ZODASIRAN (ARO-ANG3) INJECTION
AROANG3-2003
PROTOCOL AMENDMENT 5, DATED 19-AUG-2025

Amendment 5	**Version Date: 19-AUG-2025**
Amendment 4	**Version Date: 08-MAR-2023**
Amendment 3	**Version Date: 22-NOV-2022**
Amendment 2	**Version Date: 27-SEP-2022**
Amendment 1	**Version Date: 27-APR-2022**
Original Protocol:	**29-NOV-2021**

PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ARO-ANG3 IN SUBJECTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH)

Investigational Product:	ARO-ANG3 Injection
Study Phase	2
Indication:	Homozygous Familial Hypercholesterolemia
IND Number:	151756
EudraCT Number:	Not applicable
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-ANG3 Injection. I have carefully read the AROANG3-2003 study protocol.
- I agree to conduct the study according to the protocol (subject to any amendments) and in accordance with the principles of the International Council for 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

Sponsor Medical Monitor Contact
[redacted] Telephone: [redacted] [a]

[a] Regional contact information will be provided.

1. SYNOPSIS

Name of Sponsor/Company: Arrowhead Pharmaceuticals, Inc.		
Name of Investigational Product: ARO-ANG3 Injection (zodasiran)		
Name of Active Ingredient: ADS-004		
Protocol Number: AROANG3-2003, Amendment 5	**Phase:** Phase 2 Study in subjects with HoFH	**Countries:** Multiple
Title of Study: Phase 2 Study to Evaluate the Safety and Efficacy of ARO-ANG3 in Subjects with Homozygous Familial Hypercholesterolemia (HoFH)		

Background:

An emerging therapeutic target with relevance to hypercholesterolemia, hypertriglyceridemia, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) is angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 is a primarily hepatocyte synthesized member of the angiopoietin-like family of proteins. Its key role is regulation of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) metabolism. More specifically, ANGPTL3 inhibits lipoprotein lipase (LPL), which is responsible for TG hydrolysis in peripheral tissues (eg, adipose tissue, muscle). ANGPTL3 also inhibits endothelial lipase (EL)-driven HDL-C metabolism and inhibits hepatocyte uptake of apolipoprotein B (ApoB) containing lipoproteins (LDL-C and very low-density lipoprotein cholesterol [VLDL-C]) through mechanisms at least partially independent of the low-density lipoprotein (LDL) receptor (Adam 2020). Given the inhibitory role of ANGPTL3 in the metabolism of various lipoproteins and TGs, reduced expression and reduced circulating levels of ANGPTL3 are expected to increase clearance of LDL-C, HDL-C, and TGs.

Familial hypercholesterolemia (FH), including heterozygous familial hypercholesterolemia (HeFH) and homozygous (HoFH) variants, represents a unique case where LDL-C lowering therapies not requiring a functional LDL receptor may have benefit. HeFH has a frequency of approximately 1 per 500, with HoFH (the more severe phenotype) occurring in 1 per 250,000. Key mechanisms of action of statins and of proprotein convertase subtilisin kexin type-9 (PCSK9) inhibitors are inhibition of cholesterol synthesis and enhanced hepatic clearance of LDL-C through upregulation of the hepatocyte low-density lipoprotein receptor (LDLR) (Ballantyne 2015). Thus, patients with HoFH due to dysfunctional or absent LDLR can be resistant to standards of care such as statins and even resistant to alternatives such as PCSK9 inhibitors. Patients with HoFH are therefore a population with a particularly high need for additional therapy with a mechanism working outside of the LDL receptor, such as therapeutic ANGPTL3 inhibition.

One method of targeting serum ANGPTL3 is to leverage RNA interference (RNAi) mediated hepatic knockdown of this gene to prevent its production. This approach has important advantages, including less frequent dosing intervals and subcutaneous (SC) dosing.

In this clinical study, ARO-ANG3, an RNAi-based therapeutic targeting ANGPTL3, will be evaluated in subjects with HoFH.

Objectives:

Primary:

- To evaluate the efficacy and safety of ARO-ANG3 in subjects with HoFH

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

Endpoints:

Primary:

- Percent change from baseline to Week 24 in fasting calculated LDL-C and LDL-C using preparative ultracentrifugation (PUC)

Secondary:

The following secondary endpoints will be evaluated:

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

The following secondary endpoints will be evaluated in the24-month optional Extension Treatment Period:

- Percent and absolute change from baseline in fasting calculated LDL-C and fasting LDL-C (using PUC), fasting ANGPTL3, fasting total ApoB, fasting HDL-C, fasting non-HDL-C, fasting VLDL-C, fasting TC, and fasting TG at each scheduled assessment
- Subject incidence of ADAs to ARO-ANG3 at each scheduled assessment
- Subject incidence of TEAEs

Exploratory:

- Change from baseline in other fasting lipid parameters at each scheduled assessment in the 36-week Treatment Period as well as over time during the Extension Treatment Period (LDL/HDL ratio, ApoB-48, lipoprotein [LP][a], ApoB-100, ApoC-III, ApoC-II, ApoA-I, and ApoA-V)
- Plasma pharmacokinetic (PK) concentrations of ARO-ANG3 at each scheduled assessment

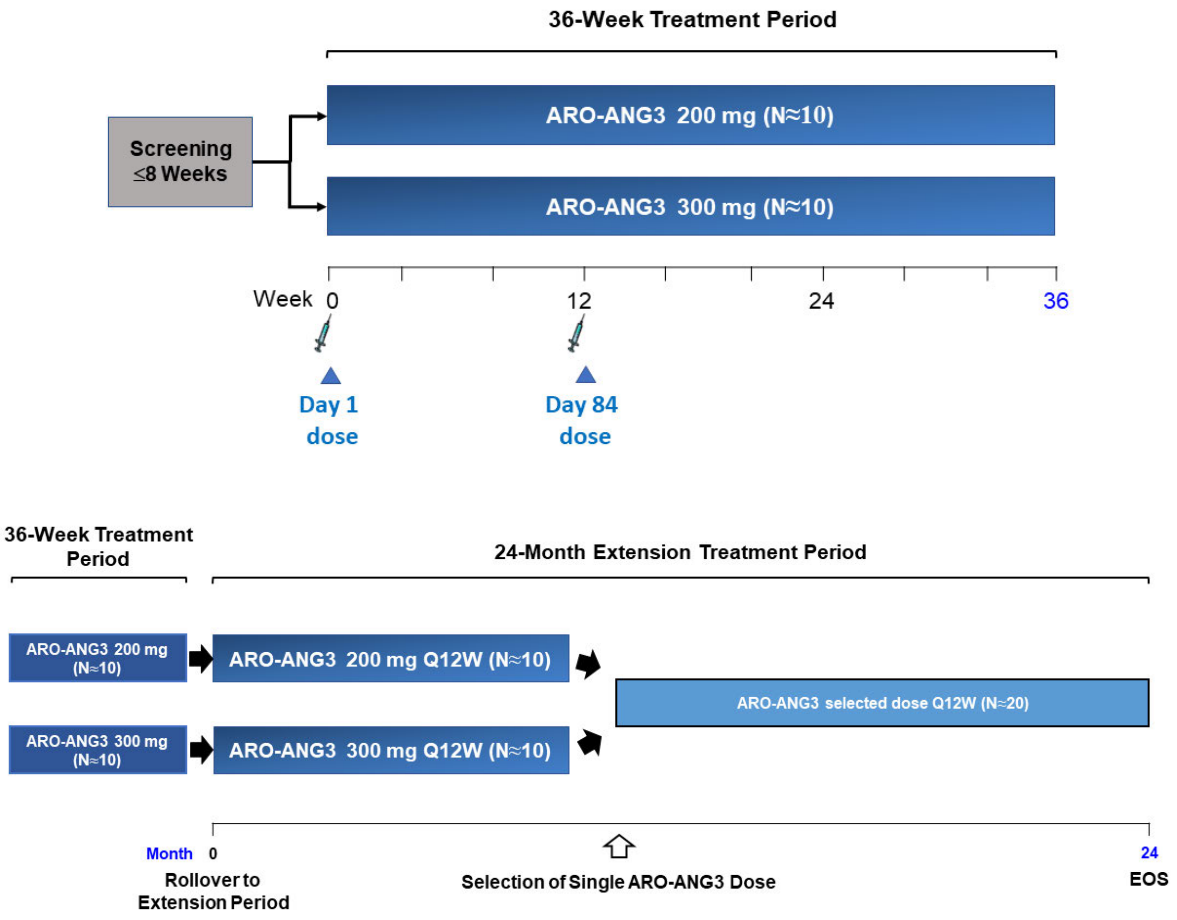
Study Design:

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

After completing the Week 36 Visit, subjects may opt to continue in the 24-month Extension Treatment Period (see Study Schema). Unless otherwise specified, a month refers to 28 consecutive days. Subjects who do not opt to continue in the Extension Treatment Period will complete Week 36/Early Termination (ET) Visit assessments. Subjects in the Extension Treatment Period will complete study visits as specified in the SOA (Table 4) and will be dosed quarterly (once every 12 weeks [Q12W]). Initially, subjects will receive the same dose level received during the 36-week Treatment Period. However, dose levels in the Extension Treatment Period may be consolidated to a single dose level based on sponsor decision after an interim analysis of safety and efficacy data at Week 24 of the 36-week Treatment Period. The interim analysis will be conducted once the data is available for a majority of enrolled subjects. Once a single dose has been selected by the sponsor, all subjects will be transitioned to the selected dose level.

The SOA is presented in Table 3 and Table 4.

Study Schema:



Abbreviations: EOS=End of Study; N=number of subjects; Q12W=once every 12 weeks.

Methodology:

Overall Screening Period (≤8 Weeks)

Subjects will have screening laboratory measurements and will be assessed for eligibility. Subjects who have met all of the protocol eligibility criteria during Screening may be enrolled to receive ARO-ANG3.

Screening Visits 1 and 2

Screening Visit 1 procedures will be conducted during Day -56 to Day -1. At Screening Visit 1, the subject will sign the informed consent before proceeding to any procedures. Screening Visit 2 will occur during Day -28 to Day -1. Screening Visit 1 assessments may be completed at Screening Visit 2, at the Investigator's discretion, only if all required assessments can be completed within 28 days prior to Day 1. See SOA (Table 3). Screening Visits 1 and 2 may occur on the same day.

Open-Label Treatment Period

Up to approximately 20 subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive 2 doses of ARO-ANG3 200 mg or 300 mg on Day 1 and Day 84 and will be evaluated over a 36-week period (see Study Schema). For a subject who discontinues from the study prematurely, if their serum ANGPTL3 level at the ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value.

Optional Extension Treatment Period

After completing the Week 36 Visit, subjects may opt to continue in the 24-month Extension Treatment Period. Therefore, the total duration of the study will be approximately 34 months. If a subject's serum ANGPTL3 level at the Extension Treatment Period Month 24 (EOS) visit or ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value, they enter the OLE of Study AROANG3-3001 (if they meet the eligibility criteria for that separate study), or until they have completed 1.5 years of monitoring, whichever occurs earlier.

All subjects who participated in Study AROANG3-2003 may enroll into the OLE Period of Study AROANG3-3001 (if they meet the eligibility criteria for that separate study).

Study Treatment

There will be 2 study treatments; both will be active at either ARO-ANG3 200 or 300 mg. Subjects participating in the Extension Treatment Period will initially continue to receive the dose level assigned in the initial 36-week Treatment Period. However, all subjects in the Extension Treatment Period may be later switched to a single dose level based on an interim analysis of safety and efficacy data.

Test Formulation

The test formulation is active ARO-ANG3 Injection. The active pharmaceutical ingredient (API), ADS-004, contained in ARO-ANG3 is a synthetic, double-stranded, small interfering RNA (siRNA) duplex conjugated to an N-acetyl-galactosamine (NAG) targeting ligand to facilitate hepatocyte delivery.

Doses and Number of Doses per Treatment

Two dose levels of ARO-ANG3 will be evaluated in subjects with HoFH.

Each subject will be randomized to receive SC injections as follows: ARO-ANG3 200 mg (n≈10) or ARO-ANG3 300 mg (n≈10) at Day 1 and Day 84 (2 doses total for each subject) in the 36-week Treatment Period. After completing the Week 36 Visit, subjects may opt to continue in the 24-month Extension Treatment Period. Subjects in the Extension Treatment Period will be dosed Q12W. Once a

single dose has been selected by the sponsor, all subjects in the Extension Treatment Period will be transitioned to the selected dose level.

Adverse Event Monitoring

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

The AE and SAE reporting period for an enrolled subject begins when the subject provides informed consent. Treatment-emergent AEs and SAEs are defined as those that occur following study drug administration or are a pre-existing 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 within 24 hours of being notified, regardless of the relationship of the SAE to study treatment. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event causality 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 or she considers the event reasonably related to the investigational product (IP), the Investigator will promptly notify the sponsor. Laboratory or diagnostic assessment (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.

Treatment Stopping Rules:

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

- Any confirmed pregnancy will lead to permanent discontinuation of study drug dosing of that subject.
- In the case of 2 or more similar SAEs, both considered at least possibly related to ARO-ANG3 in 2 subjects, a detailed safety assessment including review of aggregate safety data will be performed immediately by the sponsor after the second SAE is notified to determine if the study remains safe to proceed, should be discontinued, or should continue but with amendments.
- **Normal baseline transaminases:** In subjects with normal (per central laboratory reference range) aspartate aminotransaminase (AST) or alanine aminotransferase (ALT) levels on Day 1, treatment-emergent elevations >3× upper limit of normal (ULN) must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 2 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 2. The subject will remain on study follow-up visits until EOS as per the SOA (Table 3 and Table 4)
  - 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 international normalized ratio (INR) >1.5 (must be confirmed on repeat) and which is not explained by another plausible cause.

- **Elevated baseline transaminases:** 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), as specified below, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 2 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 2.

Study drug discontinuation criteria for increased HbA1c

- Regarding HbA1c treatment discontinuation criteria, participants should discontinue IP if they meet the following criteria (refer to Appendix 3):
  - 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 determinations will be followed for 6 months after their last dose per the Schedule of Assessments. Treatment modification guidelines for subjects with elevated HbAc1 are provided in Appendix 3.

The sponsor or Investigator can discontinue any subject at any time.

The sponsor, in consultation with the Investigator, may pause dosing of additional subjects in the study to allow for time to evaluate safety data and recommend the action to be taken, which may include, but is not limited to, one of the following:

- The study may continue without modifications
- The study may continue with modifications
- The study should be terminated

- The study should be temporarily suspended
- Other changes

Number of subjects (planned):

A total of up to approximately 20 subjects will be enrolled in the study, up to approximately 10 subjects in each of 2 cohorts.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

To be eligible for enrollment, subjects must meet all the following inclusion criteria (applicable to all cohorts):

1. Males or nonpregnant (who do not plan to become pregnant), nonlactating females ≥16 years at Screening
2. Fasting LDL-C >100 mg/dL at Screening Visit 2
3. Weight of ≥40 kg and body mass index (BMI) ≥18.5 and ≤40 kg/m^2
4. A diagnosis of HoFH based on a supportive genetic test (from a source-verifiable medical record or based on screening genotype) or clinical diagnosis. Diagnosis of HoFH may be based on at least **one** of the following (a-c);
    a. Documented functional mutation(s) in both LDLR alleles.
    Note: Subjects who have null receptor mutations on both LDLR alleles, ie, double null, are eligible.
    b. Presence of homozygous or compound heterozygous mutations in ApoB or PCSK9.
    Note: Double heterozygous (ie, mutations on different genes [eg, LDLR/PCSK9]) or subjects with homozygous low density lipoprotein receptor adaptor protein 1 (LDLRAP1) mutations are eligible.
    c. Documented history of untreated TC >500 mg/dL (12.93 mmol/L) OR treated LDL-C concentration of ≥300 mg/dL (≥8 mmol/L) either accompanied by TGs <300 mg/dL (3.39 mmol/L) AND both parents with documented TC >250 mg/dL (6.47 mmol/L) OR cutaneous or tendinous xanthoma before 10 years of age (Cuchel 2014)
5. If undergoing LDL apheresis, must have initiated LDL apheresis at least 3 months prior to Screening and must have been on a stable schedule (such as weekly [every 7±1 days], every other week [every 14±2 days], or some similar regimen) and stable settings for at least 8 weeks prior to Screening Visit 2
6. Subject is on stable (see table below for definition of stable) maximally tolerated lipid lowering therapy
7. If taking any of the following medications, must have been on a stable regimen for at least the minimum time period indicated below prior to Screening Visit 2:

Medication	Time on Stable Regimen Prior to Screening Visit 2
Immunosuppressants, including corticosteroids	≥8 weeks
Testosterone replacement therapy	≥8 weeks
Anticoagulation therapy	≥8 weeks
Atypical antipsychotics	≥8 weeks
Diabetes mellitus medications	≥8 weeks
Thyroid replacement therapy	≥8 weeks

PCSK9 inhibitors	≥8 weeks
Retinoids	≥8 weeks
Lomitapide	≥8 weeks
Beta-blockers, thiazide diuretics	≥8 weeks
Oral estrogens, tamoxifen, raloxifene	≥8 weeks
Fibrates	≥6 weeks
Statins and other lipid-lowering therapies (eg, ezetimibe)	≥4 weeks
Bempedoic acid and bile acid-binding resin (eg, cholestyramine, colestipol, or colesevelam)	≥4 weeks

Abbreviation: PCSK9=proprotein convertase subtilisin kexin type-9.

8. Subjects of childbearing potential must agree to use highly-effective contraception during the study and for at least 24 weeks from last dose of IP (see Appendix 1). Males must not donate sperm, nor can women donate eggs, during the study and for at least 24 weeks following the last dose of IP. Postmenopausal women must be amenorrheic for at least 12 months prior to Day 1 in order not to be considered of childbearing potential. Postmenopausal status will be confirmed by measurement of follicle-stimulating hormone (FSH). Pregnancy testing and contraception are not required for women with documented hysterectomy and/or oophorectomy.
9. Female subjects of childbearing potential on hormonal contraceptives must be stable on the medication for >2 menstrual cycles prior to Day 1
10. Subject is willing to strictly abide by a stable low saturated fat, low-cholesterol, heart-healthy diet for at least 4 weeks prior to Day 1
11. Willing and able to comply with clinic visits and study-related procedures
12. Provide signed informed consent or assent

NOTE: All laboratory tests used as inclusion or exclusion criteria will be assessed by a central laboratory and may be repeated once, and the repeat value may be used for inclusion purposes.

Exclusion Criteria:

Individuals who meet any of the following criteria will be excluded from the study:

1. Current use or use within the last 365 days from Day 1 of any hepatocyte targeted siRNA or antisense oligonucleoside molecule
2. Use of evinacumab within 5 months prior to Screening Visit 2
3. Fasting TG >300 mg/dL (3.39 mmol/L) at Screening
4. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
5. Newly diagnosed (within 3 months prior to subject signing informed consent) or poorly controlled diabetes (hemoglobin A1c [HbA1c] >9% [or >75 mmol/mol International Federation of Clinical Chemistry (IFCC) units])
6. Use of an investigational agent or device within 30 days or within 5 half-lives, based on plasma PK (whichever is longer), prior to Day 1, or current participation in an interventional investigational study
7. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 8 weeks prior to Day 1. (Note: topical,

intra-articular, nasal, inhaled, and ophthalmic steroid therapies are not considered as 'systemic' and are allowed.)

8. Subjects with any symptoms of myocardial ischemia, severe left ventricular dysfunction (left ventricular ejection fraction [LVEF] <30%), and New York Heart Association class III-IV within 12 months prior to Day 1
9. Subjects with a history of metastatic malignancy within 3 years of Day 1, except for locally invasive non-melanoma skin cancer, cervical in situ carcinoma, and breast ductal carcinoma-in-situ. Subjects with other curatively treated or non-metastatic locally confined tumors may be enrolled into the study following approval by the Medical Monitor and Investigator.
10. History of myocardial infarction (MI), unstable angina leading to hospitalization, coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack (TIA), carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 months prior to signing informed consent
11. Planned cardiac procedure/surgery such as CABG surgery, PCI, carotid surgery or stenting, or carotid revascularization
12. Subjects with total bilirubin >1.5x ULN, unless in previously confirmed cases of Gilbert's syndrome
13. Subjects with platelet count <100,000/mm^3
14. Unstable weight (variation >5 kg) within 2 months prior to the Screening Visit
15. Use of estrogen or testosterone therapy unless the regimen has been stable for 6 weeks prior to the Day 1 visit and there are no plans to change the regimen during the study
16. Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg at the Screening Visit or time of randomization (Week 0/Day 1), which may be reassessed after hypertension is controlled with treatment
17. 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 = 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)
18. Any concomitant medical, psychiatric condition, social situation, or any other situation that, in the Investigator's judgment, would make it difficult to comply with protocol requirements or put the subject at additional safety risk
19. Laboratory findings during the Screening Period at Screening Visit 2:
    a. Positive test for HIV, hepatitis B surface antigen (HBsAg), and/or hepatitis C antibody (associated with a positive hepatitis C virus RNA polymerase chain reaction)
    b. Positive urine pregnancy test in female subjects of childbearing potential
    c. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 (calculated by central lab)
    d. ALT or AST >3× ULN at Screening (one repeat lab is allowed)
    e. Evidence of uncontrolled hypothyroidism or thyrotoxicosis based on thyroid-stimulating hormone (TSH) outside of normal limits per central laboratory reference range (TSH <lower limit of normal [LLN] or >ULN).

NOTE: All laboratory tests used as inclusion or exclusion criteria will be assessed by a central laboratory and may be repeated once, and the repeat value may be used for exclusion purposes.

A subject will be excluded from the Extension Treatment Period of the study if any new conditions or worsening of any 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, or which could otherwise interfere with the subject participating in or completing the study, or would make it difficult to comply with protocol requirements or put the subject at additional safety risk.

Investigational product, dosage and mode of administration:

The IP, ARO-ANG3 Injection (also referred to as ARO-ANG3), is a 200 mg/mL sterile solution of ADS-004 (salt free basis), a synthetic, double-stranded, siRNA duplex conjugated to a NAG targeting ligand to facilitate hepatocyte delivery. Subjects will be randomized to receive ARO-ANG3 (ADS-004, salt free basis) 200 mg or 300 mg SC on Day 1 and Day 84.

All subjects who opt to continue in the Extension Treatment Period will initially receive ARO-ANG3 at the dose corresponding to their assigned dose level in the 36-week Treatment Period. Thus, subjects who were previously assigned ARO-ANG3 200 mg or 300 mg in the 36-week Treatment Period will receive ARO-ANG3 at the corresponding dose level in the Extension Treatment Period until a final dose is selected by the sponsor. After the majority of subjects in the 36-week Treatment Period complete the Week 36 Visit and a final dose has been selected, all subjects in the Extension Treatment Period will be transitioned to receive ARO-ANG3 at the selected dose for the remainder of their duration in the Extension Treatment Period.

Duration of treatment:

The duration of the study is approximately 34 months from Screening. The study activities and durations will be Screening (up to 8 weeks), Treatment Period (up to 36 weeks), and to the EOS Extension Treatment Period (up to 24 months). Unless otherwise specified, a month refers to 28 consecutive days.

Reference therapy, dosage, and mode of administration:

Not applicable

Criteria for evaluation:

Pharmacokinetics: Plasma concentrations of ARO-ANG3 will be measured in all subjects to evaluate predose and postdose levels per the SOA (Table 3).

Pharmacodynamics: Change from baseline in LDL-C, TG, and ANGPTL3.

Immunogenicity: ADA incidence and titer.

Efficacy: Change and percent change from baseline over time through Week 36 as well as during the Extension Treatment Period in fasting calculated LDL-C, LDL-C (PUC), ApoB, non-HDL-C, HDL-C, and TC, and other lipid parameters.

Safety: AEs and SAEs, physical examinations, vital sign measurements, 12-lead ECG, clinical laboratory tests, concomitant medications or therapy, and reasons for treatment discontinuation.

Statistical Considerations:

Sample Size Justification:

This is an exploratory study to investigate the LDL-C reduction capability of 200 mg and 300 mg ARO-ANG3 in subjects with HoFH. The sample size of approximately 20 subjects is based on clinical considerations. Based on the drug effect results from the hyperlipidemia population in the Phase 1/2a study AROANG1001, with this sample size, the study should be able to demonstrate clinically meaningful LDL-C reduction capability of ARO-ANG3 in HoFH patients. An interim analysis for this study is planned for when a majority of participants complete the Week 24 visit.

Safety:

Safety analyses will be performed based on Safety Analysis Set, which includes all subjects who received at least 1 dose of IP. TEAEs will be summarized for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or later by System Organ Class (SOC)

and Preferred Term (PT). The incidence and frequency of TEAEs, SAEs, treatment-related AEs, treatment-related SAEs, TEAEs related to an injection site reaction (ISR), and TEAEs leading to discontinuation will be summarized by SOC and PT in the same fashion. All AEs will be presented in listings. The incidence of laboratory abnormalities will be assessed using descriptive summary statistics and shift tables. 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 subject listings. Electrocardiogram parameters, changes from baseline, and qualitative assessments will be summarized. Urine pregnancy test results (female subjects of childbearing potential only) and FSH test results (females only) will be listed separately.

Efficacy:

Baseline is defined as the last value prior to administration of the first dose. Efficacy variables at baseline and each postdose visits will be summarized descriptively. Percent change and/or absolute change from baseline will be summarized by treatment group. For efficacy variables during the Extension Treatment Period, the measurements and changes and/or percent changes from baseline over time will be summarized descriptively.

After the majority of subjects in the 36-week Treatment Period complete the Week 24 Visit, an interim analysis may be conducted to review the efficacy and safety data in order to select a single dose level for all subjects in Extension Treatment Period and for the remainder of their participation in the trial.

Pharmacokinetics:

Plasma concentrations of ARO-ANG3 will be measured in all subjects to evaluate predose and postdose levels throughout the 36-week Treatment Period per the SOA (Table 3).

All PK concentrations will be listed. The PK concentration data will also be included for Population PK analysis, which will be supported by separate analysis plan and reporting.

Pharmacodynamics:

Descriptive summaries by visit will be provided for the following exploratory pharmacodynamic (PD) parameter: ANGPTL3.

Immunogenicity (Anti-Drug Antibodies):

Changes from assay negative to positive and antibody titers will be summarized by dose and number of doses administered. Descriptive statistics of immunogenicity parameters will include mean, standard deviation (SD), minimum, and maximum.

See Schedule of Assessments Table 3 and Table 4 in Section 6.1.1.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

INVESTIGATOR'S AGREEMENT 2
PROCEDURES IN CASE OF EMERGENCY 3
1. SYNOPSIS 4
2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 15
3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 21
4. INTRODUCTION 25
4.1. Overview of Homozygous Familial Hypercholesterolemia 25
4.2. Overview of ARO-ANG3 Development 26
4.2.1. Mechanism of Action of ARO-ANG3 and Therapeutic Rationale 26
4.2.1.1. Small Interfering RNA Mechanism of Action 26
4.2.2. Preclinical Studies 27
4.2.3. Clinical Studies 28
4.3. Potential Risks of Study Participation 29
4.3.1. Embryo-Fetal 29
4.3.2. Liver Function 29
4.3.3. Injection Site Adverse Events 29
4.3.4. Glycemic Control 29
5. STUDY OBJECTIVES AND ENDPOINTS 30
5.1. Objectives 30
5.1.1. Primary Objective 30
5.2. Endpoints 30
5.2.1. Primary Endpoint 30
5.2.2. Secondary Endpoints 30
5.2.3. Exploratory Endpoints 31
6. INVESTIGATIONAL PLAN 31
6.1. Overall Study Design 31
6.1.1. Overview of Study Design 31
6.1.2. Informed Consent 39
6.1.3. Screening 39

6.1.4. Treatment Period and Optional Extension Treatment Period 39
6.1.5. Pharmacokinetics 40
6.1.6. Adverse Event Monitoring 40
6.1.7. Early Termination 40
6.1.8. Postdose Follow-Up Procedures 40
6.1.9. End of Study Procedures 41
6.2. Number of Subjects 41
6.3. Treatment Assignment 41
6.4. Dose Adjustment Criteria 41
6.4.1. Safety Criteria for Adjustment or Stopping Doses 41
6.5. Criteria for Study Termination 43
6.6. Rationale for Study Design 43
6.7. Rationale for Dose and Schedule of Administration 44
7. SELECTION OF STUDY POPULATION AND WITHDRAWAL OF SUBJECTS 45
7.1. Inclusion Criteria 45
7.2. Exclusion Criteria 47
7.3. Subject Withdrawal Criteria 49
8. TREATMENT OF SUBJECTS 49
8.1. Description of Study Drug 49
8.2. Restrictions and Concomitant Medications and Procedures 50
8.2.1. Fasting 50
8.2.2. Concomitant Medications 50
8.2.3. Permitted Medications 51
8.2.4. Apheresis Concomitant Procedure 51
8.3. Notification of General Practitioner 52
8.4. Treatment Compliance 52
8.5. Randomization 52
8.6. Emergency Contact with Principal Investigator 52
9. STUDY DRUG MATERIALS AND MANAGEMENT 52
9.1. Study Drug 52
9.2. Study Drug Packaging and Labeling 53
9.3. Study Drug Storage 53

9.4. Study Drug Handling 53
9.5. Study Drug Preparation 54
9.6. Study Drug Administration 54
9.7. Study Drug Accountability 54
10. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS 55
10.1. Pharmacokinetic Assessments 55
10.1.1. Sample Collection 55
10.1.2. Sample Analysis 55
10.2. Pharmacodynamic Assessments 56
10.2.1. Sample Collection 56
10.2.2. Sample Analysis 56
10.2.3. Additional Exploratory Analysis-Future Research Samples 56
11. ASSESSMENT OF EFFICACY 56
11.1. Efficacy Assessments 56
11.1.1. Serum LDL-C and Other Lipid Parameters 56
12. ASSESSMENT OF SAFETY 57
12.1. Safety Parameters 57
12.1.1. Demographic/Medical History 57
12.1.2. Vital Signs 57
12.1.3. Physical Examination 57
12.1.4. Electrocardiogram 57
12.1.5. Laboratory Assessments 58
12.1.6. Timing of Treatments and Procedures 59
12.1.7. Pregnancy Screen 60
12.2. Adverse Events 60
12.2.1. Definition of Adverse Events 60
12.2.1.1. Adverse Event 60
12.2.1.2. Serious Adverse Event 61
12.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events 61
12.4. Timing, Frequency, and Method of Detecting Adverse Events 62
12.5. Recording Adverse Events 62
12.6. Evaluating Adverse Events 62

12.6.1. Assessment of Severity 62
12.6.2. Injection Site Reactions 63
12.6.3. Assessment of Causality 63
12.7. Follow-up of Adverse Events 64
12.8. Prompt Reporting of Serious Adverse Events 64
12.8.1. Completion and Transmission of the Serious Adverse Event Reports 64
12.8.2. Serious Adverse Event Reports to the IRB/IEC 65
12.8.3. Regulatory Requirements for Reporting of Serious Adverse Events 65
12.8.4. Post-study Adverse Events 65
12.8.5. Serious Adverse Events Related to Study Participation 65
12.9. Pregnancy Reporting 65
13. STATISTICS 66
13.1. Statistical Considerations 66
13.2. Analysis Populations 66
13.3. Sample Size Considerations 66
13.4. Interim Analysis 66
13.5. Analysis Methods 67
13.5.1. Baseline Data 67
13.5.2. Efficacy Analysis 67
13.5.3. Safety Analysis 67
13.6. Other Analyses 68
13.6.1. Pharmacokinetics 68
13.6.2. Analysis of Immunogenicity (Anti-Drug Antibodies) Data 68
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 68
14.1. Study Monitoring 68
14.2. Protocol Deviations 69
14.3. Clinical Laboratory Certification and Reference Ranges 70
14.4. Audits and Inspections 70
14.5. Institutional Review Board/Independent Ethics Committee 70
15. ETHICS 70
15.1. Ethics Review 70
15.2. Ethical Conduct of the Study 71
15.3. Written Informed Consent 71

16. DATA HANDLING AND RECORDKEEPING 72
16.1. Inspection of Records 72
16.2. Retention of Records 72
16.3. Data Protection 73
16.4. Source Documents 73
17. PUBLICATION POLICY 73
17.1. Ownership 74
17.2. Confidentiality 74
18. LIST OF REFERENCES 75
APPENDIX 1. CONTRACEPTION 77
APPENDIX 2. LIVER-RELATED STUDY MODIFICATION AND FOLLOW-UP GUIDELINES 79
APPENDIX 3. GLYCEMIC CONTROL-RELATED GUIDELINES 81

LIST OF TABLES

Table 1: Emergency Contact Information....3
Table 2: Abbreviations....21
Table 3: Schedule of Assessments, 36-Week Treatment Period (Day 1 Through Week 36)....34
Table 4: Schedule of Assessments, 24-Month Optional Extension Treatment Period....37
Table 5: Stable Medication Requirements....51
Table 6: Study Drug Description....53
Table 7: Injection Number and Volume Per Dose Cohort....54
Table 8: Plasma PK Sampling Schedule....55
Table 9: Timing of Treatments and Procedures....59
Table 10: Liver-Related Study Monitoring and Stopping Guidelines for Subjects With ALT or AST Elevations....79

LIST OF FIGURES

Figure 1: Small Interfering RNA Mechanism of Action....27
Figure 2: Study Schema....33

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
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (same as SGPT)
ANGPTL3	angiopoietin-like protein 3
API	active pharmaceutical ingredient
ApoA	apolipoprotein A
ApoB	apolipoprotein B
ApoC	apolipoprotein C
ARO	Arrowhead Pharmaceuticals, Inc.
AST	aspartate aminotransferase (same as SGOT)
AUC	area under the time-concentration curve
AUC_{inf}	AUC from time 0 extrapolated to infinity
AUC_{last}	AUC from time 0 to the last quantifiable plasma concentration
BMI	body mass index
CABG	coronary artery bypass graft
cGMP	current Good Manufacturing Practice
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EFD	embryofetal development
EL	endothelial lipase
EOS	End of Study
ET	Early Termination

Abbreviation	Definition
EU	European Union
FDA	(US) Food and Drug Administration
FH	familial hypercholesterolemia
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GD	gestational day
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio
IFCC	International Federation of Clinical Chemistry
IP	investigational product
IRB	institutional review board
ISR	Injection site reaction
IWRS	interactive web response system
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LDLRAP1	low density lipoprotein receptor adaptor protein 1
LLN	lower limit of normal
LP	lipoprotein

Abbreviation	Definition
LPL	lipoprotein lipase
LVEF	left ventricular ejection fraction
MI	myocardial infarction
mRNA	messenger RNA
NAFLD	non-alcoholic fatty liver disease
NAG	N-acetylgalactosamine
NASH	non-alcoholic steatohepatitis
NCA	noncompartmental analysis
OLE	Open-label extension
OTC	over-the-counter
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin kexin type-9
PD	pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Preferred Term
PUC	preparative ultracentrifugation
Q12W	once every 12 weeks
RISC	RNA-induced silencing complex
RNAi	RNA interference
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
siRNA	small interfering RNA
SOA	Schedule of Assessments
SOC	System Organ Class
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
ULN	upper limit of normal

Abbreviation	Definition
VLDL-C	very low-density lipoprotein cholesterol

4. INTRODUCTION

4.1. Overview of Homozygous Familial Hypercholesterolemia

An emerging therapeutic target with relevance to hypercholesterolemia, hypertriglyceridemia, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) is angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 is a primarily hepatocyte synthesized member of the angiopoietin-like family of proteins. Its key role is regulation of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) metabolism. More specifically, ANGPTL3 inhibits lipoprotein lipase (LPL), which is responsible for TG hydrolysis in peripheral tissues (eg, adipose tissue, muscle). ANGPTL3 also inhibits endothelial lipase (EL) driven HDL-C metabolism and inhibits hepatocyte uptake of apolipoprotein B (ApoB) containing lipoproteins (LDL-C and very low-density lipoprotein cholesterol [VLDL-C]) through mechanisms at least partially independent of the low-density lipoprotein (LDL) receptor (Adam 2020). Given the inhibitory role of ANGPTL3 in the metabolism of various lipoproteins and TGs, reduced expression and reduced circulating levels of ANGPTL3 are expected to increase clearance of LDL-C, HDL-C, and TGs.

In humans, homozygous loss-of-function mutations in *ANGTPL3* lead to very low or undetectable serum ANGPTL3 and low plasma levels of LDL-C, HDL-C, and TGs, a condition referred to as familial combined hypolipidemia (Musunuru 2010). Heterozygous carriers of loss-of-function mutations in *ANGPTL3* have a lower risk of coronary artery disease than noncarriers (Dewey 2017; Stitziel 2017). Patients with compound heterozygous or homozygous loss-of-function mutations can have undetectable serum ANGPTL3 with reductions in LDL-C of >65%, TG by >70%, and reductions in HDL-C by approximately 40% when compared to controls (Minicocci 2013). To date, no adverse clinical phenotype such as hepatic steatosis, obesity, or other metabolic derangements have been reported in *ANGPTL3*-deficient subjects (Dewey 2017). Importantly, the low HDL-C observed in *ANGPTL3* deficiency is due to enhanced EL activity and does not appear to increase risk of cardiovascular disease. The genetic validation consisting of low LDL-C and TGs coupled with reduced cardiovascular disease risk in *ANGPTL3*-deficient patients and proposed mechanism for these metabolic findings has promoted interest in methods capable of suppressing ANGPTL3.

Familial hypercholesterolemia (FH), including heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) variants, represents a unique case where LDL-C lowering therapies not requiring a functional LDL receptor may have benefit. Familial hypercholesterolemia is an autosomal co-dominant condition with elevated LDL-C often above 95th percentile for age and gender. If left untreated, HoFH leads to early clinical manifestations of coronary artery disease. HeFH has a frequency of approximately 1 per 500, with HoFH (the more severe phenotype) occurring in 1 per 250,000. Most cases of HoFH are due to mutations in the low density lipoprotein receptor (*LDLR)* gene coding for the LDL receptor (Ridker 1997). Key mechanisms of action of statins and of proprotein convertase subtilisin kexin type-9 (PCSK9) inhibitors are inhibition of cholesterol synthesis and enhanced hepatic clearance of LDL-C through upregulation of the hepatocyte LDLR (Ballantyne 2015). Thus, patients with HoFH due to dysfunctional or absent LDLR can be resistant to standards of care such as statins and even resistant to alternatives such as PCSK9 inhibitors. Patients with HoFH are therefore a

population with a particularly high need for additional therapy with a mechanism working outside of the LDL receptor, such as therapeutic ANGPTL3 inhibition.

One method of targeting serum ANGPTL3 is to leverage RNA interference (RNAi) mediated hepatic knockdown of this gene to prevent its production. This approach has important advantages including less frequent dosing intervals and subcutaneous (SC) dosing.

In this clinical study, ARO-ANG3, an RNAi-based therapeutic targeting ANGPTL3, will be evaluated in subjects with HoFH.

4.2. Overview of ARO-ANG3 Development

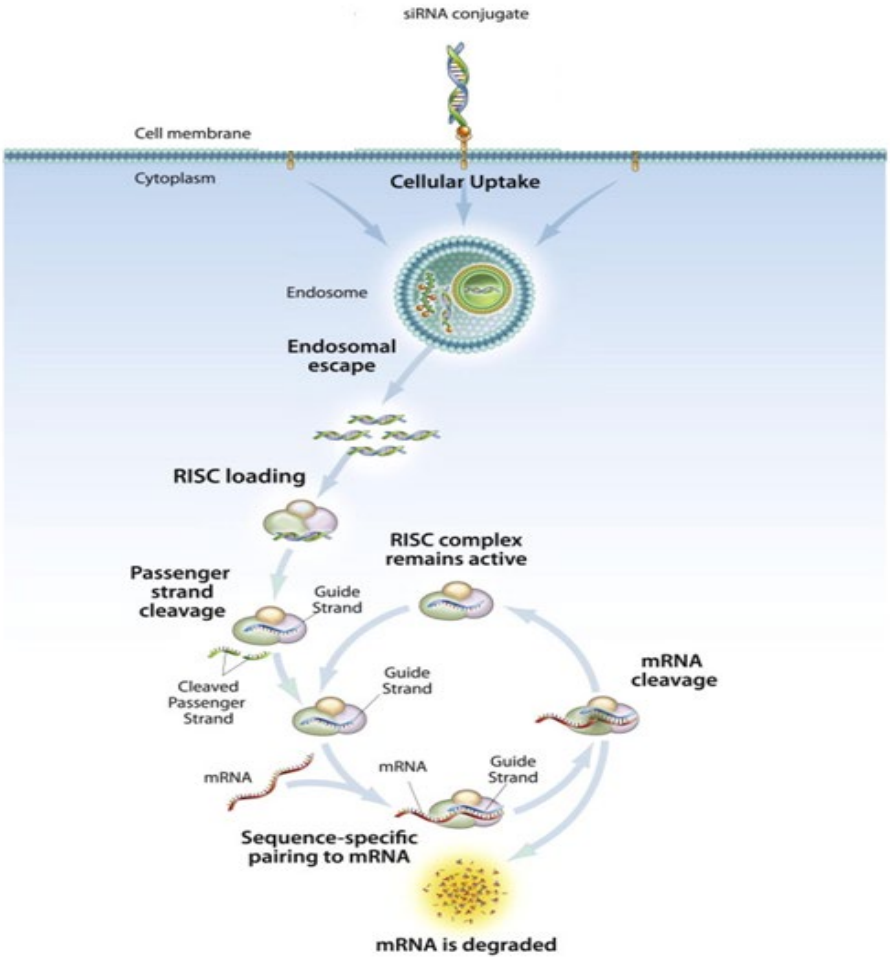
A brief overview of existing information on ARO-ANG3 Injection (zodasiran) is provided below; a comprehensive review of available data is contained in the Investigator's Brochure (IB) provided by the sponsor. The IB should be reviewed prior to initiating the study.

4.2.1. Mechanism of Action of ARO-ANG3 and Therapeutic Rationale

4.2.1.1. Small Interfering RNA Mechanism of Action

An RNAi-based therapeutic targeting ANGPTL3 has the potential to treat HoFH in a fundamentally different manner than current therapies. RNAi is a naturally occurring phenomenon by which small interfering RNAs (siRNAs) trigger a sequence-specific down-modulation of gene expression. RNAi triggers refer to synthetic siRNAs designed to target specific messenger ribonucleic acid (mRNA) expression (Figure 1). By delivering the RNAi trigger targeting ANGPTL3 to the liver, it is possible to silence expression of ANGPTL3 mRNA in hepatocytes. Since ANGPTL3 is exclusively expressed in hepatocytes, silencing of ANGPTL3 mRNA is expected to reduce both intrahepatic and plasma ANGPTL3 protein levels. Significant reduction in ANGPLT3 levels is expected to reduce plasma LDL-C and TG levels and may lead to the reduction of risk of coronary heart disease and cardiovascular events associated with hypertriglyceridemia and LDL-C in subjects with persistent dyslipidemia. Targeting ANGPTL3 may also improve insulin resistance and hepatic steatosis. The RNAi trigger molecule in ARO-ANG3 Injection was designed to avoid activity against other human mRNAs, microRNA, and other noncoding RNAs, and to avoid acting outside of the liver. Thus, ARO-ANG3 is not expected to have off-target effects.

Figure 1: Small Interfering RNA Mechanism of Action



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

4.2.2. Preclinical Studies

The sponsor is conducting a comprehensive preclinical program to support the SC administration of ARO-ANG3. Studies of potential clinical significance and relevance to this protocol are summarized below.

Proof-of-concept studies in animal models support the use of siRNA against ANGPTL3 as a potential treatment of mixed dyslipidemia. Details regarding preclinical pharmacology, pharmacokinetics (PK), and toxicology results are provided in the IB.

- Preclinical pharmacology of ADS-004, the active pharmaceutical ingredient (API) in ARO-ANG3, shows that ADS-004 treatment in transgenic mice (TgANG3) resulted in dose-dependent reduction of hepatic ANGPTL3 mRNA levels, which correlated with reduced serum ANGPTL3 of >90%. Reductions in serum ANGPTL3 were associated with reductions in serum lipids (maximum mean reduction of 91% in TG, 45% in total cholesterol [TC], and 64% in LDL-C).

- Similar reductions in liver and serum ANGPTL3 were also observed after ADS-004 doses in a diet-induced dyslipidemic rhesus monkey model. ARO-ANG3 has been well tolerated in rats and in nonhuman primate toxicology studies.
- Although the clinical study enrollment is restricted to subjects at least 16 years of age, in due diligence to patient safety, a pediatric weight of evidence assessment was conducted in compliance with International Council for Harmonisation (ICH) E11 guidance. The following data was evaluated under this assessment:
  - The lack of effects on developing organ systems in the embryofetal development (EFD) study in rats when dosed daily on gestational days (GD) 6 to 17 at 30 mg/kg/day (9- or 6-fold safety margin for the 200 or 300 mg dose, respectively) and in the rabbit EFD study when dosed once on GD11 at 50 mg/kg (15- or 10-fold safety margin for the 200 or 300 mg dose, respectively)
  - Lack of adverse events (AEs) in rats for mating and fertility at 100 mg/kg (30- or 20-fold safety margin for the 200 or 300 mg dose, respectively)
  - The existing adult clinical data in which ARO-ANG3 has generally been well tolerated, with no treatment-emergent adverse event (TEAE)-related study or drug discontinuations, and no dose-limiting toxicities. In both normal healthy volunteer and patient cohorts, there have been no safety signals from laboratory parameters, including those for liver and renal function, as well as platelet counts. Further, there have been no patterns of adverse changes in vital signs, or clinically significant changes in electrocardiograms (ECGs), indicating an acceptable safety profile.
  - The high selectivity and specificity of ARO-ANG3, as demonstrated by the lack of silencing of in silico identified off-target genes through in vitro testing.
  - The high unmet medical need of HoFH patients

  This data supports the conclusion that adequate data exists for the safety of ARO-ANG3 for administration to patients as young as 12 years of age. This conclusion is based upon the lack of adverse effects on organ systems still developing in this patient demographic when ARO-ANG3 was evaluated for safety in general toxicology studies and in studies of reproductive and developmental milestones. This conclusion is in keeping with the principles of the ICH E11 guideline where the most heavily weighted criteria to be considered are the age of the target pediatric population and the effects on the developing organ system during the conduct of the clinical study.
- Results of non-Good Laboratory Practice (GLP) and GLP short-term and chronic toxicology studies are reviewed in the IB.

4.2.3. Clinical Studies

The sponsor has completed a Phase 1/2a single- and multiple-dose study (AROANG1001) to evaluate the safety, tolerability, PK, and pharmacodynamic (PD) effect of ARO-ANG3 in adult healthy volunteers and subjects with dyslipidemia including in subjects with HeFH. Details regarding Phase 1/2a study results can be found in the IB. The sponsor has also initiated a

double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of ARO-ANG3 in adults with mixed dyslipidemia (AROANG3-2001).

4.3. Potential Risks of Study Participation

4.3.1. Embryo-Fetal

Limited GLP toxicology and clinical studies have been conducted. Accordingly, 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).

4.3.2. Liver Function

ARO-ANG3 targets the liver. siRNA literature has described alanine aminotransferase (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-ANG3 sense and antisense molecules have been screened for potential mRNA and microRNA homology and sequences with homology were excluded from consideration. Thus, no such off-target effects are anticipated. In the AROANG1001 study, infrequent, transient mild to moderate elevations in ALT were seen (refer to IB for details) without accompanying elevation in international normalized ratio (INR) or total bilirubin. To mitigate this risk, this protocol has stopping rules for ALT and aspartate aminotransferase (AST) elevation. Blood samples will be drawn frequently to evaluate liver injury and function.

4.3.3. Injection Site Adverse Events

Other SC administered siRNA drug candidates in clinical studies have been associated with mild to moderate injection site reactions (ISRs) (eg, pain, erythema). Generally mild and transient injection site AEs have been reported in the AROANG1001 study (refer to IB for details). In this study, steps will be taken to minimize ISRs such as rotating injection sites and allowing the ARO-ANG3 solution to reach room temperature prior to injection.

4.3.4. Glycemic Control

An administrative analysis in the ongoing Phase 2 AROANG3-2001 clinical trial observed an imbalance in changes in HbA1c over time, with increased HbA1c values observed in subjects who had pre-existing diabetes at baseline and particularly in a subset of subjects in the highest (200 mg) ARO-ANG3 dose group.

To mitigate the risk of worsening glycemic control, investigators will be encouraged to evaluate diabetes status and adjust diabetes treatment according to clinical practice and diabetes care guidance). 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 the protocol pre-established level, a number of criteria for study drug discontinuation have been established (Appendix 3).

Routine monitoring of serum 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 and Table 4) and Section 10.2.1).

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

- To evaluate the efficacy and safety of ARO-ANG3 in subjects with HoFH

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

5.2. Endpoints

5.2.1. Primary Endpoint

- Percent change from baseline to Week 24 in fasting calculated LDL-C and LDL-C using preparative ultracentrifugation (PUC)

5.2.2. Secondary Endpoints

The following secondary endpoints will be evaluated:

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

- Percent and absolute change from baseline in fasting TG at each scheduled assessment
- Subject incidence of treatment-emergent adverse events (TEAEs)
- Subject incidence of anti-drug antibodies (ADAs) to ARO-ANG3 at each scheduled assessment
- Proportion of subjects who met US apheresis eligibility criteria of LDL-C ≥300 mg/dL (see US [National Lipid Association] Lipid Apheresis Criteria) at Week 24
- Proportion of subjects who meet European Union (EU) apheresis eligibility criteria (see German Apheresis Working Group) at Week 24

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

- Percent and absolute change from baseline in fasting calculated LDL-C and fasting LDL-C (using PUC), fasting ANGPTL3, fasting total ApoB, fasting HDL-C, fasting non-HDL-C, fasting VLDL-C, fasting TC, and fasting TG at each scheduled assessment
- Subject incidence of ADAs to ARO-ANG3 at each scheduled assessment
- Subject incidence of TEAEs

5.2.3. Exploratory Endpoints

- Change from baseline in other fasting lipid parameters at each scheduled assessment in the 36-week Treatment Period as well as over time during the Extension Treatment Period (LDL/HDL ratio, ApoB-48, lipoprotein [LP][a], ApoB-100, ApoC-III, ApoC-II, ApoA-I, and ApoA-V)
- Plasma PK concentrations of ARO-ANG3 at each scheduled assessment

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

6.1.1. Overview of Study Design

This is an open-label clinical study with an optional Extension Treatment Period. This study will be conducted in subjects with documented HoFH based on genotype or clinical criteria at Screening. The duration of the study is approximately 34 months from Screening. The study activities and durations will be Screening (up to 8 weeks) Treatment Period (up to 36 weeks), and to the End of Study (EOS) Extension Treatment Period (up to 24 months). The SOA is presented in Table 3 and Table 4.

Overall Screening Period (≤8 Weeks)

Subjects will have screening laboratory measurements and will be assessed for eligibility. Subjects who have met all of the protocol eligibility criteria during Screening may be enrolled to receive ARO-ANG3.

Screening Visits 1 and 2

Screening Visit 1 procedures will be conducted during Day -56 to Day -1. At Screening Visit 1, the subject will sign the informed consent before proceeding to any procedures. Screening Visit 2 will occur during Day -28 to Day -1. Screening Visit 1 assessments may be completed at Screening Visit 2, at the Investigator's discretion, only if all required assessments can be completed within 28 days prior to Day 1. See SOA (Table 3). Screening Visits 1 and 2 may occur on the same day.

Open-Label Treatment Period

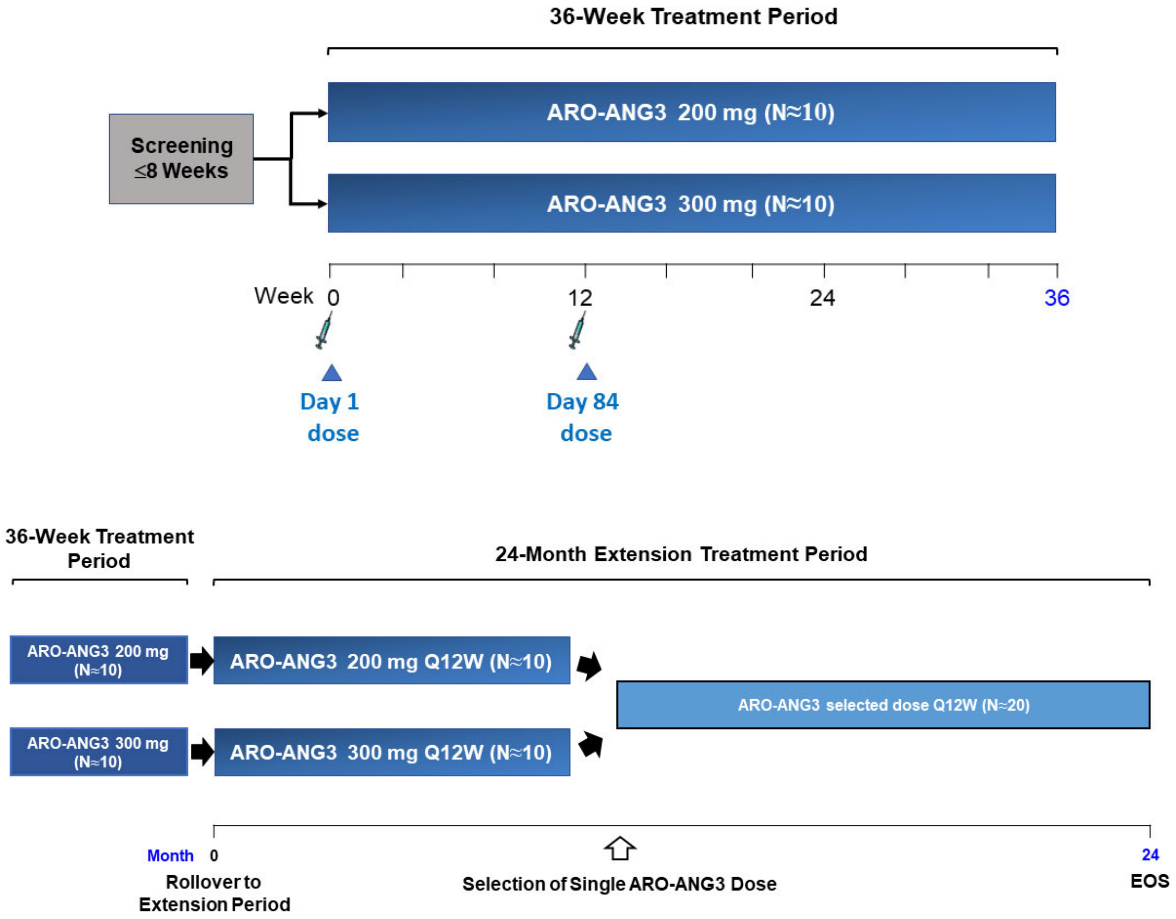
Up to approximately 20 subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive 2 doses of ARO-ANG3 200 mg or 300 mg on Day 1 and Day 84 and will be evaluated over a 36-week period (see Figure 2). For a subject who discontinues from the study prematurely, if their serum ANGPTL3 level at the Early Termination (ET) visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception (Appendix 1) until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value.

Optional Extension Treatment Period

After completing the Week 36 Visit, subjects may opt to continue in the 24-month Extension Treatment Period (see Figure 2). Unless otherwise specified, a month refers to 28 consecutive days. Subjects who do not opt to continue in the Extension Treatment Period will complete Week 36/ET Visit assessments. Subjects in the Extension Treatment Period will complete study visits as specified in the SOA (Table 4) and will be dosed quarterly (once every 12 weeks [Q12W]). Initially, subjects will receive the same dose level received during the 36-week Treatment Period. However, dose levels in the Extension Treatment Period may be consolidated to a single dose level based on sponsor decision after an interim analysis of safety and efficacy data at Week 24 of the 36-week Treatment Period. The interim analysis will be conducted once the data is available for a majority of enrolled subjects. Once a single dose has been selected by the sponsor, all subjects will be transitioned to the selected dose level. See the SOA Table 4.

All subjects who participated in Study AROANG3-2003 may enroll into the OLE Period of Study AROANG3-3001 (if they meet the eligibility criteria for that separate study). If a subject's serum ANGPTL3 level at the Extension Treatment Period Month 24 (EOS) visit or ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value, they enter the OLE of Study AROANG3-3001 (if they meet the eligibility criteria for that separate study), or until they have completed 1.5 years of monitoring, whichever occurs earlier.

Figure 2: Study Schema



Abbreviations: EOS=End of Study; N=number of subjects; Q12W=once every 12 weeks.

Table 3: Schedule of Assessments, 36-Week Treatment Period (Day 1 Through Week 36)

Assessment	Screening Visit 1 Days -56 to -1 [a]	Screening Visit 2 Days -28 to -1 [a]	Day 1 [b]	Day 2	Week 4 Day 28	Week 8 Day 56	Week 12 Day 84 [b]	24 Hours Post-dose	Week 16 Day 112	Week 20 Day 140	Week 24 Day 168	Week 28 Day 196	Week 32 Day 224	Subjects Who Do Not Opt to Continue in Extension Treatment Period: Week 36 Day 252 /Early Termination Visit [n]
Visit Windows (days)					±3	±3	±5		±5	±5	±5	±5	±5	
Informed Consent	X													
Query Stable Medication Compliance	X	X	X		X	X	X		X	X	X	X	X	X
Eligibility Criteria [c]	X	X	X											
Demographics/ Medical History	X													
Physical Examination [d]	X		X		X	X	X		X	X	X	X	X	X
BMI (height and body weight) [e]	X		X		X	X	X		X	X	X	X	X	X
Concomitant Medication/Therapies	X	X	X		X	X	X		X	X	X	X	X	X
12-lead ECG [f]		X	X				X							X
Urine Pregnancy Test (female subjects of childbearing potential) (predose on dosing days)	X	X	X [b]		X	X	X [b]		X	X	X	X	X	X
FSH (females, post-menopause confirmation)	X													
Vital Signs (BP, temp, HR, RR)	X	X	X		X	X	X		X	X	X	X	X	X

Assessment	Screening Visit 1 Days -56 to -1 [a]	Screening Visit 2 Days -28 to -1 [a]	Day 1 [b]	Day 2	Week 4 Day 28	Week 8 Day 56	Week 12 Day 84 [b]	24 Hours Post-dose	Week 16 Day 112	Week 20 Day 140	Week 24 Day 168	Week 28 Day 196	Week 32 Day 224	Subjects Who Do Not Opt to Continue in Extension Treatment Period: Week 36 Day 252 /Early Termination Visit [n]
Visit Windows (days)					**±3**	**±3**	**±5**		**±5**	**±5**	**±5**	**±5**	**±5**	
HIV, HBV, HCV screen		X												
Clinical Laboratory Tests (predose on dosing days) [g,h]		X	X [b]		X	X	X [b]		X	X	X	X	X	X
Serum Triglyceride (predose on dosing days) [g,h]		X	X [b]		X	X	X [b]		X	X	X	X	X	X
LDL-C (predose on dosing days) [g,h]		X	X [b]		X	X	X [b]		X	X	X	X	X	X
Other Lipid/Pharmacodynamic Parameters (predose on dosing days) [g,h]			X [b]		X	X	X [b]		X	X	X	X	X	X [i]
Hemoglobin A1c		X	X				X				X			X
Plasma PK [j]			X				X							
Genotyping [k]	X													
ARO-ANG3 Administration			X [l]				X [l]							
Postdose Follow-up [m]				X				X						
Anti-drug Antibodies (predose on dosing days)			X [b]		X		X [b]		X		X			X
Adverse Events Collection			X	X	X	X	X	X	X	X	X	X	X	X
Future Research Samples [o]			X											

Abbreviations: BMI=body mass index; BP=blood pressure; ECG=electrocardiogram; ET=Early Termination; FSH=follicle-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; LDL-C=lowering low-density lipoprotein cholesterol; PE=physical exam; PK=pharmacokinetic; RR=respiration rate; temp=temperature; TG=triglyceride.

[a] Screening Visits 1 and 2 may occur on the same day.

[b] Assessments completed on Day 1 and all other dosing days **are to be done predose** unless otherwise specified.

[c] Review of demographics and medical history, physical examination, BMI, concomitant medications, vital signs, FSH (females, post-menopause confirmation), and genotyping (if required) may occur up to 8 weeks (56 days) prior to Day 1 during Screening Visit 1. All other eligibility criteria assessments including laboratory value review must be completed within 28 days prior to Day 1 at Screening Visit 2. Some eligibility assessments may be repeated at both Screening Visit 1 and Screening Visit 2.

[d] A complete physical exam (PE) is to be performed at Screening and ET. A symptom-directed PE is to be performed at all other designated visits. Genitourinary exam may be deferred.

[e] Height (cm) only at Screening Visit 1; weight (kg) at all indicated visits.

[f] On nondosing days, ECG will be performed at a single timepoint prior to venipuncture and any invasive procedures. On dosing days, ECGs are to be completed predose, then 30 minutes (±30 minutes) and 2 hours (±30 minutes) postdose. Each ECG will be performed prior to any invasive procedures (eg, venipuncture). See Section 12.1.4.

[g] Blood and urine samples will be collected at Screening after obtaining informed consent. All laboratory assessments are to be conducted in the fasting state (no food or drink other than water) for at least 10 hours prior to sample collection (Section 10.2, Section 11.1.1, and Section 12.1.5) and on stable background medications (Section 7.1 and Section 8.2). For subjects who undergo apheresis, the apheresis procedure should be conducted at least 48 hours (up to 96 hours) ***after*** the laboratory assessments are completed. For subjects with scheduled apheresis and same day dosing, laboratory assessments are to be performed ***prior*** to apheresis; see Section 8.2.4. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Appendix 3).

[h] Beginning predose Day 1, fasting TG and LDL-C will be included as part of lipid/pharmacodynamic parameter collection. See Section 11.1.1.

[i] For subjects who discontinue from the study prematurely, if their serum ANGPTL3 level at the ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months and subjects of childbearing potential will continue use of highly effective contraception (see Appendix 1) until levels have returned to at least 70% of the subject's baseline value.

[j] Whole blood for the plasma PK samples will be drawn at predose, 30 minutes, and 2 hours postdose following the first and last doses. If the recommended postdose PK sample was not collected, every attempt should be made to collect this PK sample as soon as possible within the same study visit, no later than 48 hours postdose. See Section 10.1.

[k] New sample is not required if source-verifiable historical genotype is available. Genotype for HoFH related and *Lipg* mutation.

[l] For subjects who will have apheresis conducted on a **nondosing** day, ARO-ANG3 dosing should be completed a minimum of 48 hours (up to 96 hours) before the next scheduled apheresis to allow the study drug to be disposed from plasma. For subjects who will have apheresis conducted on a **dosing** day, ARO-ANG3 dosing is to occur ***after*** the apheresis procedure is completed; see Section 8.2.4.

[m] Contact (in person or via telephone) will be made to each subject and documented to verify adverse events occurring over the 24 hours following doses at Day 1 and Day 84.

[n] The Week 36 Day 252 ET visit is for subjects who are ***not*** continuing into the Extension Treatment Period. See Section 6.1.7 for more details about ET procedures. For subjects continuing into the Extension Treatment Period, see Table 4 for the Week 36/Day 252 procedures.

[o] With prior written consent a separate blood sample will be collected at Day 1 or at a subsequent study visit and reserved for research (outside of the main study). See Section 10.2.3.

Table 4: Schedule of Assessments, 24-Month Optional Extension Treatment Period

Assessments	24-Month Extension Treatment Period										
		Extension Treatment Period (Month)									
	Extension Period Day 1 [a] Week 36 Visit/ Day 252	1 [a]	2 [a]	3 [a]	6 [a]	9 [a]	12 [a]	15 [a]	18 [a]	21 [a]	24/EOS/ET
Visit Windows (days)	+5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Informed Consent to Extension Treatment Period	X										
Query Stable Medication Compliance	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (symptom directed) [b]	X	X	X	X	X	X	X	X	X	X	X
BMI (height and body weight) [c]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications/Therapies	X	X	X	X	X	X	X	X	X	X	X
Single 12-Lead ECG [d]	X			X	X	X	X	X	X	X	X
Urine Pregnancy Test (female subjects of childbearing potential) (predose on dosing days)	X [a]	X	X	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X
Vital Signs (BP, temperature, respiratory rate, heart rate)	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests (predose on dosing days) [e,f]	X [a]	X	X	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X
Lipid/Pharmacodynamic Parameters (predose on dosing days) [e,f,g]	X [a]	X	X	X [a]	X [a]	X[a]	X [a]	X [a]	X [a]	X [a]	X [g]
Hemoglobin A1c	X [a]			X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X
ARO-ANG3 Administration	X [h]			X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	X [h]	
Anti-drug Antibodies (predose on dosing days)	X [a]	X		X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X
Adverse Events Collection	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI=body mass index; BP=blood pressure; ECG=electrocardiogram; EOS=End of Study; ET=Early Termination; LDL-C=lowering low-density lipoprotein cholesterol; PE=physical exam; TG=triglyceride.

[a] Assessments on dosing days **are to be done predose** unless otherwise specified. Unless otherwise specified, a month refers to 28 consecutive days.

[b] A complete physical exam (PE) is to be performed at EOS/ET. A symptom-directed PE is to be performed at all other designated visits. Genitourinary exam may be deferred.

[c] Weight (kg) at all indicated visits.

[d] On dosing days, ECGs are to be completed predose, then 30 minutes (±30 minutes) and 2 hours (±30 minutes) postdose. ECGs will be performed prior to any invasive procedures (eg, venipuncture). See Section 12.1.4.

[e] All laboratory assessments are to be conducted in the fasting state (no food or drink other than water) for at least 10 hours prior sample collection (Section 10.2, Section 11.1.1, and Section 12.1.5) and on stable background medications (Section 7.1 and Section 8.2). For subjects who undergo apheresis, the apheresis procedure should be conducted at least 48 hours (up to 96 hours) ***after*** the laboratory assessments are completed. For subjects with scheduled apheresis and same day dosing, laboratory assessments are to be performed ***prior*** to apheresis; see Section 8.2.4. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Appendix 3).

[f] Beginning predose Day 1, fasting TG and LDL-C will be included as part of lipid/pharmacodynamic parameter collection. See Section 11.1.1.

[g] For a subject who discontinues from the study prematurely, if their serum ANGPTL3 level at the ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception (see Appendix 1) until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value, they enter the OLE of Study AROANG3-3001 (if they meet the eligibility criteria for that separate study), or until they have completed 1.5 years of monitoring, whichever occurs earlier.

[h] For subjects who will have apheresis conducted on a **nondosing** day, ARO-ANG3 dosing should be completed a minimum of 48 hours (up to 96 hours) before the next scheduled apheresis to allow the study drug to be disposed from plasma. For subjects who will have apheresis conducted on a **dosing** day, ARO-ANG3 dosing is to occur ***after*** the apheresis procedure is completed; see Section 8.2.4.

6.1.2. 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. Study participation includes all screening procedures, as well as any wash-out of excluded medications.

It is the responsibility of the Principal Investigator (PI) (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 PI (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 PI 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 PI 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 Informed Consent Form (ICF) to retain.

6.1.3. Screening

A screen failure occurs when a subject who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Subjects who fail screening and subsequently rescreen should be assigned a new participant number after being screen failed from the originally assigned subject number. The Screening Period will last up to 8 weeks (Day -56 to Day -1).

6.1.4. Treatment Period and Optional Extension Treatment Period

The duration of the study is approximately 34 months from Screening. The study activities and durations will be Screening (up to 8 weeks), Treatment Period (up to 36 weeks), and EOS Extension Treatment Period (up to 24 months). Unless otherwise specified, a month refers to 28 consecutive days.

6.1.5. Pharmacokinetics

Whole blood for the plasma PK samples will be drawn predose and 30 minutes and 2 hours postdose, following the first and last doses. If the recommended postdose PK sample was not collected, every attempt should be made to collect this PK sample as soon as possible within the same study visit, no later than 48 hours postdose.

6.1.6. 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), 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 pre-existing 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 within 24 hours of 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 PI 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 PI will promptly notify the sponsor. Laboratory or diagnostic (eg, ECG) abnormalities will be reported as AEs if considered clinically significant by the PI. Laboratory or diagnostic assessment abnormalities not reported as AEs are not to be reported as clinically significant in the study database.

6.1.7. Early Termination

If a subject discontinues from the study prematurely, every reasonable effort will be made to perform the ET 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 and Table 4) will be completed. Subjects who discontinue ARO-ANG3 due to an SAE will be encouraged to remain available for follow-up for medical monitoring until resolution.

If a subject's serum ANGPTL3 level at the ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months and subjects of childbearing potential will continue use of highly effective contraception (Appendix 1) until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value.

6.1.8. Postdose Follow-Up Procedures

After IP dosing in the 36-week Treatment Period, contact will be made to each subject and documented to verify AEs occurring over the 24 hours following IP dose at Day 1 and Day 84.

6.1.9. End of Study Procedures

End of Study and Extension Treatment Period

Subjects will have the option to enter a 24-month Extension Treatment Period once they have completed study treatment and the Week 36 Visit. All subjects who participated in Study AROANG3-2003 may enroll into the OLE Period of Study AROANG3-3001 (if they meet the eligibility criteria for that separate study).

End of Study and Subjects Not Entering the Extension Treatment Period

Subjects who complete the Week 36 Visit and do not elect to enter the 24-month Extension Treatment Period will still be required to complete follow-up procedures:

- For a subject who discontinues from the study prematurely, if their serum ANGPTL3 level at the ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception (see Appendix 1) until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value.

6.2. Number of Subjects

A total of up to approximately 20 subjects will be enrolled in the study, up to approximately 10 subjects in each of 2 cohorts.

6.3. Treatment Assignment

All potential subjects who sign an informed consent at Screening will receive a unique identifier. For subjects who are deemed eligible, this unique identifier will become the subject's permanent study subject ID. On Day 1, eligible subjects will be randomized in a 1:1 ratio into ARO-ANG3 200 mg or 300 mg dose groups. Subjects participating in the Extension Treatment Period will initially continue to receive the dose level assigned in the initial 36-week Treatment Period. Thus, subjects who were previously assigned ARO-ANG3 200 mg or 300 mg in the 36-week Treatment Period will receive ARO-ANG3 at the corresponding dose level in the Extension Treatment Period until a final dose is selected by the sponsor. After the majority of subjects in the 36-week Treatment Period complete the Week 36 Visit and a final dose has been selected, all subjects in the Extension Treatment Period will be transitioned to receive ARO-ANG3 at the selected dose for the remainder of their duration in the Extension Treatment Period.

Subjects who drop out prior to their EOS visit for reasons other than an AE may be replaced.

6.4. Dose Adjustment Criteria

6.4.1. Safety Criteria for Adjustment or Stopping Doses

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

- Any confirmed pregnancy will lead to permanent discontinuation of study drug dosing of that subject.

- In the case of 2 or more similar SAEs, both considered at least possibly related to ARO-ANG3 in 2 subjects, a detailed safety assessment including review of aggregate safety data will be performed immediately by the sponsor after the second SAE is notified to determine if the study remains safe to proceed, should be discontinued, or should continue but with amendments.
- **Normal baseline transaminases**: In subjects with normal (per central laboratory reference range) AST or ALT levels on Day 1, treatment-emergent elevations >3× upper limit of normal (ULN) must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 2 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 2. The subject will remain on study follow-up visits until EOS as per the SOA (Table 3 and Table 4)
  - 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
- **Elevated baseline transaminases**: 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), as specified below, must be confirmed by repeat blood draw within 72 hours of initial results. Refer to Appendix 2 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 2.

Study drug discontinuation criteria for increased HbA1c

- Regarding HbA1c discontinuation criteria, participants should discontinue IP if they meet the following criteria (refer to Appendix 3):

- 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 determinations will be followed for 6 months after their last dose per the Schedule of Assessments. Treatment modification guidelines for subjects with elevated HbAc1 are provided in Appendix 3.

The sponsor or Investigator can discontinue any subject at any time.

The sponsor, in consultation with the Investigator, may pause dosing of additional subjects in the study to allow for time to evaluate safety data and recommend the action to be taken, which may include, but is not limited to, one of the following:

- The study may continue without modifications
- The study may continue with modifications
- The study should be terminated
- The study should be temporarily suspended
- Other changes

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

The primary objective of the study is to evaluate the safety and efficacy of ARO-ANG3 in subjects with documented HoFH based on genotype or clinical criteria at Screening.

The primary rationale for the study of ARO-ANG3 in HoFH subjects is to evaluate the effect of an ANGPTL3 silencing siRNA therapy with long duration of action (eg, 12 weeks of near maximal effect after a single dose) in a patient population with hypercholesterolemia due to defective LDL-C receptor activity. ANGPTL3 inhibition lowers TG and LDL-C through a non-LDL receptor dependent mechanism (Adam 2020). This may have benefit in patients with HoFH who lack functional LDL-C receptor activity. Studies with monoclonal antibodies (evinacumab) targeting ANGPTL3 in a HoFH population have demonstrated approximately 50% lowering of LDL-C even on top of standard of care (Raal 2020). However, evinacumab requires monthly

intravenous infusions. ARO-ANG3 will be studied as a Q12 week SC injection. Additionally, compared with the potent effect of ARO-ANG3 in lowering TG levels, other first-line therapies have modest effects on TGs. For example, subjects with severe hypertriglyceridemia receiving omega-3 fatty acid only had a 33% placebo-adjusted reduction in TG (Bays 2011) and subjects with mild TG elevations receiving gemfibrozil had a 31% reduction in TG (Rubins 1999). Thus, additional TG and LDL-C lowering effect is expected when ARO-ANG3 is used even on top of optimal lipid-lowering therapy. Concomitant use of other prescription or over-the-counter (OTC) lipid management regimens (eg, nicotinic acid or niacin, omega-3 fatty acids) will be permitted as long as the subject has maintained a stable regimen for the specified duration prior to collection of screening laboratory tests and for the duration of the study participation (Table 5).

The duration of the treatment is intended to ensure adequate exposure to ARO-ANG3 to evaluate the safety and efficacy and to assess the duration of treatment efficacy. The primary analysis will be at Week 24.

6.7. Rationale for Dose and Schedule of Administration

The rationale for the doses selected is primarily from the single escalating and multiple escalating dose components of the AROANG1001 Phase 1/2a clinical study. Based on efficacy and safety data from that study, 200 mg ARO-ANG3 was the highest dose selected for use in a separate Phase 2b study of subjects with mixed dyslipidemia. Overall, there was no appreciable difference in the safety profile of the 200 mg dose compared with higher or lower dose levels in the Phase 1 study, as described in the safety data summary provided in the IB. In the Phase 1 clinical study, there was a modest dose response in ANGPTL3 reduction with dose escalation from 200 mg to 300 mg. However, this ANGPTL3 dose response did not clearly translate into improved LDL-C reductions in healthy volunteers and in HeFH patients. HoFH patients have much higher LDL-C and thus the additional reduction in ANGPTL3 that could be achieved with 300 mg may yield additional LDL-C reductions in the HoFH population. As such, both 200 mg and 300 mg doses of ARO-ANG3 will be investigated in this Phase 2 study in the open-label 36-week Treatment Period. Subjects participating in the 24-month Extension Treatment Period will initially continue to receive the dose level assigned in the initial 36-week Treatment Period. However, all subjects in the Extension Treatment Period may be later switched to a single dose level based on a primary analysis of safety and efficacy data.

In the Phase 1 study evaluating ARO-ANG3 in healthy volunteers, single doses and multiple doses (Days 1 and 29) of 35, 100, 200, or 300 mg ARO-ANG3 consistently reduced serum LDL-C and TG levels through Week 12. Reductions in LDL-C reached a nadir at -23% following a single dose of ARO-ANG3, while TG reduction reached a nadir at -66% from baseline with the 200 mg dose. In the multi-dose cohorts, the 200 mg dose maintained >40% reductions in LDL-C from Week 4 through Week 16 (Day 113) and >60% reduction in TG from Week 1 through Week 16. A clearer dose response is seen with ANGPTL3 with dose-dependent decreases in ANGPTL3 demonstrated with increasing single doses. Summary PD data are provided in the IB.

The observations regarding an increase in HbA1c in subjects treated with ARO-ANG3 made during an administrative analysis from the ongoing Phase 2 study have been addressed by the updated risk mitigation strategies in the study protocols as outlined in Section 4.3.4. It is also important to note that epidemiological studies have shown a lower prevalence of diabetes in

patients with HoFH when compared to the general population. In some recent publications, prevalence of diabetes in the HoFH population has been reported to be as low as 0.8%. Given that increase in HbA1c with ARO-ANG3 administration was mainly observed in subjects with pre-existing diabetes (especially those with poorly controlled diabetes), these findings are unlikely to impact subjects with HoFH (Hegele-Baass 2020). The results of the administrative analysis also demonstrate a robust and clinically relevant pharmacodynamic profile for ARO-ANG3 in the patient populations being studied. Based on this information, the benefits of more effective LDL and remnant cholesterol lowering (such as reduced risk of cardiovascular disease) outweigh the risk of worsening diabetes. Therefore, in subjects with HoFH, the 200 mg dose will continue to be evaluated until further evidence becomes available in this patient population.

Given safety and efficacy results from the Phase 1 study, 200 mg or 300 mg ARO-ANG3 doses administered on Day 1 and Day 84 will be used in the current study population of subjects with HoFH. The proposed study design is intended to evaluate the duration of effect after the second dose of ARO-ANG3 is administered at Day 84. This study design will address whether treatment with ARO-ANG3 can provide further LDL-C lowering in subjects who have elevated LDL-C. Details of the analyses used for dose selection are provided in the Statistical Analysis Plan (SAP).

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 (applicable to all cohorts):

1. Males or nonpregnant (who do not plan to become pregnant), nonlactating females ≥16 years at Screening
2. Fasting LDL-C >100 mg/dL at Screening Visit 2
3. Weight of ≥40 kg and body mass index (BMI) ≥18.5 and ≤40 kg/m^2
4. A diagnosis of HoFH based on a supportive genetic test (from a source-verifiable medical record or based on screening genotype) or clinical diagnosis. Diagnosis of HoFH may be based on at least **one** of the following (a-c);
    a. Documented functional mutation(s) in both LDLR alleles

        Note: Subjects who have null receptor mutations on both LDLR alleles, ie, double null, are eligible.

    b. Presence of homozygous or compound heterozygous mutations in ApoB or PCSK9

        Note: Double heterozygous (ie, mutations on different genes [eg, LDLR/PCSK9]) or subjects with homozygous low density lipoprotein receptor adaptor protein 1 (LDLRAP1) mutations are eligible.

c. Documented history of untreated TC >500 mg/dL (12.93 mmol/L) OR treated LDL-C concentration of ≥300 mg/dL (≥8 mmol/L) either accompanied by TGs <300 mg/dL (3.39 mmol/L) AND both parents with documented TC >250 mg/dL (6.47 mmol/L) OR cutaneous or tendinous xanthoma before 10 years of age (Cuchel 2014)

5. If undergoing LDL apheresis, must have initiated LDL apheresis at least 3 months prior to Screening and must have been on a stable schedule (such as weekly [every 7±1 days], every other week [every 14±2 days], or some similar regimen) and stable settings for at least 8 weeks prior to Screening Visit 2
6. Subject is on stable (see table below for definition of stable) maximally tolerated lipid lowering therapy
7. If taking any of the following medications, must have been on a stable regimen for at least the minimum time period indicated below prior to Screening Visit 2:

Medication	**Time on Stable Regimen Prior to Screening Visit 2**
Immunosuppressants, including corticosteroids	≥8 weeks
Testosterone replacement therapy	≥8 weeks
Anticoagulation therapy	≥8 weeks
Atypical antipsychotics	≥8 weeks
Diabetes mellitus medications	≥8 weeks
Thyroid replacement therapy	≥8 weeks
PCSK9 inhibitors	≥8 weeks
Retinoids	≥8 weeks
Lomitapide	≥8 weeks
Beta-blockers, thiazide diuretics	≥8 weeks
Oral estrogens, tamoxifen, raloxifene	≥8 weeks
Fibrates	≥6 weeks
Statins and other lipid-lowering therapies (eg, ezetimibe)	≥4 weeks
Bempedoic acid and bile acid-binding resin (eg, cholestyramine, colestipol, or colesevelam)	≥4 weeks

Abbreviation: PCSK9=proprotein convertase subtilisin kexin type-9.

8. Subjects of childbearing potential must agree to use highly-effective contraception during the study and for at least 24 weeks from last dose of IP (see Appendix 1). Males must not donate sperm, nor can women donate eggs, during the study and for at least 24 weeks following the last dose of IP. Postmenopausal women must be amenorrheic for at least 12 months prior to Day 1 in order not to be considered of childbearing potential. Postmenopausal status will be confirmed by measurement of follicle-stimulating hormone (FSH). Pregnancy testing and contraception are not required for women with documented hysterectomy and/or oophorectomy.

9. Female subjects of childbearing potential on hormonal contraceptives must be stable on the medication for >2 menstrual cycles prior to Day 1
10. Subject is willing to strictly abide by a stable low saturated fat, low-cholesterol, heart-healthy diet for at least 4 weeks prior to Day 1
11. Willing and able to comply with clinic visits and study-related procedures
12. Provide signed informed consent or assent

NOTE: All laboratory tests used as inclusion or exclusion criteria will be assessed by a central laboratory and may be repeated once, and the repeat value may be used for inclusion purposes.

7.2. Exclusion Criteria

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

1. Current use or use within the last 365 days from Day 1 of any hepatocyte targeted siRNA or antisense oligonucleoside molecule
2. Use of evinacumab within 5 months prior to Screening Visit 2
3. Fasting TG >300 mg/dL (3.39 mmol/L) at Screening
4. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
5. Newly diagnosed (within 3 months prior to subject signing informed consent) or poorly controlled diabetes (hemoglobin A1c [HbA1c] >9% [or >75 mmol/mol IFCC units])
6. Use of an investigational agent or device within 30 days or within 5 half-lives, based on plasma PK (whichever is longer), prior to Day 1, or current participation in an interventional investigational study
7. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 8 weeks prior to Day 1. (Note: topical, intra-articular, nasal, inhaled, and ophthalmic steroid therapies are not considered as ‘systemic’ and are allowed.)
8. Subjects with any symptoms of myocardial ischemia, severe left ventricular dysfunction (left ventricular ejection fraction [LVEF] <30%), and New York Heart Association class III-IV within 12 months prior to Day 1
9. Subjects with a history of metastatic malignancy within 3 years of Day 1, except for locally invasive non-melanoma skin cancer, cervical in situ carcinoma, and breast ductal carcinoma-in-situ. Subjects with other curatively treated or non-metastatic locally confined tumors may be enrolled into the study following approval by the Medical Monitor and Investigator.
10. History of myocardial infarction (MI), unstable angina leading to hospitalization, coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic

attack (TIA), carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 months prior to signing informed consent

11. Planned cardiac procedure/surgery such as CABG surgery, PCI, carotid surgery or stenting, or carotid revascularization
12. Subjects with total bilirubin >1.5x ULN, unless in previously confirmed cases of Gilbert's syndrome
13. Subjects with platelet count <100,000/mm^3
14. Unstable weight (variation >5 kg) within 2 months prior to the Screening Visit
15. Use of estrogen or testosterone therapy unless the regimen has been stable for 6 weeks prior to the Day 1 visit and there are no plans to change the regimen during the study
16. Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg at the Screening Visit or time of randomization (Week 0/Day 1), which may be reassessed after hypertension is controlled with treatment
17. 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 = 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)
18. Any concomitant medical, psychiatric condition, social situation, or any other situation that, in the Investigator's judgment, would make it difficult to comply with protocol requirements or put the subject at additional safety risk
19. Laboratory findings during the Screening Period at Screening Visit 2:
    a. Positive test for HIV, hepatitis B surface antigen (HBsAg), and/or hepatitis C antibody (associated with a positive hepatitis C virus RNA polymerase chain reaction)
    b. Positive urine pregnancy test in female subjects of childbearing potential
    c. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 (calculated by central lab)
    d. ALT or AST >3× ULN at Screening (one repeat lab is allowed)
    e. Evidence of uncontrolled hypothyroidism or thyrotoxicosis based on thyroid-stimulating hormone (TSH) outside of normal limits per central laboratory reference range (TSH <lower limit of normal [LLN] or >ULN)

NOTE: All laboratory tests used as inclusion or exclusion criteria will be assessed by a central laboratory and may be repeated once, and the repeat value may be used for exclusion purposes.

A subject will be excluded from the Extension Treatment Period of the study if any new conditions or worsening of any 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, or which could otherwise interfere with the subject participating in or completing the study, or would make it difficult to comply with protocol requirements or put the subject at additional safety risk.

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 PI, 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. Description of Study Drug

The IP, ARO-ANG3 Injection (also referred to as ARO-ANG3), is a synthetic, double-stranded, siRNA duplex conjugated to an N-acetyl-galactosamine (NAG) targeting ligand to facilitate hepatocyte delivery. Subjects will be randomized to receive 200 mg or 300 mg ARO-ANG3 SC on Day 1 and Day 84 during the 36-week Treatment Period. Subjects participating in the Extension Treatment Period will initially continue to receive the dose level assigned in the initial 36-week Treatment Period. However, all subjects in the Extension Treatment Period may be later switched to a single dose level based on a primary analysis of 36-week Treatment Period safety and efficacy data.

The sponsor is responsible for the supply of ARO-ANG3 together with detailed instructions (in a Pharmacy Manual) describing preparation of ARO-ANG3.

8.2. Restrictions and Concomitant Medications and Procedures

8.2.1. Fasting

On the day of dosing or on other days with blood draws for lipid parameter measurements, subjects will have fasted from food (no food or drink other than water) for at least 10 hours prior to blood draw unless otherwise specified. Subjects only need to fast prior to laboratory sample collection but *not* prior to IP administration, nor during postdose PK sample collection.

Recreational Drugs and 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, not more than 14 units per week for women and men; 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.

8.2.2. Concomitant Medications

Use of all other medications and nutritional supplements known to alter serum lipids, including (but not limited to) PCSK9 inhibiting monoclonal antibodies, statins, ezetimibe, fibrates, and niacin is permitted as long as that therapy has been stable for the specified duration prior to the Screening Visit 2. Subjects should continue taking their background lipid-lowering therapy for the duration of the study, starting at Screening and continuing through the EOS visit. Any changes in standard of care lipid-lowering regimen during the study are discouraged; if changes occur, they should be documented in the eCRF. In cases where a subject is taking lower than the recommended statin dose (as defined by local standard of care), the reason will be clearly documented in the eCRF by the Investigator.

Subjects taking any of the concomitant medications specified in Table 5 must be on a stable regimen for the minimum duration specified below prior to collection of screening laboratory blood tests and for the duration of the study through Week 24 and EOS visit in accordance with the SOA (Table 3 and Table 4). In cases where any concomitant medication specified in Table 5 is initiated after Day 1, continued participation in the study must be approved by the sponsor's Medical Monitor. Adjustments to background medication specified in Table 5 during the study are only allowed 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.

Corticosteroids

Subjects should avoid the use of systemic corticosteroids unless used as replacement therapy for pituitary or adrenal disease, with a stable regimen for at least 8 weeks prior to randomization.

Topical, intra-articular, nasal, inhaled, and ophthalmic steroid therapies are not considered as 'systemic' and are allowed.

8.2.3. Permitted Medications

Subjects taking any of the medications described in Table 5 must be on a stable regimen as required in the inclusion criteria described in Section 7.1.

Table 5: Stable Medication Requirements

Medication	Time on Stable Regimen Prior to Screening Visit 2
Immunosuppressants, including corticosteroids	≥8 weeks
Testosterone replacement therapy	≥8 weeks
Anticoagulation therapy	≥8 weeks
Atypical antipsychotics	≥8 weeks
Diabetes mellitus medications	≥8 weeks
Thyroid replacement therapy	≥8 weeks
PCSK9 inhibitors	≥8 weeks
Retinoids	≥8 weeks
Lomitapide	≥8 weeks
Beta-blockers, thiazide diuretics	≥8 weeks
Oral estrogens, tamoxifen, raloxifene	≥8 weeks
Fibrates	≥6 weeks
Statins and other lipid-lowering therapies (eg, ezetimibe)	≥4 weeks
Bempedoic acid and bile acid-binding resin (eg, cholestyramine, colestipol, or colesevelam)	≥4 weeks

Abbreviation: PCSK9=proprotein convertase subtilisin kexin type-9.

8.2.4. Apheresis Concomitant Procedure

If a subject is undergoing LDL apheresis, they must have initiated LDL apheresis at least 3 months prior to Screening Visit 2 and must have been on a stable schedule (such as weekly [every 7±1 days], every other week [every 14±2 days], or some similar regimen) and stable settings for at least 8 weeks prior to Screening Visit 2. Day 1 and subsequent IP dosing and study visits should be scheduled based on the already set apheresis schedule.

If apheresis is being conducted on a nondosing day (separate from the dosing day)

For subjects who will have apheresis conducted on a nondosing day, the following process should be followed:

- ARO-ANG3 dosing will be completed a minimum of 48 hours up a maximum of 96 hours before the next scheduled apheresis. This is to allow the study drug to be disposed from plasma.

If apheresis is being conducted on the same day as dosing

For subjects who will have apheresis conducted on a dosing day, the following process should be followed:

- Blood draws for lipid parameters are to be conducted ***before*** the apheresis procedure
- ARO-ANG3 dosing is to occur ***after*** the apheresis procedure is completed

For subjects undergoing apheresis, the frequency of apheresis can be decreased (eg, change from once every week to once every 2 weeks) if LDL is stable for at least 3 months while they are on the study.

8.3. Notification of General Practitioner

It is the responsibility of the PI 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, or AEs and concomitant drugs to be avoided.

8.4. Treatment Compliance

All study treatment will be administered at the study site. The IP will be dispensed by clinical study site staff members on the day of dosing and recorded in the drug accountability records. The date, time, and duration of study treatment administration will be recorded on the eCRF on dosing days.

8.5. Randomization

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

8.6. Emergency Contact with Principal Investigator

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

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

The sponsor is responsible for the supply of active drug supplies together with detailed instructions (see Pharmacy Manual) describing preparation of ARO-ANG3. Accordingly, ARO-ANG3 will be supplied as single sterile 2-mL vials containing ARO-ANG3, with the correct dose of ARO-ANG3 prepared by the pharmacy prior to dosing subjects, as described in the Pharmacy Manual.

9.2. Study Drug Packaging and Labeling

ARO-ANG3 will be supplied as a sterile Type-1 glass 2.0-mL vial (1.2 mL nominal volume, 1.0 mL withdrawable volume).

Table 6: Study Drug Description

Strength	200 mg/mL
Appearance	Clear, colorless to yellow solution
Inactive ingredients	0.5 mM sodium phosphate monobasic, 0.5 mM sodium phosphate dibasic in water for injection
Shipment and Storage	Refrigerated, 2 ºC to 8 ºC

9.3. Study Drug Storage

ARO-ANG3 will be supplied by the sponsor and labeled with the drug name, batch number, expiration date (as applicable), and storage conditions.

Investigational product supplies will be stored at clinical sites securely under the appropriate conditions. The IP must be stored in a secure area with access limited to the PI and authorized staff and under the physical conditions that are consistent with the IP-specific requirements.

9.4. Study Drug Handling

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. It is also the responsibility of the Investigator to ensure that the integrity of packaged study product not be jeopardized prior to dispensing.

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. 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.

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 provided to define the procedures for dispensing.

For this study, used and partially used drug vials will be retained for an adequate period (where allowable by local policy) to allow accountability. No additional samples of study drug will be retained.

9.5. Study Drug Preparation

ARO-ANG3 will be prepared, per the Pharmacy Manual, by a staff Pharmacist or other designated, 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 study 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 will be labeled per current Good Manufacturing Practice (cGMP) and Good Clinical Practice (GCP).

9.6. Study Drug Administration

Each dose of study drug (ARO-ANG3) will be administered by SC injection by the Investigator or appropriately trained and qualified clinical staff designated by the Investigator. 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 or similar needle. The abdomen is the preferred site. Injection site is to be varied (no multiple injections into the same exact site; alternating various locations on the abdomen is acceptable). Injection site location is to be recorded in the eCRF and mapped for later observation. Prior to IP administration, the ARO-ANG3 vial must be allowed sufficient time to reach room temperature. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

Table 7: Injection Number and Volume Per Dose Cohort

ARO-ANG3 Dose	Concentration	Total Injection Volume	No. of Injections per Planned Dose	Total No. of Study Injections During the Study
200 mg	200 mg/mL	1.00 mL	Single	2
300 mg	200 mg/mL	1.50 mL	Single	2

9.7. Study Drug Accountability

All material supplied is for use only in this clinical study and should not be used for any other purpose. The PI is responsible for the IP accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the PI 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. A 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.

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

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

The date and time of dose preparation and release will be maintained to support administration of IP. The pharmacy will dispense the study medication and the study center will administer the study medication only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the IP as assigned by the IWRS. Investigational product administration will be documented and recorded on the eCRFs. The inventory must be available for inspection by the monitor during the study. Drug supplies will either be collected at the end of the study by the study monitor or returned by the PI or designee to the sponsor or the designated sponsor-approved depot.

10. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

10.1. Pharmacokinetic Assessments

10.1.1. Sample Collection

Plasma concentrations of ARO-ANG3 will be measured in all subjects to evaluate predose and postdose levels throughout the 36-week Treatment Period per the SOA (Table 3) and Table 8. Blood samples will be collected for PK analysis from subjects through vein puncture or an indwelling cannula. Refer to Section 12.1.6 for the timing and order of study procedures. 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. An explanation must be given for any blood sample taken outside of the set sampling times.

Refer to the Laboratory Manual for additional details on clinical laboratory tests.

Table 8: Plasma PK Sampling Schedule

Study Day	Plasma PK Sampling		
	Predose [a]	Postdose	
		0.5 h (30 minutes) (±5 min)	2 h (±5 min)
Day 1	X	X	X
Week 12 (Day 84)	X	X	X

Abbreviations: PK=pharmacokinetic.
[a] Anytime during the study visit and before the first dose of study drug.

10.1.2. Sample Analysis

Whole blood will be collected and processed per the Laboratory Manual. Plasma samples will be assayed by a validated anion-exchange high-performance liquid chromatographic fluorescence method using a peptide nucleic acid (PNA) probe specific to the antisense strand of ARO-ANG3. The criteria for repeat analysis, as defined in the respective in-house procedure, will be followed. The validation study conducted by the appointed bioanalytical laboratory to establish validity, including accuracy, precision, reproducibility, specificity, recovery, and frozen stability of the analytical method, will be appended to the final report.

10.2. Pharmacodynamic Assessments

Serum samples for PD assessments of LDL-C, TG, and ANGPTL3 will be collected as described in Section 11.1.1 and SOA (Table 3 and Table 4) after a fast of at least 10 hours. Refer to the Laboratory Manual for additional details on clinical laboratory tests.

10.2.1. Sample Collection

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 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 in the SOA visit windows (Table 3 and Table 4) 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 Section 11.1.1 and the SOA (Table 3 and Table 4). An explanation must be given for any blood sample taken outside of the set sampling times. HbA1c will be evaluated on an ongoing basis against treatment discontinuation criteria (Appendix 3).

10.2.2. Sample Analysis

LDL-C, TG, and ANGPTL3 protein will be measured as described in Section 11.1.1 with validated clinical assays. The validation studies for LDL-C, TG, and ANGPTL3 conducted by the appointed clinical laboratory to establish validity, including accuracy, precision, reproducibility, dilutability, and storage stability of the analytical method, will be appended to the final report.

10.2.3. Additional Exploratory Analysis-Future Research Samples

With prior written consent, a separate blood sample will be collected either at Day 1 or at a subsequent study visit and reserved for research (outside of the main study) that may be conducted in the future, including for purposes of exploratory biomarker analyses or to evaluate genes relevant to drug efficacy or metabolism.

11. ASSESSMENT OF EFFICACY

11.1. Efficacy Assessments

In the event of logistical disruptions (eg, coronavirus disease 2019 [COVID-19]-related) where a subject does not have direct access to the site, laboratory samples may be collected at alternative locations (eg, home health, local laboratory) using the central laboratory kit and shipped to the central laboratory for analysis (see Section 12.1.5).

11.1.1. Serum LDL-C and Other Lipid Parameters

Blood samples for lipid parameters 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 in the SOA visit windows (Table 3 and Table 4) 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 and Table 4). The actual sample times (times samples are 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 serum LDL-C and TG will be collected at Screening Visit 2 after at least a 10-hour fast. Fasting serum LDL-C, TG, and other lipid parameters (TC, non-HDL-C, HDL-C, VLDL-C, ApoB-48, LP[a], ApoB-100, total Apo[B], ApoC-III, ApoC-II, ApoA-I, and ApoA-V) will be collected on Day 1 prior to dosing after at least a 10-hour fast. The Day 1 values will be used as each subject's baseline value for data analysis purposes. Fasting serum TG will be measured as per the SOA (Table 3 and Table 4) and assessed by a central laboratory standard method. LDL-C will be measured as per the SOA and assessed by a central laboratory by the Friedewald calculation and ultracentrifugation methodology (PUC).

Refer to the Laboratory Manual for additional details on clinical laboratory tests.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Demographic/Medical History

Subject demographics (eg, date of birth, race and ethnicity, sex) and medical history will be collected during Screening. Medical history will include medication use over the previous 30 days, including vitamins, OTC medications, prescription drugs, recreational drugs, 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 and Table 4). All vital signs will be measured after the subject has been resting in a semi-supine position for at least 3 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Vital signs will be obtained prior to venipuncture and other invasive procedures.

12.1.3. Physical Examination

A complete physical examination will be performed at Screening and as per SOA (Table 3 and Table 4). At Screening, height (without shoes) and weight (without shoes) will be measured to determine BMI. At all other time points outlined in the SOA, 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 and Table 4) 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. Each electrocardiogram will be performed prior to venipuncture and any other invasive procedures (refer to Section 12.1.6). Any clinically significant abnormality should be documented as an AE or SAE, as applicable.

12.1.5. Laboratory Assessments

All laboratory samples will be collected before the IP dose is administered at any visit. All laboratory assessments are to be conducted in the fasting state (no food or drink other than water) for at least 10 hours prior to sample collection. Subjects do not require fasting prior to post dose PK sample collection.

Blood and urine samples will be collected at the site and shipped to the central laboratory for analysis. In the event of logistical disruptions (eg, COVID-19 related) where a subject does not have direct access to the site, laboratory samples may be collected at an alternative location (eg, home health, local laboratory) using the central laboratory kit and shipped to the central laboratory for analysis. If a central laboratory kit collection is not available, local laboratory safety testing may only be permitted in limited circumstances and only with prior sponsor approval.

In accordance with the SOA (Table 3 and Table 4), blood and urine samples will be collected for the laboratory tests detailed below to establish baseline data and eligibility for enrollment. One repeat screening laboratory draw is allowed per assessment to establish eligibility. The results will be assessed by the Investigator or medically qualified designee before study enrollment. Any abnormal and clinically significant laboratory result, as per the Investigator's medical judgment should be documented as an AE or SAE, as applicable.

Clinical laboratory tests will be performed on subjects' blood and urine at specified time points listed in the SOA (Table 3 and Table 4). Refer to the Laboratory Manual for additional details on clinical laboratory tests.

Serum LDL-C and Other Lipid Parameters: Laboratory assessment samples are to be obtained at designated visits as detailed in Section 11.1.1.

Biochemistry: Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, estimated glomerular filtration rate, creatine kinase, uric acid, phosphate, total calcium, anion gap, albumin, globulins, protein, total bilirubin, amylase, lipase, HbA1c, serum insulin, C-peptide, conjugated bilirubin, gamma glutamyltransferase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, TSH, and C-reactive protein.

Hematology: Hemoglobin, red blood cell count, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Coagulation: Partial thromboplastin time, prothrombin time with INR, and fibrinogen.

Urinalysis: Leukocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketone, bilirubin, and glucose.

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

Serology: HIV, HBsAg, and hepatitis C antibody screen. If necessary, subjects will be counseled by the Investigator, or medically trained designee, concerning the blood tests for HBsAg and hepatitis C antibody, and their subsequent results.

Follicle-Stimulating Hormone (FSH): Postmenopausal status (females) will be supported based on FSH level consistent with postmenopausal state.

Immunogenicity: Subjects will be assessed for ADA incidence and titer.

The Day 1 value will be used as each subject's baseline value for data analysis purposes or as otherwise specified. If Day 1 or as otherwise specified values are erroneous or not available and repeat blood draw is not possible, the Screening value may be used as baseline.

During the study, the central laboratory will notify the Investigator and Medical Monitor of any abnormal test results that occur after start of treatment. These abnormal test results will be repeated to confirm the nature and degree of the abnormality. The Investigator will contact the subject to provide appropriate medical follow-up including dietary and medication compliance counseling, which may include modification to the subject's lipid-lowering regimen. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical Monitor must be consulted. The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the Investigator. Criteria for reporting laboratory values as an AE are provided in Section 12.2.

12.1.6. Timing of Treatments and Procedures

The scheduling of all pre- and post-Day 1 study visits will be based upon and in relation to the Day 1 visit date. Actual times of procedures for each subject will vary depending on scheduling and will be recorded in the eCRF.

In the event of multiple procedures scheduled at the same time, noninvasive procedures (ie, vital signs, ECGs, AE assessment) will be conducted prior to invasive procedures (ie, blood sample collection). Timing of activities may be adjusted slightly to accommodate all procedures.

The time windows presented in Table 9 are allowed for study assessments and visits.

Table 9: Timing of Treatments and Procedures

Treatment or Procedure Category	Time Window
Predose	Any time during the study visit and before first dose
Plasma PK postdose (0.5 hour) 30 minute sampling time point	±5 minutes
Plasma PK postdose 2 hour sampling time point	±5 minutes
Day 1	Not applicable
Week 4 and Week 8	±3 days
All other postbaseline visits	±5 days

Abbreviation: PK=pharmacokinetic.

12.1.7. Pregnancy Screen

Female subjects of childbearing potential will have urine pregnancy tests at each Screening Visit, Day 1 (baseline), and at subsequent study visits as indicated in the SOA (Table 3 and Table 4). Female subjects not of childbearing potential must be either surgically sterile or postmenopausal (defined as cessation of regular menstrual periods for at least 12 months) with supportive FSH consistent with postmenopausal state based on laboratory reference ranges.

Female subjects who become pregnant following Day 1 will permanently discontinue study drug dosing (see Section 6.4.1) and will remain in the study and be followed until delivery for pregnancy-related outcomes.

See Appendix 1 for additional guidance on pregnancy tests and requirements for contraception.

12.2. Adverse Events

The 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 a pregnancy and appropriate follow-up. Any known pregnancy that occurs during the study or within 24 weeks following the last dose of study drug (whichever is later) 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 patient 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 pre-existing medical condition increases in severity or frequency after study drug administration.

Adverse events will not include:

- A medical or surgical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE)
- A pre-existing 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 or preplanned 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, 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 medically important event or reaction that 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 or 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 (CS) 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 pre-existing 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 collected through the EOS or through 30 days after the last dose, whichever is longer (Section 12.8.4).

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

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 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, or severe using the following definitions:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities. Medical intervention not indicated.
- **Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities. Minimal, local or noninvasive medical intervention indicated.
- **Severe**: An event that prevents normal everyday activities and requires emergent invasive intervention which may include hospitalization.

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 serious criteria as described in Section 12.2.1.2.

12.6.2. Injection Site Reactions

All ISRs will be captured as AEs. Injection site reactions will be assessed at every visit starting on Day 1 as per the SOA (Table 3 and Table 4). Injection site reactions are graded based on CTCAE.

- Grade 1: Tenderness with or without associated symptoms (eg, warmth, erythema, itching).
- Grade 2: Pain; lipodystrophy; edema; phlebitis.
- Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Results in death.

12.6.3. 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 Contract Research Organization (CRO), and the institutional review board (IRB) or independent ethics committee (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 within 24 hours. 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 or 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 12.6.3. 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 well-being will be reported to the sponsor emergency contact listed in Table 1.

Sponsor Emergency Contact
Sponsor Medical Monitor Contact [redacted] Telephone: [redacted]

12.8.2. Serious Adverse Event Reports to the IRB/IEC

The PI, 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/IEC.

12.8.3. Regulatory Requirements for Reporting of Serious Adverse Events

The PI (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 reporting obligations.

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

12.8.4. 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 PI is not obligated to actively seek AEs in former study subjects. However, if the PI learns of any SAE at any time after a subject has been discharged from the study, and he or she considers the event reasonably related to the IP, the PI will promptly notify the sponsor.

12.8.5. 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).

12.9. 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 during the study or within 24 weeks following the last dose of ARO-ANG3 (whichever is later) should also be reported by the subject to the PI.

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 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.

13. STATISTICS

13.1. Statistical Considerations

Descriptive summaries will be presented for primary, secondary, and exploratory endpoints by treatment group. Any proposed amendments to the 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 (FAS)	All randomized subjects who receive at least 1 dose of IP. All efficacy analyses will be performed using the FAS.
Safety analysis set	All subjects who receive at least 1 dose of IP. All safety and tolerability analyses will be performed using this set.
PK analysis set	All subjects who receive at least 1 dose of IP and have at least one measurable PK concentration.

Abbreviations: FAS=full analysis set; IP=investigational product; PK=pharmacokinetic.

13.3. Sample Size Considerations

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

13.4. Interim Analysis

An interim analysis is planned for this study after a majority of participants complete the Week 24 visit.

13.5. Analysis Methods

13.5.1. Baseline Data

Demographics will be tabulated by subject and summarized by treatment group. Eligibility assessments at baseline, including medical/surgical history data, physical examination data (including height and weight), and HoFH genotype completed at Screening or from a source-verifiable document will be listed for each subject.

Medical history will be coded using the MedDRA and summarized. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary into drug class (Anatomical Therapeutic Chemical level 4) and Preferred Term (PT) and summarized by treatment group.

13.5.2. Efficacy Analysis

Baseline is defined as the last value prior to administration of the first dose. Efficacy variables at baseline and each postdose visits will be summarized descriptively. Percent change and/or absolute change from baseline will be summarized by treatment group. All efficacy data will be listed.

For efficacy variables during the Extension Treatment Period, the measurements and changes and/or percent changes from baseline over time will be summarized descriptively.

After the majority of subjects in the 36-week Treatment Period complete the Week 24 Visit, an interim analysis may be conducted to review the efficacy and safety data in order to select a single dose level for all subjects in Extension Treatment Period, and for the remainder of their participation in the trial.

13.5.3. Safety Analysis

In general, safety measurements will be summarized descriptively by treatment group. Post treatment safety assessments will be compared with measurements recorded at baseline. Treatment-emergent AEs will be summarized using the MedDRA Version 24.0 or later by System Organ Class (SOC) and PT for each treatment group. Overall summaries of TEAEs will be tabulated by seriousness, severity, and relationship to the IP. The incidence and frequency of TEAEs, TEAEs related to LISR, serious TEAEs, and serious TEAEs leading to discontinuation will be summarized by SOC and PT. Treatment-related TEAEs will also be summarized in a similar manner. Treatment-emergent AEs will also 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 and shift tables. 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 subject listings. Electrocardiogram parameters, changes from baseline, and qualitative assessments will be summarized. Pregnancy and FSH test results (females) will be listed separately by time point.

All safety and tolerability analyses will be performed using the Safety Analysis Population.

13.6. Other Analyses

13.6.1. Pharmacokinetics

All PK concentrations will be listed, summarized, and plotted by treatment, as data applicable. The PK concentration data will be analyzed using standard noncompartmental analysis (NCA) method, and PK parameters including but not limited to C_{max}, AUC from time 0 to the last quantifiable plasma concentration (AUC_{last}), and AUC from time 0 extrapolated to infinity (AUC_{inf}) will be calculated as data permits.

13.6.2. Analysis of Immunogenicity (Anti-Drug Antibodies) Data

Changes from assay negative to positive and antibody titers will be summarized by cohort, dose, and dosing frequency. Descriptive statistics of immunogenicity parameters will include mean, SD, median, minimum, maximum, percent coefficient of variation, and geometric mean.

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 PI 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 PI 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 PI will conduct the study in compliance with the approved protocol and will not implement any deviation from or changes to the protocol, except where necessary to eliminate an immediate hazard to study subjects.

Deviations may result from the action or inaction of the subject, PI, 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, PK blood draws, medical history, etc – either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, failure to obtain IRB 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 PI 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 PI 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 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 PI and clinical site agree to notify sponsor as soon as possible following awareness of an impending regulatory inspection. The PI 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 (FWA) 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 PI must submit such written approval to the sponsor before he or she can enroll any subject into the study.

The PI 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 PI 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 PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB 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 PI 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. Study participation includes all screening procedures, as well as any wash-out of excluded medications.

It is the responsibility of the PI 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 PI 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 PI 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 PI 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 PI 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 PI 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 PI must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the PI 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 PI 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 PI 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

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 (EDC) 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]

18. LIST OF REFERENCES

Adam RC, Mintah IJ, Alexa-Braun CA, Shihanian LM, Lee JS, Banerjee P, et al. Angiopoietin-like protein 3 governs LDL-cholesterol levels through endothelial lipase-dependent VLDL clearance. J Lipid Res. 2020;61(9):1271-86.

Baass A, Paquette M, Bernard S, Hegele RA. Familial chylomicronemia syndrome: an under-recognized cause of severe hypertriglyceridaemia. J Intern Med. 2020;287(4):340-348. doi:10.1111/joim.13016

Ballantyne C. Clinical lipidology: a companion to Braunwald's heart disease. Philadelphia, PA: Saunders/Elsevier; 2015.

Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011;108(5):682-90.

Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35(32):2146-57.

Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, et al. Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease. N Engl J Med. 2017;377(3):211-21.

Janas MM, Harbison CE, Perry VK, Carito B, Sutherland JE, Vaishnaw AK, et al. The Nonclinical Safety Profile of GalNAc-conjugated RNAi Therapeutics in Subacute Studies. Toxicol Pathol. 2018;46(7):735-45.

Minicocci I, Santini S, Cantisani V, Stitziel N, Kathiresan S, Arroyo JA, et al. Clinical characteristics and plasma lipids in subjects with familial combined hypolipidemia: a pooled analysis. J Lipid Res. 2013;54(12):3481-90.

Musunuru K, Pirruccello JP, Do R, Peloso GM, Guiducci C, Sougnez C, et al. Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. N Engl J Med. 2010;363(23):2220-7.

Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, et al. Evinacumab for Homozygous Familial Hypercholesterolemia. N Engl J Med. 2020;383(8):711-20.

Regev A, Palmer M, Avigan MI, Dimick-Santos L, Treem WR, Marcinak JF, et al. Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2019;49(6):702-13.

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336(14):973-9.

Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341(6):410-8.

Stitziel NO, Khera AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE, et al. ANGPTL3 Deficiency and Protection Against Coronary Artery Disease. J Am Coll Cardiol. 2017;69(16):2054-63.

APPENDIX 1. CONTRACEPTION

Female subjects 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 (FSH) 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 at Screening or on Day 1 predose will not be enrolled in the study. Female subjects who become pregnant following Day 1 will permanently discontinue study drug dosing and will remain in the study and be followed until delivery for pregnancy-related outcomes.

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 the End of Study (EOS) visit or last dose of study treatment, whichever is later. For a subject who discontinues from the study prematurely, if their serum ANGPTL3 level at the ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value.

For subjects who continue in the 24-month Extension Treatment Period, if a subject's serum ANGPTL3 level at the Extension Treatment Period Month 24 (EOS) visit or ET visit has not returned to at least 70% of their predose baseline value, the subject's serum ANGPTL3 will be monitored every 2 months, and subjects of childbearing potential will continue use of highly effective contraception until the serum ANGPTL3 level has returned to at least 70% of the subject's baseline value, they enter the OLE of Study AROANG3-3001 (if they meet the eligibility criteria), or until they have completed 1.5 years of monitoring, whichever occurs earlier.

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 investigational product (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 2. LIVER-RELATED STUDY MODIFICATION AND FOLLOW-UP GUIDELINES

Table 10: Liver-Related Study Monitoring and Stopping Guidelines for Subjects With ALT or AST Elevations

Treatment-Emergent ALT or AST	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
Normal baseline: ALT or AST >3× ULN Elevated baseline [a]: ALT or AST >2× baseline or ≥300 U/L (whichever occurs first)	Normal Subjects with Gilbert's syndrome or hemolysis - no change in baseline TBL	None	Confirm ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [b] Follow-up for symptoms.
Normal baseline: ALT or AST >5× ULN Elevated baseline [a]: ALT or AST >3× baseline or ≥300 U/L (whichever occurs first)	Normal Subjects with Gilbert's syndrome or hemolysis - no change in baseline TBL	None	Interrupt IP. Confirm ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [b] 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: ALT or AST >3× ULN Elevated baseline [a]: ALT or AST >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 ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [b] 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: ALT or AST >3× ULN Elevated baseline [a]: ALT or AST >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	None	Interrupt IP. Confirm ALT, AST, ALP, TBL within 72 hours. Initiate close observation and workup for competing etiologies. [b] IP can be restarted only if an alternative etiology is identified and liver enzymes return to

Treatment-Emergent ALT or AST	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
	bilirubin if baseline >0.5 mg/dL		baseline. IP cannot be restarted if hepatic decompensation occurred. Refer to guidelines for close observation below. Follow-up for symptoms.

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

Guidelines for Close Observation for Potential Drug Induced Liver Injury:

Within 72 hours, perform a complete 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, OTC medications, recreational drug use, and special diets
- Alcohol consumption
- Exposure to environmental chemical agents
- Past medical history
- Complete review of systems
- Liver biochemistries including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and INR.

Evaluate subjects 2 or 3 times a week for signs and symptoms of clinical hepatitis and obtain liver biochemistries until biochemistries stabilize.

If biochemistries stabilize and the subject is asymptomatic, monitor liver biochemistries once a week until they return to baseline.

Subjects who live far from study sites may be evaluated locally for history, physical exam, and laboratories, if the results are communicated promptly to the site Investigator.

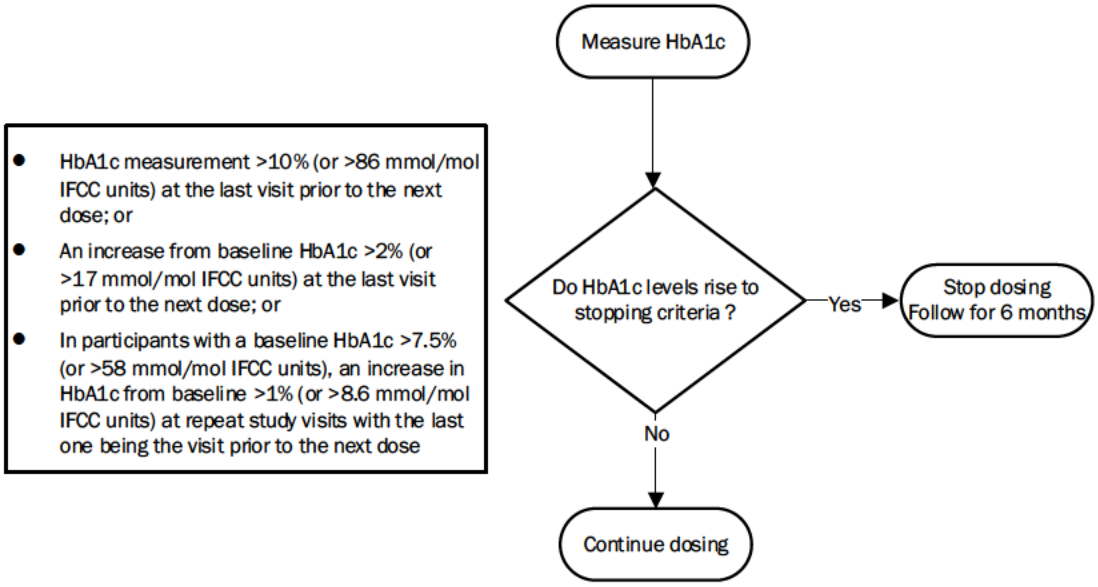
APPENDIX 3. GLYCEMIC CONTROL-RELATED GUIDELINES

HbA1c Investigational Product Discontinuation Criteria

Participants should discontinue IP if they meet the following criteria:

- HbA1c measurement >10% (or >86 mmol/mol 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.

Participants who discontinue IP due to the above criteria will be followed for 6 months after their last dose per the Schedule of Assessments.



Guidelines for Excessive Increases in HbA1c

The following guidelines should be followed for increases in HbA1c:

- Investigators should evaluate diabetes status and adjust diabetes treatment according to clinical practice and diabetes care guidance.
- At the Investigator's discretion, any participants 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.