimen unless medically indicated and at the discretion of the Investigator (refer to Section 8.1). In response to diabetes evaluations, adjustments to treatment medication are allowed at the discretion of the Investigator (refer to Section 8.1).

The open-label Treatment Period will begin on Day 1 and will continue for 24 months. Dietary counseling will commence at Day 1 and will be reinforced at intervals throughout the Treatment

Period. This approach is necessary to minimize the potential effects of dietary changes that can alter TG levels and other lipid parameters.

Compared with the potent effect of ARO-APOC3 in lowering TG levels, other first-line therapies have modest effects on TGs. For example, patients with SHTG receiving omega-3 fatty acids only had a 33% placebo-adjusted reduction in TG (Bays 2011), and patients with mild TG elevations receiving gemfibrozil had a 31% reduction in TG (Rubins 1999). Thus, additional TG and lipid-lowering effect is expected when ARO-APOC3 is used on top of optimal lipid-lowering therapy. In this Phase 2 open-label study, concomitant use of optimal statin therapy, nicotinic acid/niacin, omega-3 fatty acids (prescription or over-the-counter [OTC]), fibrates, or other lipid management regimens will be permitted as long as the subjects maintain a stable regimen during the Treatment Period unless adjustments are medically indicated.

The 24-month duration of the treatment is intended to ensure adequate exposure to ARO-APOC3 to evaluate the long-term safety and efficacy for its long-term use at the assigned dose level.

6.7. Benefit-Risk Assessment

ARO-APOC3 has been shown from numerous clinical trial data to have a favorable benefit-risk profile to date with an acceptable and manageable safety profile. Final data from the Phase 1 Study AROAPOC31001 showed that administration of ARO-APOC3 at doses from 10 to 100 mg resulted in significant and durable reduction of serum APOC3 when compared with placebo in healthy volunteers, together with meaningful reduction in TG in patients with HTG and chylomicronemia.

Cumulative PD data from clinical studies showed silencing of APOC3 led to substantial reductions in the levels of serum TG with ARO-APOC3 compared to placebo.

Upon administration of ARO-APOC3 compared to placebo, results from the Phase 1 study in normal healthy volunteers (NHVs) demonstrated reductions from baseline of serum APOC3 in a dose-dependent manner of up to -94%. There were also reductions in TG (up to -66%), non HDL-C (up to -31%) and increases in serum high-density lipoprotein cholesterol HDL-C (up to +74%) with a dose response generally correlating to APOC3 serum level reductions in participants receiving active drug. Results for repeat doses of ARO-APOC3 in NHVs demonstrated consistent reductions of APOC3 (up to -94%), TGs (up to -75%), and non-HDL-C (up to -39%) and increases in HDL-C (up to +75%). These responses were sustained through Week 16 (12 weeks after the last dose).

Results from the Phase 1 study in subjects with HTG and/or CM demonstrated similar or even larger effects of ARO-APOC3 at similar doses. Reductions in serum APOC3 (up to -98%), serum TGs (up to -88%), non-HDL-C (up to -55%), and an increase in HDL-C levels (up to +122%) were observed. The effects of ARO-APOC3 treatment on these and other key lipid parameters were sustained through Week 16 (12 weeks after the last dose).

The Phase 2 study (AROAPOC3-2001) in subjects with SHTG demonstrated reductions in serum TG (up to -80%) and serum APOC3 (up to -78%) with ≥90% of subjects achieving the therapeutic goal of TG levels <500 mg/dL (<5.65 mmol/L) at Week 24. In AROAPOC3-2001, a numerical decrease in AP events was observed in subjects treated with ARO-APOC3 (1 subject each for the 3 ARO-APOC3 groups) versus placebo (3 subjects) at Week 48. In general, ARO-APOC3 was well tolerated and has an acceptable safety profile that was manageable.

In the course of the review of data, an apparent increase in the level of HbA1c was observed when comparing subjects in the placebo group to those receiving ARO-APOC3. The increase in HbA1c was observed mostly in subjects with preexisting diabetes and was most notable in the ARO-APOC3 50 mg dose cohort. There is overall clinical benefit given the meaningful improvement in lipids and lipoprotein metabolism, particularly a decrease in triglycerides, may minimize the risk of pancreatitis and coronary artery disease, which is the goal of therapy in these patient population.

This observation does not impose an immediate health risk although well controlled diabetes is required to minimize long term diabetes-driven complications, because worsening of diabetes control can be managed with diet, treatment adjustments, and compliance to treatment.

For a more detailed description of potential risks of study participation, see Section 4.3.

Under Amendment 2 of the protocol (dated 22 November 2022), dosing of the subjects in the 50 mg dose cohort of this OLE AROAPOC3-2003 was adjusted as follows:

- The 50 mg dosing group was discontinued.
- If assigned to the 50 mg dose group, a subject transitioned to the 25 mg dose group at the next dosing visit as long as HbA1c discontinuation criteria (refer to Appendix 4) have not been met.
- Discontinuation criteria have been added for subjects with elevated HbA1c during the OLE (see Appendix 4).

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

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

Therefore, in light of the risk mitigation strategies put in place to address the increased HbA1c (see Appendix 4), and the clinically meaningful decreases in triglycerides, likely reducing the risk for pancreatitis, the benefit risk assessment remains acceptable in this patient population.

6.8. Rationale for Dose and Schedule of Administration

Results from a population PD model developed based on the Phase 1 study (AROAPOC3-1001) were supportive of the dosing interval of 3 months, which was studied in the Phase 2 dose-finding study. In the Phase 2 study in adults with SHTG (SHASTA-2), 3 doses of ARO-APOC3 (10, 25, or 50 mg) were administered on Day 1 and Week 12. The 10 mg ARO-APOC3 dose showed lower effect on serum APOC3 (71% reduction at Week 24) and TG levels (75% reduction), with lower percentage of subjects achieving the therapy goal of TG levels <500 mg/dL (<5.65 mmol/L) at Week 24 (12 weeks post the second dose), compared with the 25 and 50 mg doses. The 25 and 50 mg doses resulted in similar and substantial reductions in serum APOC3 (73% and 79% reduction at Week 24, respectively) and TG levels (76% and 80% reduction at Week 24, respectively), with ≥90% of subjects achieving the therapeutic goal of TG levels <500 mg/dL (<5.65 mmol/L) at Week 24. Observed PD data from this Phase 2 study in the SHTG population were generally consistent with the prospective prediction from the Phase 1 model. A population PD model using the Phase 2 study data was further developed to help support selection of the 25 mg dose. The results showed that an every 3 month (Q3M) dosing

interval for ARO-APOC3 should generate a moderate peak-to-trough fluctuation in serum APOC3 protein and fasting TG levels. Between the 25 and 50 mg dose levels, the separation in model-predicted PD responses are minimal, which was directly observed in the Phase 2 study. The approximate PD steady state is projected to be attained following the third Q3M dose on Month 6 by modeling. In addition, ARO-APOC3 was generally well tolerated at all dose levels in all clinical studies performed to date (Phase 1 and Phase 2 studies), with TEAEs similar to those observed in the placebo group.

Collectively, this evidence supports the selection of the 25 mg dose administered Q3M as the single dose. Compared to the 50 mg dose, the 25 mg dose has a more favorable safety profile and is effective based on the magnitude of reduction in APOC3 and TG levels, bringing almost all subjects below the threshold associated with elevated pancreatitis risk.

7. SELECTION OF STUDY POPULATION AND WITHDRAWAL OF SUBJECTS

7.1. Inclusion Criteria

To be eligible for enrollment, subjects must meet all the following inclusion criteria:

1. Adults ≥18 years of age who are nonpregnant, nonlactating, and do not plan to become pregnant during the study
2. Able and willing to provide written informed consent prior to the performance of any study specific procedures
3. Completed the 48-week study treatment period in the parent study

7.2. Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Subject was permanently discontinued from ARO-APOC3 in the parent study due to:
   a. Elevated AST or ALT, or
   b. Elevated HbA1c (see Appendix 4).
2. Any new condition or worsening of existing condition (eg, renal, hematologic, gastrointestinal, endocrine, cardiovascular, pulmonary, immunologic, psychiatric) or any other situation that, in the Investigator's judgment, would make the subject unsuitable for enrollment, could interfere with the subject participating in or completing the study, would make it difficult to comply with protocol requirements, or put the subject at additional safety risk
3. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)

7.3. Subject Withdrawal Criteria

Subjects will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator, medically trained designee, or sponsor may withdraw a subject from the study, per the following criteria, to protect the subject's health:

- The need to take medication that may interfere with study measurements, or is incompatible with the IP
- Intolerable/unacceptable adverse experiences
- Major violation of or deviation from study protocol procedures
- Noncompliance of subject with protocol
- Subject is unwilling to proceed or consent is withdrawn

- Withdrawal from the study if, in the Investigator's judgment, it is in the subject's best interest

The date and reasons for withdrawal, along with any AEs and any necessary medical treatment will be recorded on the eCRF.

If a subject is withdrawn from the study due to significant AE or SAE, the Investigator, or medically trained designee, will evaluate the urgency of the event. If the situation warrants, the Investigator, or medically trained designee, will take appropriate diagnostic and therapeutic measures. If the situation is not an immediate emergency, the Investigator, or medically trained designee, at the clinical study facility will attempt to contact the medical monitor or medically qualified designee for consultation. No medical help, diagnosis, or advice will be withheld from the subject due to an inability to contact the medical monitor. The subject will be encouraged to remain available for follow-up medical monitoring. The sponsor will be notified as soon as possible of any subject withdrawals.

8. TREATMENT OF SUBJECTS

8.1. Restrictions and Concomitant Medications

Fasting: On the day of dosing or on other days with blood draws for lipid parameter measurement, subjects will have fasted for at least 10 hours prior to IP administration or blood draw unless otherwise specified.

Recreational Drugs & Alcohol: Subjects will be instructed to abstain from consuming alcohol for at least 48 hours prior to their clinic visit on dosing days and during the clinic visit. In addition, subjects will be instructed to refrain from regular use of alcohol (ie, more than 14 units per week [1 unit=80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol]) for the study duration. Subjects must abstain from use of recreational drugs throughout the study.

Concomitant Medications: Use of optimal statin therapy, nicotinic acid/niacin, omega-3 fatty acids (prescription or OTC), fibrates, or other lipid management regimens is acceptable. Adjustments to medication regimens during the study, including lipid-lowering and diabetes mellitus therapies, are permitted if, at the discretion of the Investigator, this is needed to provide adequate supportive care. These changes must be documented in the eCRF no later than at the next study visit. Subjects will be instructed to inform the Investigator of the details (indication, dose, and dates of administration) if they do take any medication, and these details will be recorded in the eCRF. Before making any changes to a subject's prescription lipid-lowering therapy, the Medical Monitor or designee should be notified. Use of apheresis during the study will also be recorded in the eCRF.

8.2. Notification of General Practitioner

It is the responsibility of the Investigator or designee to notify, where applicable, with the consent of the subject, the general practitioner of the subject's participation in the study, by sending a letter stating the nature of the study, treatments, expected benefits, AEs, and concomitant drugs to be avoided.

8.3. Treatment Compliance

All study drug will be administered at the study site. The date and time of SC injection administration of study drug will be recorded on the eCRF on dosing days.

8.4. Randomization and Blinding

Not applicable.

8.5. Emergency Contact With Investigator

Suitable arrangements will be made for subjects to contact the Investigator or medically trained designee in the event of an emergency.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

ARO-APOC3 is administered SC. The API contained in ARO-APOC3 is a synthetic, double-stranded, siRNA duplex conjugated to a NAG targeting ligand to facilitate hepatocyte delivery.

The sponsor is responsible for the supply of ARO-APOC3 together with detailed instructions (in the Pharmacy Manual) describing preparation and administration. ARO-APOC3 will initially be supplied as a sterile Type-1 glass 2.0-mL vial (0.7 mL nominal volume, 0.5 mL withdrawable volume). Upon approval of Protocol Amendment 3 by the competent authorities and IECs/IRBs, ARO-APOC3 will be supplied in a PFS (25 mg) form.

Where self-administration is approved by the competent authority and ethical review committee (IRB/IEC), the sponsor will also provide self-administration instructions after introduction of the 25 mg PFS.

Each PFS unit contains 25 mg of ADS-005 in isotonic saline. The container closure for ARO-APOC3 Injection PFS is a 1 mL long type 1 clear glass syringe with 29 gauge staked needle and rigid needle shield and bromobutyl fluorotec coated plunger. The final assembly of the syringe includes a standard plunger rod and finger flange. Each PFS will be packed individually in a carton. Additional information about the IP is presented in Table 4.

Table 4: Investigational Product

	ARO-APOC3	
	Vial	**Prefilled Syringe (0.5 mL Syringe Volume)**
Strength	200 mg/mL	50 mg/mL (salt free basis)
Appearance	Clear, colorless to light yellow solution	Clear, colorless to yellow solution
Inactive Ingredients	0.5 mM sodium phosphate monobasic, 0.5 mM sodium phosphate dibasic in water for injection	0.9% sodium chloride in water for injection
Shipment and Storage	Refrigerated, 2ºC to 8ºC	Refrigerated, 2 ºC to 8 ºC

ARO-APOC3 will be prepared, per the Pharmacy Manual, by a pharmacist or qualified staff at the clinical sites. Aseptic technique will be used to ensure sterility of the solution to be injected. The time of preparation for active drug must be documented and tracked to demonstrate administration within prepared drug stability boundaries. Please refer to the Pharmacy Manual for more detailed instructions.

The IP vials and PFSs will be labeled per current Good Manufacturing Practice (cGMP)/Good Clinical Practice (GCP).

Each 25 mg PFS supplied to sites will be packaged individually and will include the drug name, batch number, expiration date (as applicable), and storage conditions. The label will also include a unique syringe ID number, the drug name, batch number, expiration date (as applicable), and storage conditions. The label should match the ID number listed on the interactive web response system (IWRS) dispensation transaction confirmation.

The IP supplies will be stored at clinical sites securely under the appropriate conditions.

9.2. Study Drug Storage

The sponsor will provide the Investigator with a sufficient quantity of clinical drug supplies. The Investigator must ensure that deliveries of IP from the sponsor are correctly received by a responsible person, that all receipts of drug shipments are recorded on the appropriate drug accountability forms prepared by the pharmacy at the clinical site, and that the products are stored in a secure area under recommended storage conditions. The IP must be stored in a secure area with access limited to the Investigator and authorized staff and under the physical conditions that are consistent with the IP-specific requirements. It is also the responsibility of the Investigator to ensure that the integrity of packaged study product not be jeopardized prior to dispensing.

9.3. Study Drug Preparation

An authorized and trained staff member at each clinical study site will dispense the IP per predefined drug dispensing requirements. The dispensing will be verified by a second member of

site staff. The IP will be dispensed by clinical study site staff members on the day of dosing and recorded in the drug accountability records. A Pharmacy Manual will be prepared to define the procedures for dispensing.

9.4. Study Drug Administration

Only subjects enrolled in the study may receive IP in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer IP. Upon approval of Protocol Amendment 3, subjects will be offered the possibility of self-administering the study drug at the study site, under supervision of the PI or designated staff. Self-administration using the PFS by study subjects must be documented in source records and recorded on the eCRF.

Injections will be made into the SC tissue at an appropriate site (eg, abdomen, thigh, upper arm) using a 25- to 30-gauge, ½-inch needle. The abdomen is the preferred site. The injection site is to be varied (no multiple injections into the same exact site but alternating various locations on the abdomen is acceptable). The injection site location is to be recorded in the eCRF. Prior to dose administration, IP must be allowed sufficient time to come to room temperature. Small air bubbles in the PFS are considered acceptable. Subcutaneous injections with a small amount of air in the PFS is harmless and adds no additional risks to study participants. Furthermore, the small amount of air in the PFS does not impact the volume of IP administered. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

9.5. Study Drug Accountability

All material supplied is for use only in this clinical study and should not be used for any other purpose. The Investigator is responsible for the IP accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain IP accountability records throughout the course of the study. This person will document the amount of IP received from the sponsor and the amount administered to subjects. The clinical research associate (CRA) will perform initial and ongoing IP accountability. Used vials of study drug will be retained, sequestered per subject (where allowable by local policy), and made available to the CRA during IP reconciliation. Following dispensation and administration, PFS will be disposed of in a puncture-resistant biohazard container and in accordance with local policy. The PFS label will have a tear-off portion that will include the information required to be documented in the Subject Dispensing Log. The tear-off portion of the label must be attached to the Subject Dispensing Log.

A drug dispensing log must be kept current and will contain the following information:

- The identification of the subject to whom the IP was dispensed
- The date(s), quantity lot number(s) and expiration dates of the IP dispensed to the subject

The date and time of dose preparation and release will be maintained to support administration of IP. Each subject will be given only the IP as assigned by the interactive web response system. Investigational product administration will be documented and recorded on the eCRFs. The inventory must be available for inspection by the CRA during the study. Drug supplies will

either be collected at the end of the study by the study monitor or returned by the Investigator or designee to the sponsor or the designated sponsor-approved depot.

10. PHARMACODYNAMIC ASSESSMENTS

Serum samples for PD assessments of ApoC-III, ApoB-48, ApoB-100, ApoC-II, ApoA-I, and ApoA-V will be collected as described in the SOA (Table 3) after a 10-hour fast. Refer to the Laboratory Manual for additional details on clinical laboratory tests.

10.1. Sample Collection for Analysis

Blood samples for PD analysis will be collected from subjects through an indwelling cannula or through a fresh vein puncture. The actual blood collection time will be recorded in the source documents as soon as possible after sampling and recorded in the eCRF. All times must be recorded in the 24-hour format. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections for the actual time of sample collection will be incorporated at the time of data analysis. Blood samples will be collected at time points outlined in the SOA (Table 3). An explanation must be given for any blood sample taken outside of the set sampling times.

11. ASSESSMENT OF EFFICACY

Fasting blood samples will be collected from subjects through an indwelling cannula or through a fresh vein puncture. The actual blood collection time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections, for the actual time of sample collection will be incorporated at the time of data analysis.

The actual sample times (times samples taken) will be recorded in the eCRF and will be entered at the time of or as soon as possible after sampling. All times must be recorded in the 24-hour format. An explanation must be given for any blood sample taken outside of the set sampling times.

Fasting lipid parameters for efficacy (TG, LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, Lp(a), and total ApoB) will be assessed by the central laboratory using standard methods. LDL-C will be measured using the Martin-Hopkins methodology at all study visits in addition to an ultracentrifugation methodology at the Day 1 and Month 24/EOS visits only.

Lipid parameter results will be provided to the Investigator starting after completion of the Month 1 study visit. Thereafter, available lipid parameter results will be provided to the Investigator by the central laboratory through the Month 24/EOS Visit.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The following safety assessments will be obtained at the time points outlined in the SOA (Table 3).

12.1.1. Demographic/Medical History

Subject demographics (eg, date of birth, race and ethnicity, sex) and medical history will be collected on Day 1. Medical history will include medication use over the previous 30 days, including vitamins, OTC medications, prescription drugs, recreational drugs or supplements, and alcohol and tobacco use.

12.1.2. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the SOA (Table 3). All vital signs will be measured after the subject has been resting in a sitting position for at least 3 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Vitals signs will be obtained prior to venipuncture and other invasive procedures.

12.1.3. Physical Examination

A complete physical examination will be performed at Day 1. At all other time points, a symptom-directed physical examination will be performed if indicated.

12.1.4. Electrocardiogram

A single 12-lead ECG measurement will be obtained at time points outlined in the SOA (Table 3) after the subject is semi-supine for at least 3 minutes. Any abnormal and clinically significant ECGs, as per the Investigator's medical judgment, will be repeated in triplicate, with each measurement approximately 1 minute apart. Any clinically significant abnormality should be documented as an AE or SAE, as applicable. ECGs will be performed prior to venipuncture and any other invasive procedures.

12.1.5. Laboratory Assessments

12.1.5.1. Hematology, Coagulation, Blood Chemistry, and Urinalysis

Laboratory assessment samples for hematology, coagulation, blood chemistry, and urinalysis (Table 5) are to be obtained at designated visits as detailed in the SOA (Table 3).

Table 5: Laboratory Assessments

Hematology	**Blood Chemistry**	**Urine Analysis**
Basophils	Alanine Aminotransferase	Appearance
Basophils/Leukocytes	Albumin	Bilirubin
Eosinophils	Alkaline Phosphatase	Erythrocytes
Eosinophils/Leukocytes	Aspartate Aminotransferase	Glucose
Ery. Mean Corpuscular Hemoglobin	Bicarbonate	Hemoglobin
Ery. Mean Corpuscular HGB Concentration	Bilirubin	Ketones
Ery. Mean Corpuscular Volume	Blood Urea Nitrogen	Leukocytes
Erythrocytes	Calcium	Leukocyte Esterase
Follicle-Stimulating Hormone	Carbon Dioxide	Nitrites
Hematocrit	Chloride	pH
Hemoglobin	Cholesterol	Protein
Leukocytes	Creatine Kinase	Specific Gravity
Lymphocytes	Creatinine (EGFR)	Urobilinogen
Monocytes	Direct Bilirubin	
Neutrophils Band Form	Gamma Glutamyl Transferase	
Neutrophils	Glomerular Filtration Rate	
Platelets	Glucose	
HgbA1C	HDL Cholesterol	
Coagulation	Lactate Dehydrogenase	
Activated Partial Thromboplastin Time	LDL Cholesterol	
Prothrombin	Phosphate	

Hematology	Blood Chemistry	Urine Analysis
Prothrombin Intl. Normalized Ratio	Phosphorus	
Prothrombin Time	Potassium	
fibrinogen	Protein	
	Sodium	
	Triglycerides	
	Amylase	
	Lipase	
	Uric Acid	
	Anion gap	
	globulins	
	protein	
	Total bilirubin	
	Serum insulin	
	C peptide	
	Conjugated bilirubin	
	C-reactive protein	
Pregnancy Test: A urine HCG pregnancy test will be performed on all women of childbearing potential (premenopausal women only) per Schedule of Assessments.		

Abbreviations: EGFR= estimated glomerular filtration rate; Ery.=erythrocyte; HCG=human chorionic gonadotropin; HDL=high-density lipoprotein; HGB=hemoglobin; LDL=low-density lipoprotein.

Blood and urine samples will be collected to perform clinical laboratory tests. The results will be assessed by the Investigator, or medically qualified designee, before study enrollment. Any abnormality in laboratory values deemed clinically significant by the Investigator, or medically qualified designee should be documented as an AE or SAE, as applicable.

12.1.5.2. Anti-Drug Antibodies

Anti-drug antibodies will be assessed from serum samples.

12.1.6. Acute Pancreatitis Events

All treatment-emergent AEs and SAEs reported by the Investigator through Month 24/EOS that are consistent or possibly represent 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× ULN
3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT), MRI, or transabdominal ultrasonography

This committee will meet to review and assess the blinded data as described in the independent adjudication committee charter.

12.1.6.1. Detecting and Reporting Pancreatic Events

During each study visit, the Investigator and clinical staff will be responsible for educating and/or reminding study subjects on the signs and symptoms of acute pancreatitis and when to seek care. The Investigator or medically qualified designee will also be responsible for detecting, recording, and reporting pancreatic events that meet the criteria and definition of acute pancreatitis (according to the 2013 Atlanta definition) and events that possibly represent pancreatitis.

Adverse events terms that could signal a potential case of pancreatitis are listed below according to the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs). These PTs represent possible pancreatitis events but are not limited to the following:

Any preferred term that includes pancreatitis	Abdominal rigidity
Amylase increased	Acute abdomen
Blood bilirubin increased	Ascites
Lipase increased	Gastrointestinal pain
Hyperamylasaemia	Intra-abdominal pressure increased
Hyperbilirubinaemia	Jaundice
Hyperlipasaemia	Nausea
Pancreatic enzymes increased	Pancreatic duct rupture
Ultrasound pancreas abnormal	Peripancreatic fluid collection
Abdominal distension	Vomiting
Abdominal pain	Vomiting projectile
Abdominal rebound tenderness	

After the initial AE of pancreatitis or possible pancreatitis events, the Investigator will follow each subject and provide further information on the subject's condition as deemed appropriate.

The Investigator will follow all pancreatitis or possible pancreatic AEs until resolution, until the condition stabilizes, or until the event is otherwise explained. Once resolved, the Investigator or medically qualified designee will update the appropriate AE eCRF page and SAE report form (if the event is serious). The Investigator or medically qualified designee will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the possible pancreatic AE or SAE.

New or updated information regarding an SAE will be recorded on a new SAE report form marked as follow-up with the appropriate follow-up number added to the report. The follow-up report will be signed and dated by the Investigator.

12.1.6.2. Hospitalization for Abdominal Pain

All SAEs resulting in hospitalizations for abdominal pain will also be recorded as described in Section 12.1.6.

12.2. Adverse Events

The Principal Investigator (PI) and clinical facility staff are responsible for detection, recording, and reporting of events that meet the criteria and definition of various AEs as listed below. Adverse events will be recorded from time of signed consent through to the EOS visit; only AEs that occur postdose will be considered treatment-emergent. The PI and clinical facility staff are responsible for detection, recording, and reporting of pregnancy and appropriate follow-up. Any known pregnancy that occurs within 24 weeks following the last dose of study drug should be reported by the subject to the PI. Information regarding any reported pregnancy should be collected for up to 1 year after birth.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or diagnostic test), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether related to this product or not (refer to ICH E2a: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 27 October 1994*).

Treatment-emergent AEs will be defined as AEs with onset after administration of the study drug, or when a preexisting medical condition increases in severity or frequency after study drug administration.

Adverse events will not include:

- A medical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE)
- A preexisting disease or condition present at the start of the study that does not worsen during the study
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or “social” admissions)
- An overdose of either the IP or a concurrent medication without any resulting signs or symptoms

12.2.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the IP, comparator, or placebo, that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the subject was at immediate risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe)
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events

Abnormal assessments (eg, ECGs and vital signs) that are judged by the PI as clinically significant or result in clinical sequelae will be recorded as AEs. Laboratory abnormalities will be reported by the PI as AEs if the abnormality is considered clinically significant or results in clinical sequelae. Laboratory abnormalities or other abnormal assessments not reported as AEs are not to be reported as clinically significant in the study database.

Clinically significant abnormal laboratory findings or other clinically significant abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs.

The PI (or medically qualified designee) will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

12.4. Timing, Frequency, and Method of Detecting Adverse Events

Any preexisting conditions or signs and/or symptoms present in a subject prior to the start of the study (ie, before informed consent) should be recorded as Medical/Surgical History.

All AEs occurring after informed consent and on or before the final visit must be reported as AEs; only AEs that occur postdose will be considered treatment-emergent. All AEs must be recorded irrespective of whether they are considered related to study drug. AEs will be recorded through the EOS visit or through 30 days after the last dose, whichever is longer (Section 12.8.4.1).

At each visit/assessment in the period defined above, AEs will be evaluated by the PI (or medically qualified designee) and recorded.

12.5. Recording Adverse Events

When an AE occurs, it is the responsibility of the PI or medically qualified designee to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The PI or medically qualified designee will then record the AE on the AE eCRF. Additional reporting requirements for an AE meeting serious criteria are discussed in Section 12.2.1.2.

The PI or medically qualified designee will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In all cases, when available, the diagnosis should be reported as the event and not the individual signs/symptoms. It is not acceptable for the PI to send photocopies of the subject's medical records to the sponsor in lieu of completion of the appropriate AE eCRF pages.

12.6. Evaluating Adverse Events

12.6.1. Assessment of Severity

The PI or medically qualified designee will assess severity for each AE reported during the study. The assessment will be based on the PI's (or medically qualified designee's) clinical judgment. The severity of all AEs will be graded using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
- **Life-threatening:** An event that places the participant at immediate risk of death or is disabling.
- **Death:** An event that results in death.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the severity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the predefined outcomes as described in Section 12.2.1.2.

12.6.2. Assessment of Causality

The PI (or medically qualified designee) is obligated to assess the relationship between IP and the occurrence of each AE. The PI (or medically qualified designee) will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases,

concomitant therapy, other risk factors, and the temporal relationship of the event to the IP will be considered and investigated. The PI (or medically qualified designee) will also consult the IB in the determination of his/her assessment.

There may be situations when an SAE has occurred and the PI has minimal information to include in the initial SAE report. However, it is very important that the PI (or medically qualified designee) always assess causality for every event prior to transmission of the SAE report form. The PI (or medically qualified designee) may change his/her opinion of causality considering follow-up information, amending the SAE report form accordingly. The causality assessment is one of the criteria used when determining global regulatory reporting requirements.

The PI (or medically qualified designee) will provide the assessment of causality utilizing three possible categories: Not Related, Possibly Related and Probably Related.

An AE will be considered "not related" to the use of the product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the product and the onset of the AE (eg, the event occurred either before, or too long after, administration of the product for it to be considered product-related)
- A causal relationship between the product and the AE is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

An AE will be considered "Possibly related" when there is a reasonable possibility that the incident, experience, or outcome may have been caused by the product under investigation.

An AE will be considered "Probably related" when there are facts, evidence, or arguments to suggest that the event is related to the product under investigation.

12.7. Follow-up of Adverse Events

After the initial AE, the PI is required to proactively follow each subject and provide further information on the subject's condition as deemed appropriate.

All AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE eCRF page and SAE report form (if event is serious) will be updated. The PI, or medically qualified designee, will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. In the event of a fatal outcome in an SAE, the PI, or medically qualified designee, will attempt to obtain postmortem findings, including histopathology, and provide all additional information in a follow-up SAE report.

New or updated information regarding an SAE will be recorded on a new SAE report form marked as follow-up with the appropriate follow-up number added to the report. The follow-up report will be signed and dated by the PI.

12.8. Prompt Reporting of Serious Adverse Events

Any AE meeting serious criteria MUST be reported promptly to the sponsor's designated Pharmacovigilance CRO immediately and to the IRB or IEC in accordance with applicable local/institutional requirements.

12.8.1. Completion and Transmission of the Serious Adverse Event Reports

Once a PI becomes aware that an SAE has occurred in a study subject, she/he will report the information on an SAE report form to the designated Pharmacovigilance CRO immediately. The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the PI (or medically qualified designee). If the PI does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The SAE report form will be updated when additional information is received.

The PI (or medically qualified designee) will always provide an assessment of causality at the time of the initial report as described in Section 12.6.2. However, as new information becomes available, causality may be modified.

Email transmissions of the SAE report forms are the preferred methods to transmit this information to the designated Pharmacovigilance CRO. Facsimile is acceptable if email is unavailable. In rare circumstances, notification by telephone is acceptable with a copy of the SAE report sent by overnight mail. Initial notification via the telephone does not replace the need for the PI, or medically qualified designee, to complete and sign the SAE report form within the outlined time frames.

The sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses. Any event that in the opinion of the PI may be of immediate or potential concern for the subject's health or wellbeing will be reported to the sponsor emergency contact listed in Table 1.

12.8.2. Pregnancy Reporting

Pregnancy occurring in a subject or in the female partner of a male subject during the study must be reported on a pregnancy notification form or on an SAE form to the designated Pharmacovigilance CRO within 24 hours of initially becoming aware of the pregnancy by the PI. Any known pregnancy that occurs within 24 weeks following the last dose of IP should also be reported by the subject to the Investigator.

Pregnancies are not SAEs. However, pregnancy data will be collected at the initial notification, birth/termination of pregnancy, and for up to 1 year after birth or until the end of the pregnancy.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female subject or female partner of a male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy.

Any SAE that occurs during pregnancy (eg, serious maternal complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, etc.) must be reported in accordance with the procedure for reporting SAEs.

12.8.3. Serious Adverse Event Reports to the IRB/IEC

The Investigator, or responsible person per local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the appropriate IRB or IEC.

12.8.4. Regulatory Requirements for Reporting of Serious Adverse Events

The Investigator (or medically qualified designee) will promptly report all SAEs in accordance with the procedures detailed in Section 12.8.1. Prompt notification of SAEs by the PI is essential so that the sponsor may comply with its regulatory obligations.

Any SAEs requiring expedited reporting will be reported by the sponsor to relevant regulatory authorities, Investigators, and IRBs or IECs in accordance with the sponsor's procedures and local regulatory requirements as applicable.

Serious adverse events will be reported if either the PI or the sponsor deems that the event is related to the IP. Furthermore, medication errors, pregnancies, and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

Special attention should be given to the subjects' underlying disease, concomitant medications, drug mechanistic factors, and other contributing factors when considering whether any given event is associated with a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence, similar events, drug class effect, and the totality of available safety data and reference safety information.

In the case where limited information that informs causal attributions is provided by the reporting investigator, the sponsor will issue queries directly or via the contract research organization to the reporting investigator to collect sufficient clinical data and medical information about the study participant to inform causality.

If the Arrowhead Global Safety Reviewer/Officer disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report and the case will be reported to EU Health Authorities in accordance with REGULATION (EU) No 536/2014) and local and global reporting regulations.

12.8.4.1. Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

For countries within the European Economic Area (EEA), the sponsor or its authorized representative will report in an expedited manner to concerned Regulatory Authorities and Ethics Committees suspected unexpected serious adverse reactions (SUSARs) in accordance with REGULATION (EU) No 536/2014 and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The sponsor shall report electronically to the EudraVigilance database all relevant information about the following SUSARs:

- All SUSARs related to an IP that occurred in any of the countries participating in the study, even if the sponsor is aware of it only after the end of the study.

- All SUSARs related to the same active substance that occurred in a study conducted in third countries by the same sponsor or by another sponsor within the same parent company or who develops the medicinal product jointly.

Regarding fatal or life-threatening SUSARs, the reporting period begins the day the sponsor becomes aware of the reactions. The sponsor will report them as soon as possible and no later than 7 days.

For non-fatal or non-life-threatening SUSARs, the reporting period begins the day the sponsor becomes aware of the reactions. The sponsor will report them as soon as possible and no later than 15 days.

12.8.5. Post-study Adverse Events

A post-study AE is defined as any event that occurs outside of the AE detection period defined in Section 12.4. The Investigator is not obligated to actively seek AEs in former study subjects. However, if the Investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the IP, the Investigator will promptly notify the sponsor.

12.8.6. Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly (Section 12.8.1).

13. STATISTICS

13.1. Statistical Considerations

Statistical analyses and descriptive summaries will be presented for primary, secondary, and exploratory endpoints using appropriate methods. All data in this OLE study will be summarized as an overall treatment group. Any proposed amendments to the Statistical Analysis Plan (SAP) will only occur prior to database lock. Descriptive statistics will be presented for all analyses unless otherwise specified. For continuous variables, data will be presented as number (n), mean, median, standard deviation (SD), minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percent.

Additional details of all planned analyses for this study will be provided in the SAP, which will be finalized prior to database lock.

13.2. Analysis Populations

For the purposes of analysis, the following analysis sets are defined:

Subject Analysis Set	Description
Full analysis set	All enrolled subjects
Safety analysis set	All subjects who are exposed to study intervention during this extension study

The full analysis set is used to analyze endpoints related to the efficacy objectives, and the safety analysis set is used to analyze the endpoints and assessments related to safety.

13.3. Sample Size Considerations

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

13.4. Analysis Methods

Descriptive summaries will be provided for safety and efficacy assessments, as applicable.

For efficacy endpoints, change and/or percent change from baseline or response rate over time will be summarized. Baseline will be defined as the baseline from the parent study. The change or percent change from the measurements at enrollment of this OLE study will also be explored. Baseline of efficacy endpoints is defined as the study baseline from AROAPOC3-2001 and AROAPOC3-2002 studies.

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

Treatment-emergent AEs will be summarized using the latest version of MedDRA by System Organ Class (SOC) and PT. The incidence of AEs, SAEs, related AEs, related SAEs, and AEs leading to discontinuation will be summarized by SOC, PT, and severity. All AEs will also be presented in listings. The duration of AEs will be determined and included in listings along with

the action taken and outcome. The incidence of laboratory abnormalities will be assessed using descriptive summary statistics. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Abnormal physical examination findings will be summarized by time point and presented in listings. ECG parameters, changes from baseline, and qualitative assessments will be summarized.

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

Descriptive summaries will be provided for the following PD parameters: ApoC-III, ApoB-48, ApoB-100, ApoC-II, ApoA-I, and ApoA-V.

13.5. Interim Analysis

No interim analysis is planned for this OLE study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Arrowhead is responsible for assuring the proper conduct of the study about protocol adherence and validity of the data recorded on the eCRFs. Subject confidentiality will be maintained.

In accordance with applicable regulations, GCP, and Arrowhead procedures, Arrowhead will be responsible for assigning a study monitor (CRA) who will contact the site to organize a visit prior to subject enrollment to review the protocol and data collection procedures with site staff. In addition, the assigned study monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objective or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these site visits, the study monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.
- Check IP accountability.
- Review blood and urine samples and ensure they are labeled and stored correctly.

This will be done to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, a study monitor will conduct the following activities in conjunction with the Investigator or site staff as appropriate:

- Return of all study data to Arrowhead
- Data queries
- Accountability, reconciliation, and arrangements for unused IP(s)
- Inventory and final disposition (eg, destruction, shipping to repository, etc.)
- Review of site study records for completeness

14.2. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. The Investigator will conduct the study in compliance with the approved protocol and will not implement any deviation from or changes to the protocol without prior agreement by the sponsor and review and documented approval from the IRB or IEC of an amendment, except where necessary to eliminate an immediate hazard to study subjects.

Deviations may result from the action or inaction of the subject, Investigator, or site staff. Examples of deviations include, but are not limited to:

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

Protocol deviations impacting subject safety or eligibility will be reported to the sponsor or CRO within 2 business days of occurrence and to the IRB or IEC competent regulatory authority per local regulatory requirements.

The Investigator is responsible for ensuring that any known protocol deviations are recorded and reported as agreed. The nature and reasons for protocol deviations will be recorded.

14.3. Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the Investigator or designee will obtain a copy of the certification form, with certification number and expiration date for all clinical laboratories (excluding central laboratories) used in the study. Reference ranges for each clinical laboratory test used in this study will be obtained from the appropriate central laboratory, which will perform the test for the study. In the event of coronavirus disease 2019 (COVID-19) or similar event related restrictions prohibiting subject site visits, local labs with associated local lab reference ranges may be utilized with prior sponsor approval.

14.4. Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, Arrowhead may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and clinical site agree to notify sponsor as soon as possible following awareness of an impending regulatory inspection. The Investigator and clinical site agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues

14.5. Institutional Review Board/Independent Ethics Committee

Prior to initiation of the study, written IRB or IEC approval of the protocol and ICFs, based on the principles of ICH GCP procedures, will be received. A copy of the signed and dated letter of approval will be provided to the clinical site and Arrowhead prior to study commencement. Any written information or advertisements to be used for subject recruitment will be approved by the IRB or IEC prior to use. A list of the IRB or IEC voting members, their titles or occupations, Federal Wide Assurance number (where applicable), and their institutional affiliations will be requested before study initiation.

Protocol modifications that may impact subject safety or the validity of the study will be approved by the IRB or IEC, following written agreement from the sponsor.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit such written approval to the sponsor before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. The sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB and/or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements. The protocol will be submitted for approval to the IRB or IEC, and written approval obtained before subjects are enrolled. The composition of the IRB or IEC will also be provided to the sponsor. If approval is suspended or terminated by the IRB or IEC, the Investigator will notify the sponsor immediately.

Where applicable, the clinical site and Arrowhead agree to abide by the local compensation guidelines for injury resulting from participating in a company-sponsored research project. Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability.

15.3. Written Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

It is the responsibility of the Investigator or medically qualified designee to obtain a written informed consent from everyone participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Investigator or medically qualified designee must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided to the Investigator by Arrowhead or its designee.

For this study, each eligible subject will be required to provide written informed consent before participation in the study.

All eligible subjects will have the study explained by the Investigator or medically qualified designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomforts, risks and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each subject will acknowledge receipt of this information by giving written informed consent for participation in the study. The subject will be given a copy of the signed ICF to retain.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

The sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relevant to the conduct of the study.

16.2. Retention of Records

Following closure of the study, the Investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection) and to allow for any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. When permitted by local laws/regulations or institutional policy, some of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

Arrowhead will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Arrowhead standards/procedures; otherwise, the retention period will default to 15 years, whichever is the longer time period.

The material to be stored shall include, but is not limited to, the following:

- Signed and dated copy of the final study protocol and any amendments
- Signed and dated letter of IRB or IEC approval, letter of constitution of the IRB or IEC, and copies of any other correspondence relevant to the study with the IRB or IEC or regulatory authorities
- The IRB- or IEC-approved ICF

- Current curriculum vitae (signed and dated) of the Investigator and coworkers with major responsibilities in the study
- Site Signature and Delegation of Responsibility Log
- Food and Drug Administration Form 1572 (where applicable)
- Financial Disclosure Form(s)
- Blank case report form (CRF)/eCRF
- Signed subject ICFs
- Laboratory reference ranges (signed and dated)
- The completed Clinical Trial Notification Application Form (where applicable)
- Clinical raw data including the source data forms, all clinical laboratory report forms, subject CRFs, drug accountability forms, and dispensing records, etc

16.3. Data Protection

Subjects will be assigned a unique identifier by the site. Any subject records or datasets that are transferred to the sponsor will contain the identifier only not the subject name.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by the sponsor, Arrowhead Pharmaceuticals, Inc., and its designated representatives, by the IRB/IEC responsible for reviewing the study, by regulatory authorities such as the US Food and Drug Administration, the European Medicines Agency, and other health agencies that regulate this research, and by the study doctor, study staff, and other authorized healthcare providers at the study site.

The sponsor complies with data minimization principles and will collect and process the minimum amount of personal data necessary for purposes of the study. The sponsor has implemented information security policies and procedures designed to prevent unauthorized persons from gaining access to personal data collected and processed in the context of the study ("Clinical Data") and to ensure that persons authorized to access Clinical Data gain access only in accordance with their access rights. The sponsor also maintains policies and procedures for detecting, monitoring, and responding to data security incidents and, as appropriate, for reporting data security incidents to regulators and/or individuals. The sponsor carries out periodic risk assessments/reviews and, as appropriate, updates its information security policies and procedures.

Clinical Data received by the sponsor is pseudonymized/key-coded and the key is retained by the study site. Where third party processors are engaged to process Clinical Data, due diligence is carried out to ensure such third parties are capable of maintaining appropriate security measures to protect Clinical Data. For transfers of Clinical Data to countries outside of the European Economic Area and United Kingdom, consistent with the requirements of the General Data Protection Regulation ("GDPR"), the sponsor will ensure that appropriate safeguards are in place

such as “standard contractual clauses” or such transfers will be made in reliance on an Article 49 GDPR derogation.

16.4. Source Documents

Source documents must be maintained for each subject in the study, consisting of all demographic and medical information, including clinical laboratory data, and entered into the electronic data capture system as per study requirements. A copy of the signed ICF must be retained. All information in the eCRFs must be traceable to these source documents in the subject's file.

Data recorded in all subjects’ eCRFs will be subject to a quality control review.

17. PUBLICATION POLICY

[redacted]

17.1. Ownership

[redacted]

17.2. Confidentiality

[redacted]

[redacted]

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APPENDIX 1. LOCAL INJECTION SITE REACTIONS

Best Practices for Subcutaneous Administration of Study Drug to Avoid the Risk of a Local Injection Site Reaction

For the clinical study site staff involved in administering subcutaneous (SC) injections of study drug, below are some key recommendations to help minimize the risk of an injection site reaction:

1. Proper Injection Technique: Ensure that injections are administered properly. This includes using appropriate needle size (if not using PFS), rotating injection sites, and injecting at the correct depth and angle.
    a. Sites to ensure study drug administration staff are properly trained in administering subcutaneous injections. This includes understanding the correct technique, needle selection, angle (see #5 below), and injection sites appropriate for SC administration.
2. Room Temperature Medication: allow the study drug to come to room temperature before administering the injection. Cold medication can be more painful and may increase the risk of a reaction.
3. Assess Injection Sites: Before administering the injection, assess the patient's skin for signs of bruising, swelling, or inflammation.
4. Educate on the importance of rotating injection sites to avoid developing lumps or nodules or absorption issues.
    a. Avoid injecting into the muscle, sensitive spots (around the umbilicus), or those close to blood vessels, joints, or areas with visible signs of inflammation, redness, or tenderness.
    b. Avoid overusing any one area. If the patient is on Insulin or other subcutaneously administered drugs, ask about the locations of the most recent injections and avoid them, also ask the patient about the most convenient, least sensitive spots.
5. Injection Technique: Use the proper injection technique, including pinching the skin and inserting the needle at the correct angle, usually 45 degrees, to 90 degrees unless using PFS (the angle depends on the length of the needle and the amount of subcutaneous tissue).
6. Inject the medication slowly and avoid rapid injections to minimize discomfort and tissue trauma.
7. Cold Compress or Ice Pack (if needed): Applying an ice pack to the injection site before and after the injection can help reduce pain and inflammation.
8. Hydration: Ensure study participants are well hydrated before and after the injection. Staying hydrated can help reduce the risk of a LISR.
9. Hand Hygiene, Gloves and Cleanliness: Ensure that the injection site is clean and sterile before administering the injection. Clean the site with an alcohol swab (60–70% alcohol) and allow it to dry (30 seconds) before inserting the needle. Do not allow the needle to be in contact of any nonsterile surface.

10. Monitor for Adverse Reactions: Monitor the patient for any signs of adverse reactions, such as redness, swelling, pain, or itching at the injection site. If any reactions occur, assess their severity and provide appropriate care.

Documentation and Follow-Up

Document the injection site, the exact timing of the study drug administered, and any adverse reactions in the Case Report Form (CRF). Follow up with the subject to ensure that any injection site reactions are resolved. Record onset of any LISR, resolution state, and time. Note: Most LISRs reported were mild, needed no intervention or management, and resolved no later than 48 hours after onset.

As indicated in the study protocol, all AEs and SAEs are reported according to MedDRA Terms and graded according to Common Terminology Criteria for Adverse Events (CTCAE) (v5.0) (FDA 2007; NIH 2017).

Note: For subcutaneous administration, moderate LISR are either reactions with erythema, induration, swelling >5 cm or associated with pain >24 hours interfere with daily activity and require the use of non-narcotic pain management (FDA 2007).

By following the guidelines above and the best practices and tips, the study staff can help minimize the risk of injection site reactions when administering subcutaneous study drugs and ensure the safety and comfort of clinical trial patients.

APPENDIX 2. CONTRACEPTION

Women not of childbearing potential must be either surgically sterile or postmenopausal (defined as cessation of regular menstrual periods for at least 12 months without an alternative medical cause) with supportive follicle-stimulating hormone test consistent with postmenopausal state based on laboratory reference ranges.

If a subject's urine pregnancy test is positive, the subject will be referred to their primary care provider for follow-up. Female subjects with a positive pregnancy test on Day 1 predose will not be enrolled in the study. Female subjects who become pregnant after Day 1 and will not receive subsequent administration of investigational product.

All subjects (female subjects of childbearing potential with male partners and male subjects with female partners of childbearing potential) must consent to use highly effective contraception during the study and for at least 24 weeks following last dose of IP, whichever is later.

The following are acceptable methods of highly effective contraception:

- Using twice the normal protection of birth control by using a condom AND one other form of contraception; either birth control pills (The Pill), or injectable birth control, birth control patch or contraceptive implant associated with inhibition of ovulation, or intrauterine device; or
- Surgical sterilization as a single form of birth control: ie, tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy or equivalently effective surgical form of birth control; or
- True sexual abstinence for the duration of the study and for at least 24 weeks following the EOS visit or after the last dose of IP, whichever is later, is acceptable only when in line with the preferred and usual lifestyle of the subject.

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not considered "true" abstinence and are not acceptable methods of contraception.

APPENDIX 3. LIVER-RELATED STUDY MODIFICATION AND FOLLOW-UP GUIDELINES FOR SUBJECTS

Liver-related study monitoring and stopping guidelines for subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations at baseline are described in Table 6.

In subjects with normal (per central laboratory reference range) AST or ALT on Day 1, treatment-emergent elevations >3× ULN at least possibly related to investigational product (IP) per study Investigator, must be confirmed by repeat blood draw within 72 hours of initial results. Some subjects enrolling into this study may have baseline elevations in transaminases. In subjects with elevated AST or ALT on Day 1, treatment-emergent elevations >2× baseline or ≥300 U/L (whichever occurs first) at least possibly related to IP per study Investigator, as specified below, must be confirmed by repeat blood draw within 72 hours of initial results.

Table 6: Liver-Related Study Modification and Follow-Up Guidelines for Subjects

Treatment-Emergent AST or ALT	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
Normal baseline: AST or ALT >3× ULN Elevated baseline: AST or ALT >2× baseline or ≥300 U/L (whichever occurs first)	Normal Subjects with Gilbert's syndrome or hemolysis - no change in baseline TBL	None	Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [a] Follow-up for symptoms.
Normal baseline: AST or ALT >5× ULN Elevated baseline: AST or ALT >3× baseline or ≥300 U/L (whichever occurs first)	Normal Subjects with Gilbert's syndrome or hemolysis - no change in baseline TBL	None	Discontinue IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [a] Refer to guidelines for close observation below. Follow-up for symptoms.

Treatment-Emergent AST or ALT	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
Normal baseline: AST or ALT >3× ULN Elevated baseline: AST or ALT >2× baseline or ≥300 U/L (whichever occurs first)	Normal Subjects with Gilbert's syndrome or hemolysis - no change in baseline TBL	Symptoms of clinical hepatitis – severe fatigue, nausea, vomiting, right upper quadrant pain or; immunologic reactions (eg, rash, >5% eosinophilia)	Interrupt IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [a] IP can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred. Refer to guidelines for close observation below. Follow-up for symptoms.
Normal baseline: AST or ALT >3× ULN Elevated baseline: AST or ALT >2× baseline or ≥300 U/L (whichever occurs first)	TBL >2× ULN or increased INR to >1.5 In subjects with Gilbert's syndrome or hemolysis - doubling of direct bilirubin if baseline >0.5 mg/dL	None	Interrupt IP. Confirm AST, ALT, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [a] Initiate close observation and workup for competing etiologies. [a] IP can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred.

Abbreviations: ALP=alkaline phosphatase; ALT= alanine aminotransferase; AST= aspartate aminotransferase; INR=international normalized ratio; IP=investigational product; ULN=upper limit of normal.
Note: Elevated baseline is defined as ALT/AST >ULN.
[a] Acute and chronic viral hepatitis (hepatitis A - E), cholelithiasis, alcohol, other drugs both prescribed and over-the-counter herbs and supplements.
Source: (FDA 2009; Regev 2019)

Guidelines for Close Observation for Potential Drug-Induced Liver Injury:

Within 72 hours, perform a history, physical, and liver biochemistries, including evaluation of:

- New or worsening signs and symptoms of clinical hepatitis such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Concomitant medications, including acetaminophen, dietary supplements, herbal remedies, over-the-counter medications, recreational drug use, and special diets
- Alcohol consumption
- Exposure to environmental chemical agents
- Past medical history
- Complete review of systems
- Liver biochemistries including ALT, AST, alkaline phosphatase, total bilirubin, and INR

If the subject's biochemistries stabilize and the subject is asymptomatic, monitor the subject's liver biochemistries until they return to baseline.

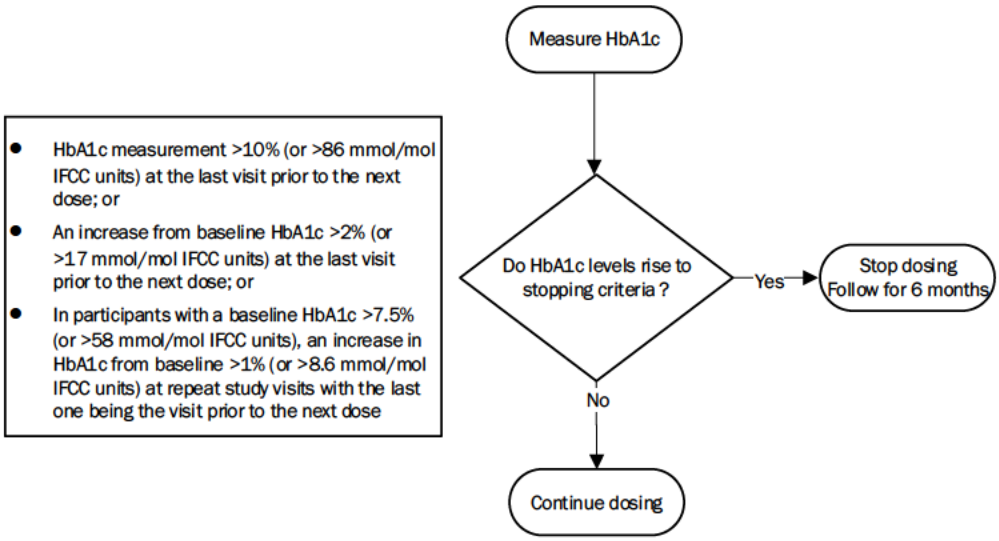
Subjects who live far from study sites may be evaluated locally if the results are communicated promptly to the site Investigator.

APPENDIX 4. GLYCEMIC CONTROL-RELATED GUIDELINES

Glycated hemoglobin (HbA1c) Investigational Product Discontinuation Criteria

Participants should discontinue investigational product (IP) if they meet the following criteria:

- HbA1c measurement >10% (or >86 mmol/mol International Federation of Clinical Chemistry [IFCC] units) at the last visit prior to the next dose; or
- An increase from baseline HbA1c >2% (or >17 mmol/mol IFCC units) at the last visit prior to the next dose; or
- For participants with a baseline HbA1c >7.5% (or >58 mmol/mol IFCC units) who had an increase from baseline >1% (8.6 mmol/mol IFCC units) at repeat study visits with the last one being the visit prior to the next dose.



Guidelines for Excessive Increases in HbA1c

The following guidelines should be followed for increases in HbA1c:

- Investigators are encouraged to evaluate diabetes status and adjust diabetes treatment according to clinical practice and diabetes care guidance.
- At the Investigator's discretion, any subject with worsening diabetic control may return for an unscheduled visit for evaluation of HbA1c prior to the next planned dose to confirm continued treatment eligibility.
- The participants who discontinue IP due to the above criteria will be followed for 6 months after their last dose per the Schedule of Assessments.

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