A Phase 3 Study to Evaluate the Efficacy and Safety of VSA001 Injection in Chinese Adults with Familial Chylomicronemia Syndrome

Study number: VSA001-3001

Product ID:	VSA001
Sponsor:	Visirna Therapeutics HK Limited
Version No.:	3.5
Version Date:	March 10, 2025

History and Summary of Protocol Revision

Document Revision History:

Version No.	Version date	Description and Justification of Revision
1.0	December 9, 2022	New document, not applicable
2.0	February 20, 2023	The following revisions were made based on the review opinions at the academic conference of Shanghai Huashan Hospital: 1. Given that there is currently no PK data for the Chinese population, the subgroup analysis results of the completed Phase 1/2a clinical study of VSA001 Injection are summarized in Section 3.2.3, which shows no significant differences in PK, PD, and safety between Asian and non-Asian participants; 2. In Section 5.1.2, "PI or designee" conducting informed consent was changed to "PI or designated study doctor" to comply with GCP; 3. In Section 5.1.5, the time window for PK blood collection is changed from 15 minutes to 30 minutes to facilitate clinical implementation; 4. In Section 7.2.5, "general practitioner" was replaced with "treating physician" to comply with clinical practice in China. In addition, the wordings in the initial version of the protocol (including completeness, consistency, typos, word order, language style, abbreviations, etc.) were corrected and revised; and the operational details were improved (e.g., the sampling time points for test items and the categories of laboratory tests were refined in the Schedule of Activities and Sections 10 and 11).
3.0	March 10, 2023	The following revisions were made based on the review opinions from the Ethics Committee of Shanghai Huashan Hospital: 1. In Section 3.2.3., the safety results from the latest interim analysis of the Phase 2b clinical study of VSA001 conducted in other indication population (patients with severe hypertriglyceridemia) abroad were added; 2. Section 5.1.1. summarizes the overall design of this study as a randomized, double-blind, placebo-controlled, dose-selection study and clarifies the dose finding objective by setting up two parallel dose groups; 3. In Section 7.2.2., "recreational drug use" was replaced with "drug abuse" to comply with Chinese regulations and the understanding of clinicians; 4. Appendix 4. Food Fatty Acid Content Table was added for the investigator to guide participants in low-fat diet treatment. In addition, errors in Protocol v2.0 were corrected by supplementing or revising the following operational details: 1. It is described in Note "b" under the "Schedule of Activities: Randomized Period" that urine pregnancy tests on Day 1 and subsequent dosing visit days will be performed pre-dose at the

		local laboratory and must be negative; 2. Specific test items for lipid parameters at screening, baseline (Day 1), and follow-up visits are described in Note "j" under the "Schedule of Activities: Randomized Period" and in Section 10.1; 3. In the "Schedule of Activities", the time points and frequency of dietary assessments were adjusted, and the time window for ECG sampling was adjusted (extended to 30 min); 4. In Section 5.4.1., the planned data safety reviews were changed from "evaluations for imbalances between active and placebo groups for AEs and SAEs" to "assessments for significant safety events such as AEs and SAEs between 50 mg dose group and 25 mg dose group".
3.1	June 8, 2023	The following updates were made based on the latest data from the global clinical studies of VSA001: 1. Elevation of glycated hemoglobin (HbA1c) was added as a possible reason for discontinuation of treatment in the "Synopsis"; 2. HbA1c testing at Months 2, 13, and 14 and its purpose were added in the "Schedule of Activities"; 3. Poor glycemic control was added as a potential risk of participation in the study in Section 3.3.4.; 4. The benefit-risk assessment results of continuing the evaluation of 25 mg and 50 mg doses in patients with familial chylomicronemia syndrome (FCS) were added in Section 3.3.5.; 5. Elevation of HbA1c was added as a new situation that may warrant discontinuation of study treatment in Section 5.4.1.; 6. The statement "Adjustment of diabetes treatment regimen is allowed during the study)" was added in Section 5.6.; 7. The rationale for continuing the evaluation of 25 mg and 50 mg dose levels in FCS participants was added in Section 5.7.; 8. Principles for discontinuation of treatment in participants with elevated HbA1c were added in Section 7.4.; 9. Appendix 5 Glycemic Control-Related Guidelines in Diabetes was added. 10. The estimated upper limit of enrollment was updated in "Synopsis" and Sections 12.3, 5.1.1, and 5.2. In addition, operational details in the body text and the "Schedule of Activities" were supplemented and corrected, and the typos in "Appendix 2 Liver-related Study Modification and Follow-up Guidelines" were corrected.
3.2	August 8, 2023	The following revisions were made based on the updated safety information of the global studies, feedback on feasibility collected during the implementation of the protocol, and the review opinions from the Ethics Committee of Shanghai Huashan Hospital: 1. Procedure for handling participants with acute pancreatitis who

		are unblinded and directly transferred to the open-label treatment phase was added in "Methodology" of the Synopsis and in Section 5.1.1. "Overview of Study Design"; 2. The number of screening tests for triglycerides was increased to a total of three in "Inclusion Criterion #3" of the Synopsis and in Section 6.1 "Participant Inclusion Criteria"; 3. The screening period was extended to 56 days in the Synopsis, "Schedule of Activities: Randomized Period", and Section 5.1. "Overall Study Design", highlighting that the eligibility criteria will be judged based on the values of liver function, blood glucose, and CBC tests within 28 days prior to randomization; 4. In the "Schedule of Activities: Randomized Period", the "blood glucose" was moved from "Routine laboratory tests h" to "Liver function tests and CBC i", and "liver function, blood glucose, and CBC" tests were added for Day 15 to enhance safety monitoring of liver enzymes and blood glucose (adding testing at Months 1, 2, 3, 5, 7, 8, 10, and 11); 5. The alert value reporting range of >4000 mg/dL (45 mmol/L) for triglyceride (TG) was added in Section 7.2.4. "Central Laboratory Lipid Testing"; 6. The note "(or carbon dioxide)" was added after the blood chemistry parameter "bicarbonate" in Section 11.1.5.2. to cover different names of this test item in study sites; the test item "anion gap" was deleted because most of the participating sites could not provide test reports containing this item; 7. Guidelines for further monitoring and resumption of medication after treatment discontinuation in patients with poor glycemic control (elevated glycated hemoglobin) were added to Appendix 5; 8. Appendix 6 was added, which provides a categorized summary of specific laboratories for laboratory test items; Others: In Section 11. "Assessment of Safety", duplicate descriptions were deleted, and operational details were refined; and relevant sections were corrected accordingly to ensure consistency.
3.3	May 23, 2024	Prefilled syringe (PFS) is the proposed market dosage form of VSA001 for subcutaneous administration, which can facilitate clinical use and reduce the risk of medication errors. In the extension period of this study, the Sponsor will provide PFS after relevant approvals are obtained and PFS is imported, by which time all participants would have received the active drug. Therefore, the following updates were made accordingly: 1. PFS was added to the "Abbreviations" in the Synopsis; 2. The description of sample size re-estimation in the "Synopsis" and Sections 12.3 was deleted based on the actual number of participants enrolled in the study; 3. PFS-related content was added in Section 8. Study Drug Materials and Management; 4. Relevant details on treatment discontinuation were added to

		Appendix 5 Glycemic Control-Related Guidelines in Diabetes; Others: Operational details in the protocol were updated, and typos in the protocol content were corrected to maintain consistency.
3.4	September 2, 2024	Based on the analysis results of the Phase 3 global FCS study (AROAPOC3-3001) of this product, the proposed market dose of VSA001 is 25 mg. In the extension period of this study, all participants will receive VSA001 25 mg Q3M after approval of this version, so the following updates were made accordingly: 1. The doses of the extension phase were combined into 25 mg Q3M in the "Study Design Diagram" in the Synopsis and Section 5.1.1. Overview of Study Design; 2. The time windows for visits at Months 7, 8, and 11 of the randomized period and all visits of the extension period in the "Schedule of Activities" of the Synopsis were updated to ± 10 days; 3. Relevant details on treatment discontinuation in Appendix 5 Glycemic Control-Related Guidelines in Diabetes were optimized; 4. In Appendix 6. Instructions on Clinical Laboratory Tests, ADA testing facility was changed to Chongqing Denali Medpharma Co., Ltd.
3.5	March 10, 2025	It is planned to provide the participants with the opportunity to continue medication after the end of the study, and update the global clinical study data of VSA001 in the protocol. The specific updates are as follows: 1. Section 7.6 Drug Therapy after the End of Study was added to provide the participants with the opportunity to continue the treatment after the end of the study, so that participants can obtain continuous benefits; 2. In Section 3.2.3 Clinical Studies, Section 3.3.4 Poor Glycemic Control, Section 3.3.5 Benefit-Risk Assessment, and Section 5.7 Rationale for Dose and Schedule of Administration, the global clinical study data of VSA001 were updated to provide the latest study progress and results.

Signature Page of Sponsor

This study protocol (A Phase 3 Study to Evaluate the Efficacy and Safety of VSA001 Injection in Chinese Adults with Familial Chylomicronemia Syndrome) has been reviewed and approved by the following representative of Visirna Therapeutics HK Limited.

YOU Dong	<signed>
Name (Print)	**Signature**
Executive Vice President, Medicine	
Title	**Date (DDMMMYYYY)**

INVESTIGATOR'S AGREEMENT

Protocol Title: A Phase 3 Study to Evaluate the Efficacy and Safety of VSA001 Injection in Chinese Adults with Familial Chylomicronemia Syndrome

Protocol Number: VSA001-3001

Version: Protocol Amendment 3.5

By my signature below, I attest to the following:

- I have received and read the Investigator's Brochure for VSA001 (ARO-APOC3).
- I have carefully read this study protocol.
- I agree to conduct the trial according to the protocol (subject to any amendments) and in accordance with the principles of International Council for Harmonisation (ICH) E6 Good Clinical Practice guidelines and all applicable regulations or requirements.
- I understand that any changes to the protocol must be approved by the Sponsor, Visirna Therapeutics HK Limited, the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and in certain cases, the National Medical Products Administration (NMPA) 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

Medical Monitor Contact:

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SYNOPSIS

Title of Study:

A Phase 3 Study to Evaluate the Efficacy and Safety of VSA001 Injection in Chinese Adults with Familial Chylomicronemia Syndrome

Name of Sponsor/Company:

Visirna Therapeutics HK Limited

Name of Investigational Product:

VSA001 Injection (also referred to as ARO-APOC3 Injection, Plozasiran)

Name of Active Ingredient:

VSA001(ARO-APOC3)

Registration classification:

Chemical Drug Class 1

Indication:

Familial Chylomicronemia Syndrome (FCS)

Protocol No.:	**Phase:**	**Country:**
VSA001-3001	3	**China**

Study Center(s):

Multiple sites, China

Background:

Familial chylomicronemia syndrome (FCS) is a severe and ultrarare genetic disease, with a prevalence of approximately 1 in 1,000,000 based on incomplete statistics, often caused by various monogenic mutations. FCS leads to extremely high fasting triglyceride (TG) levels, typically over 900 mg/dL. Such severe elevations lead to various serious signs and symptoms including acute pancreatitis (which can be fatal), chronic daily abdominal pain, type 2 diabetes mellitus, hepatic steatosis, and cognitive issues (aka “brain fog”). Currently, the therapeutic options that can adequately treat FCS are very limited with only one antisense oligonucleotide inhibitor of apolipoprotein C3 (APOC3, APOC-III), approved in Europe.

APOC3 is an 8.8 kilodalton (kDa) protein component of triglyceride-rich lipoproteins (TRLs) such as very-low-density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL-C), chylomicrons, high-density lipoprotein cholesterol (HDL-C), and remnant particle lipoproteins. APOC3 is synthesized predominantly in hepatocytes. It inhibits the hydrolysis of TG on TRLs at the muscle and adipose tissue capillary level through inhibition of lipoprotein lipase (LPL), and delays clearance of lipoprotein remnants by the liver by inhibiting hepatocyte receptor-mediated uptake. APOC3 functions as a key regulator of fasting and postprandial plasma TG levels.

VSA001 (ARO-APOC3) is a synthetic, double-stranded, hepatocyte-targeted RNA interference (RNAi) trigger (also referred to as a small interfering RNA [siRNA]) designed to specifically silence messenger RNA (mRNA) transcripts from the APOC3 gene using an RNAi mechanism. Given the important role of APOC3 in serum TG level modulation and its primary source of synthesis in hepatocytes, reduction of APOC3 through a hepatocyte-targeted RNAi strategy is likely to reduce circulating TG, benefiting several patient populations, including patients with FCS.

Objectives:

The primary objective of this study is to evaluate the efficacy and safety of VSA001 in Chinese adults with FCS.

Endpoints:

Primary and secondary endpoints are for the randomized period only, except as noted.

Primary endpoints:

- Percent change from baseline at Month 10 in fasting serum TG

Key secondary endpoints:

- Percent change from baseline at Months 10 and 12 (averaged) in fasting serum TG
- Percent change from baseline at Month 10 in fasting serum APOC3
- Percent change from baseline at Month 12 in fasting serum APOC3

Other secondary endpoints:

- Percent change from baseline at Month 10 in fasting serum non-high density lipoprotein cholesterol (non-HDL-C) and HDL-C
- Percent change from baseline at Month 12 in fasting serum TG, non-HDL-C, and HDL-C
- Proportion of participants achieving fasting serum TG of <500 mg/dL at Month 10
- Proportion of participants achieving fasting serum TG of <500 mg/dL at Month 12
- Change and percent change from baseline at each scheduled assessment in fasting serum TG up to Month 12
- Participant incidence of treatment emergent adverse events (TEAEs) (either period)
- Incidence of positively adjudicated events of acute pancreatitis (either period)

Exploratory study endpoints:

Exploratory endpoints are for both the randomized period and the extension period, except as noted.

- Change and percent change from baseline at each scheduled assessment in fasting serum lipid parameters (total cholesterol, low-density lipoprotein cholesterol [LDL-C], HDL-C, non-HDL-C, VLDL-C, total apolipoprotein B [APOB], APOB-48, lipoprotein(a) [LP(a)], APOB-100, APOC2, APOC3, apolipoprotein A-I [APOA1], and apolipoprotein A-V [APOA5]), with all values drawn after at least a 10-hour fast.
- Changes from baseline at each scheduled assessment in fasting serum blood glucose, glycated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide
- Change and percent change from baseline at each scheduled assessment in fasting serum TG, APOC3, non-HDL-C, and HDL-C (extension period only)
- Proportion of participants reaching fasting serum TG of <500 mg/dL at each scheduled assessment
- Incidence of hospitalizations for abdominal pain
- Participant incidence of emergent apheresis
- Pharmacokinetic (PK) parameters of VSA001
- Incidence of anti-drug antibodies to VSA001
- Change from baseline at each scheduled assessment in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 score
- Change from baseline at each scheduled assessment in EORTC QLQ-PAN26 score
- Change from baseline at each scheduled assessment in EuroQol 5-dimension instrument (EQ-5D-5L) score

Estimand of primary endpoint:

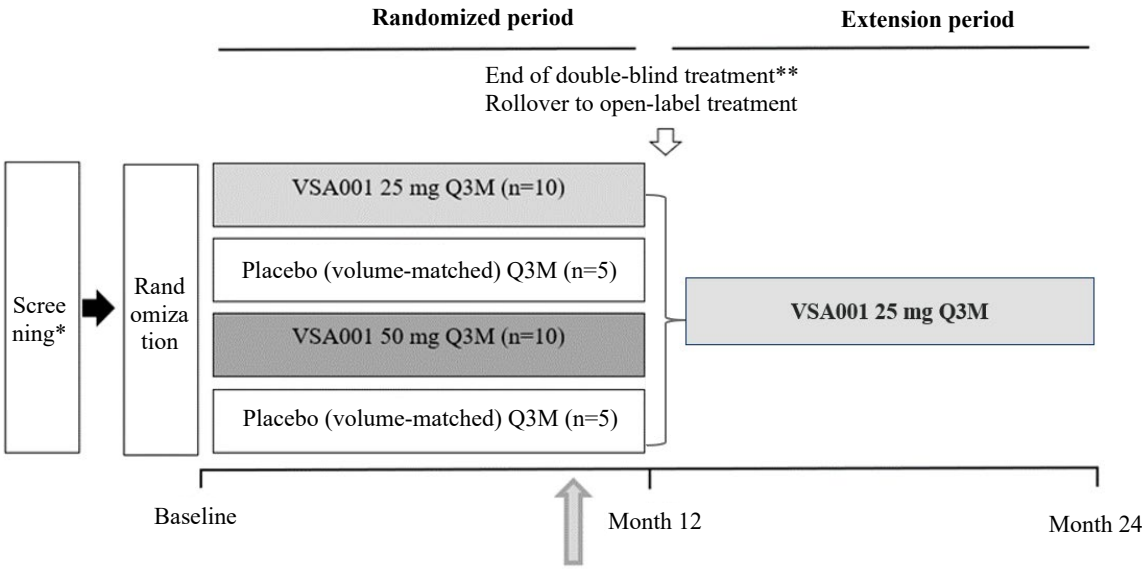
The key clinical question of interest

Difference in medians of percent change from baseline in fasting serum TG at Month 10 in the test group (VSA001 25 mg or VSA001 50 mg Q3M) relative to control group (placebo Q3M) in Chinese adults with FCS, regardless of discontinuation of treatment for any reason/concomitant therapy/rescue medication/background treatment changes/other intercurrent events.

Definition of estimand

- Treatment policy strategy: randomization to the test group (VSA001 25 mg Q3M /VSA001 50 mg Q3M) or control group (placebo Q3M) for 10 months of treatment, regardless of discontinuation of treatment for any reason/concomitant therapy/rescue medication/background treatment changes/other intercurrent events
- Target population: adult patients with FCS who meet the eligibility criteria
- Variable: percent change from baseline in fasting serum TG at Month 10
- Treatment policy strategy - intercurrent events: regardless of discontinuation of treatment for any reason/concomitant therapy/rescue medication/background treatment changes/other intercurrent events
- Population-level summary: median percent change from baseline in fasting serum TG in treatment and control groups

Study design:



Q3M=every 3 months

* Stabilization of diet, medications, and laboratory values will be reviewed during screening period

** Participants in the 50 mg group who have entered the open-label period before dose combination will switch to 25 mg at the next treatment visit

Methodology:

This study will be conducted in adult patients with FCS. Participants with diagnosis of FCS will initiate a treatment stabilization period for at least 4 weeks, during which diet, lifestyle, and medication regimen will be stabilized. Enrolled participants will be counseled to remain on a diet comprising ≤20 g of fat per day and stable treatment regimen throughout the study, as per the Principal Investigator's (PI's) discretion and in accordance with the standard of care in China.

In the randomized period, approximately 30 participants who have met all protocol eligibility criteria during screening (including 10% dropout) will be randomized in a double-blinded fashion to receive 4 total doses of VSA001 Injection or matching placebo, administered subcutaneously (SC) once every 3 months (Q3M). Blinding will be preserved to the extent possible; however, treatment unblinding may occur, at the PI's or medical monitor's discretion, when deemed necessary for treatment of an adverse event (AE) or for a safety event-related decision or a decision to be made regarding trial continuation in an individual participant.

Participants who complete the randomized period will continue in an open-label extension period, where all participants will receive VSA001. In the early stage of the extension period, participants will remain blinded to their original treatment assignment and will initially receive VSA001 at the dose corresponding to their study treatment dose in the randomized period. Thus, participants who received VSA001 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (i.e., VSA001 25 mg Q3M or 50 mg Q3M).

Based on the analysis results of the Phase 3 global FCS study (AROAPOC3-3001) of this product, the proposed market dose of VSA001 is 25 mg. In the extension period of this study, all participants should receive VSA001 25mg Q3M after approval of the protocol (V3.4). However, participants in the 50 mg group who entered the open-label period earlier will timely switch to 25 mg at the next treatment visit.

For any participant experiencing acute pancreatitis, the participant may be unblinded and transitioned to the open-label treatment period of the study after assessment by the Investigator. This will be documented via the Interactive Web Response System (IWRS).

- If the participant had been assigned to receive placebo, they will be re-assigned to receive open-label treatment with VSA001 if they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and relevant procedures will start from Month 12 of the Schedule of Activities.
- If the participant had been assigned to receive VSA001, they will restore open-label treatment with VSA001 if they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and until at least 3 months have passed since the receiving the last dose of study drug, i.e., starting from Month 12 of the Schedule of Activities. Treatment adjustments to participants with alanine aminotransferase (ALT) increased or aspartate aminotransferase (AST) increased will be based on the Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis (Regev A, 2019).

Study Duration:

The duration of the study is expected to be 30 months; the enrollment will last 6 months, and follow-up will last 24 months. Statistical data of the trial supporting NDA will be cut off at Month 12 after the first dose in the randomized period.

Main Inclusion and exclusion criteria:

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

1. Males or non-pregnant (who do not plan to become pregnant), non-lactating females ≥18 years of age;
2. Able and willing to provide written informed consent prior to the performance of any study-specific procedures;
3. Fasting TG ≥10 mmol/L (~880 mg/dL) at screening, that is refractory to standard lipid lowering therapy (sample drawn after at least the minimum time on stable lipid-lowering regimen described in Table 2). Three repeat tests are allowed to qualify.
4. A diagnosis of FCS based on a documented history of fasting TG levels in excess of 1000

mg/dL (for at least 1 prior occasion) in the absence of clear triggering factors (e.g., alcohol, binge eating, etc.), and at least one of the following:

a. A supportive genetic test (from a source-verifiable medical record or based on screening genotype). Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including *LPL*, *APOC2*, *APOA5*, *GPIHBP1*, *GPD1*, or *LMF1*; or evidence of low LPL activity (<20% of normal) based on source-verifiable documentation; or

b. Documented history of recurrent episodes of acute pancreatitis, not caused by alcohol or cholelithiasis; or

c. Documented history of recurrent hospitalizations for severe abdominal pain without other explainable cause; or

d. Documented history of childhood or adolescent pancreatitis; or

e. Family history of hypertriglyceridemia-induced pancreatitis.

5. Willing to follow dietary counseling as per PI judgment based on local standard of care, consistent with the diet control regimen with an intake of ≤20 g of fat per day during the study.
6. If on medications for management of type 2 diabetes, or other medications allowed in Table 2, the dosing regimen must be stable before collection of qualifying lipid parameter at screening.
7. Participants with a medical history of clinical atherosclerotic cardiovascular disease (ASCVD) or those with elevated 10-year ASCVD risk (e.g., ≥7.5% per American Heart Association/American College of Cardiology risk calculator) must be on appropriate lipid-lowering therapy as per local standard of care (i.e., including moderate to high intensity statin, as determined by PI according to participant's condition) prior to collection of qualifying TG levels.
8. Participants of childbearing potential must agree to use a highly effective form of contraception (see Appendix 1), during the study and for at least 24 weeks after the last dose of investigational product (IP). Women of childbearing potential on a hormonal contraceptive must be stable on the medication for ≥1 menstrual cycle prior to Day 1 of the study. Participants must not plan to donate sperm or eggs during the study and for at least 24 weeks after the last dose of IP.

Note: All laboratory tests (except for coagulation) used as inclusion criteria will be assessed by a central laboratory and may be repeated once (except for TG), and the repeat value may be used for inclusion purposes. Local laboratory testing may be permitted in limited circumstances and only with prior Sponsor approval.

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

1. Current use or use within the last 1 year (before screening) of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule.
2. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening;
   b. HbA1c ≥ 9.0% at screening.
3. Active pancreatitis within 12 weeks before Day 1.
4. History of acute coronary syndrome events within 24 weeks of Day 1.
5. History of major surgeries within 12 weeks of Day 1.
6. Any of the following abnormal laboratory values at screening:
   a. ALT or AST ≥ 3 × ULN at screening;
   b. Total bilirubin ≥1.5×ULN (if the participant has a prior diagnosis and documentation of Gilbert's syndrome, then total bilirubin must be ≤3 mg/dL at screening);

c. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 at screening, using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation;
d. Spot urine protein/spot urine creatinine ratio greater than 3 g/day;
e. Clinically significant abnormality in prothrombin time, partial thromboplastin time, or INR.

7. Uncontrolled hypertension (blood pressure >160/100 mmHg at screening); if untreated, participant may be rescreened once hypertension is treated and controlled.
8. Use of any of the following:
   a. Systemic use of corticosteroids or anabolic steroids within 4 weeks prior to Day 1 or planned use during the study;
   b. Current use of glucagon-like peptide-1 (GLP-1) receptor agonists or planned use during the study;
   c. Plasma apheresis within 4 weeks prior to Day 1 or planned during the study;
   d. Blood donation of 50 to 499 mL within 4 weeks of collection of qualifying lipid parameter collection or of >499 mL within 8 weeks of qualifying lipid parameter collection.
9. On treatment with human immunodeficiency virus (HIV) antiretroviral therapy (Note: determination of HIV status is not a required study procedure).
10. Seropositive for hepatitis B virus (HBV) or hepatitis C virus (HCV) (hepatitis B surface antigen [HBsAg] and HBV DNA positive, or HCV RNA positive).
11. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%.
12. Clinical evidence of primary hypothyroidism (screening TSH > ULN and free T4< LLN), primary subclinical hypothyroidism (screening TSH > ULN and free T4 WNL), or secondary hypothyroidism (screening TSH < LLN and free T4 < LLN).
13. History of hemorrhagic stroke within 24 weeks of first dose.
14. History of bleeding diathesis or coagulopathy.
15. Current diagnosis of nephrotic syndrome.
16. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol).
17. History of malignancy within the last 2 years prior to the date of consent requiring systemic treatment except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Currently receiving systemic cancer treatment(s) or, in the PI's opinion, at risk of relapse for recent cancer.
18. 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.
19. Any concomitant medical or psychiatric condition or cognitive disorder caused by serious social situation or any other situation that, in the PI's judgment, would make it difficult to comply with protocol requirements or put the participant at additional safety risk.

Note: All laboratory tests used as exclusion criteria may be repeated once and the repeat value may be used for exclusion purposes.

Participant Withdrawal Criteria:

Withdrawal means that the participant is no longer receiving the study treatment (early termination of the study treatment). There are two conditions in which participants can withdraw study treatment:

- Withdrawal decided by participants

Participants may discontinue study treatment or withdraw from the study at any time. Reasons for withdrawal from the study may include, but are not limited to:

1. The participant withdraws his/her informed consent;
2. The participant is lost to follow-up/dies.

- The investigator may also terminate the participant's participation in the study at any time at his or her discretion. Reasons for the investigator's decision to withdraw a participant from the study may include:

1. According to the judgment of the investigator, intolerable AEs have occurred;
2. Unexpected medical conditions: the restrictions of this protocol are not conducive to the health of the participants, and the protocol treatment should be discontinued;
3. According to the judgment of the investigator, there is a co-morbidity that is likely to significantly affect the assessment of clinical status or that is likely to affect the safety of the participant;
4. Poor compliance and unable to receive treatment and attend visits as scheduled;
5. For other reasons, the investigator judges that it is not appropriate for the participant to continue the study (such as pregnancy).

Investigational drug, dosage and administration:

The test formulation is active VSA001 administered SC. The active pharmaceutical ingredient contained in VSA001 is a synthetic, double-stranded siRNA duplex conjugated to a NAG-targeting ligand to facilitate hepatocyte delivery.

Dosage: VSA001 (25 mg or 50 mg) administration on Day 1, then Q3M.

Duration of treatment:

The duration of the study is approximately 112 weeks from screening to the End-of-Study (EOS) examination. The screening period will last up to 8 weeks (Day -56 to Day -1). The treatment period will last up to 104 weeks (52 weeks in the randomized period and 52 weeks in the extension period).

Reference therapy, dose and administration:

The placebo is normal saline (0.9%) administered SC, volume-matched to the corresponding VSA001 dose volume.

Treatment compliance:

All study treatments will be administered at the study site. The investigational product (IP) will be dispensed by clinical study site staff members on the day of dosing and recorded in the drug accountability records. The date and time of study treatment administration will be recorded on the electronic Case Report Form (eCRF) on dosing days. Any confirmed pregnancy in the study will lead to permanent discontinuation of IP dosing of that participant.

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

- A need for apheresis or other emergent interventions indicated to lower TG
- Elevation of glycated hemoglobin meeting the criteria for treatment discontinuation
- In participants with normal AST and ALT on Day 1, treatment emergent elevations ≥3× ULN at least possibly related to IP per study Investigator (must be confirmed by repeat blood draw within 72 hours of initial results)
- In participants with elevated AST or ALT on Day 1, treatment emergent elevations >2× baseline at least possibly related to IP per study Investigator (must be confirmed by repeat blood draw within 72 hours of initial results)

Refer to "Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis" (Regev

A, 2019) for adjustments of treatment for participants with elevated AST or ALT.

Concomitant medications:

Use of optimal statin therapy, nicotinic acid, niacin, omega-3 fatty acids (prescription or OTC), or fibrates or other lipid management regimens, is acceptable if the participant has been on a stable regimen for at least 4 weeks as confirmed at screening and if the participant is willing to maintain a constant dosing regimen during the treatment period. Adjustments to medication regimens during the study, including lipid-lowering and diabetes mellitus therapies, are only allowed if, at the discretion of the PI, they are needed to provide adequate supportive care.

Statistical method:

Sample Size Considerations

Participants will be randomized in a 2:1:2:1 ratio into VSA001 25 mg dose group and volume-matched placebo group, VSA001 50 mg dose group and volume-matched placebo group. The two placebo groups will be pooled for statistical analysis, i.e. the randomization ratio of active groups to pooled placebo group is 1:1:1.

The significance of the median difference in percent change from baseline in TG at Month 10 between each active treatment group and placebo group will be judged using the Wilcoxon (Mann-Whitney) rank-sum test with correction for continuity. Type I errors will be controlled using Holm's method.

These estimates assume an average of 75% and 80% reduction from baseline in fasting TG at Month 10 in participants receiving VSA001 25 mg and VSA001 50 mg, respectively, and a 5% reduction in participants receiving placebo. The standard deviation is assumed to be 40% for all three groups, and the level of significance α is set to be two-sided 0.05.

It is expected that 27 participants completing the 10-month follow-up will provide a power of greater than 85% to detect at least one VSA001 group with statistically significant differences versus the pooled placebo group. Assuming a dropout rate of 10% at Month 10, a total of approximately 30 participants would need to be enrolled. Taking into account the effects of uncertainties such as competitive enrollment, block randomization, and COVID-19, approximately 36 participants will be enrolled.

General rules for statistical analysis and data processing rules:

SAS® system 9.4 or higher version will be used for analysis, and all tables, images, and listings will be generated as RTF/PDF files.

The Statistic Analysis Plan (SAP) will be finalized before the database lock.

Data will be analyzed by treatment group: VSA001 25 mg, VSA001 50 mg, or pooled placebo. In descriptive statistical analysis, the number (N) of participants in each treatment group or in the pooled group, the number and percentage (%) of participants and the number and percentage of missing participants under each classification level will be provided for categorical data, unless otherwise indicated. For continuous variables, data will be presented as number of participants in the treatment groups or total group (N), number of participants without missing results (n) and number of participants with missing results (nmiss), arithmetic mean, standard deviation, median, minimum, and maximum.

Efficacy Analysis

For endpoint analysis based on Month 10 data, the laboratory value will be the arithmetic mean of two values taken 2-7 days apart during Month 10. If only one value is available during Month 10, then this value will be used for endpoint analysis. For data analysis purposes, baseline for fasting serum TG will be defined as the arithmetic mean of Day 1 pre-dose assessment and the last fasting assessment prior to Day 1. If only one pre-dose value is available, the pre-dose value closest to the first dose will be used.

<u>Primary Efficacy Endpoint Analysis</u>

The significance of the median difference between active treatment and placebo will be judged using the Wilcoxon (Mann-Whitney) rank-sum test with correction for continuity.

The median difference between groups and its 95% confidence interval will be estimated using the Hodges-Lehmann method.

Analysis of Key Secondary Efficacy Endpoints and Other Continuous Efficacy Endpoints

Same as methods for primary analyses of the primary efficacy endpoint.

Exploratory endpoint analysis

Descriptive statistics will be provided for the secondary endpoints. For the analysis of exploratory endpoints, descriptive summaries will be provided, as applicable, and any inferential statistics (i.e., p-values) will be considered only as exploratory.

Safety Analysis

Incidence and severity of treatment-emergent adverse events

In general, safety analyses will be performed and the results summarized by cohort and treatment group. Adverse events (AEs) will be coded using the latest version of MedDRA by System Organ Class (SOC) and Preferred Term (PT). All treatment-emergent adverse events (TEAEs) will be summarized by seriousness, severity, and relationship to IP. The incidence and frequency of TEAEs, serious adverse events (SAEs), and serious TEAEs leading to discontinuation, will be summarized by cohort per SOC, PT, and severity. Treatment-related TEAEs (TRAEs) will also be summarized in a similar manner. AEs will also be summarized in participant listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome. The incidence/change of biomarkers will be summarized using descriptive statistics (shift tables may be provided). 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 participant listings.

Others

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

For long-term safety endpoints, descriptive statistics will be provided by active dose received.

Immunogenicity Analysis

Anti-drug Antibody Test Positivity and Titer

The number of participants to test positive for ADA at baseline and post-treatment will be summarized. Maximum ADA titer and range of titer values will be presented. VSA001 treatment-induced ADA formation, if any, will be analyzed to ascertain if the ADA response duration is transient or persistent using the definitions in the white paper published by Shankar et al (2014). The effect of ADA development on VSA001 PK, pharmacodynamics (PD), efficacy, and safety will be analyzed.

Definitions of analysis sets

Analysis dataset	Definition/Criteria
Full analysis set (FAS)	• Intention-to-treat analysis set: Including all randomized participants. • For FAS-based analyses and outputs, participant grouping will be based on the treatment assigned at randomization.

Per protocol set (PPS)	• PPS will include participants in the FAS without major protocol deviations that would affect efficacy assessments. • See the Protocol Deviation Management Plan/Medical Monitoring Plan for the definition of protocol deviations requiring removal of participants from the PPS. The rules for ultimate inclusion of participants in the PPS will be reviewed and determined at the data review meeting prior to database lock. • For PPS-based analyses and outputs, participant grouping will be based on the actual treatment received.
Safety set (SS)	• SS will include all randomized participants who have received at least 1 dose of the study drugs. • For SS-based analyses and outputs, participant grouping will be based on the group of the actual treatment received.
PK Analysis Set (PKS)	• PKS will include all participants who have been randomized and received at least one dose of study drug and have at least one evaluable plasma concentration data after dosing.

Planned Analyses

Primary Analysis

The primary analysis will include data from the randomized period. The primary analysis is planned when all randomized participants complete the randomized period or discontinue from study, whichever is earlier.

Final Analysis

The final analysis will include data from the randomized and extension periods. The final analysis is planned when all participants complete the extension period or discontinue from study, whichever is earlier.

Multiplicity

Placebo groups will be pooled for descriptive summary and statistical analysis. In this study, the primary efficacy endpoint and key secondary endpoints will be tested in sequence using the Fixed Sequence Design. When comparing the difference between each VSA001 treatment group and placebo group separately in the testing of each endpoint, type I error within each endpoint will be controlled using Holm's method.

The testing sequence of the fixed sequence procedure is shown in the table below:

Endpoints	**Test Sequence**
Percent change from baseline at Month 10 in fasting TG (primary endpoint)	1
Percent change from baseline at Months 10 and 12 in fasting TG (mean)	2
Percent change from baseline at Month 10 in fasting APOC3	3
Percent change from baseline at Month 12 in fasting APOC3	4

Schedule of Activities: Randomized Period

Visit	Screening	Randomized period														
					Month											
					1	2	3	4	5	6	7	8	9	10	11	12[a]
Study Day	Day -56 to Day -1	Day 1[b]	Day 2	Day 15	Day (±5 days)						Day (±10 days)		Day (±5 days)		±10 days	±5 days
					30	60	90[b]	120	150	180[b]	210	240	270[b]	300	330	360[b]
Informed Consent	X															
Dietary counseling/maintain diet[c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Review with participant signs and symptoms of pancreatitis and when to seek medical care	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria[d]	X	X														
Height and Weight[e]	X	X					X			X			X			X
Vital signs (BP, temperature, respiratory rate, heart rate)	X	X		X			X			X			X			X
Demographics	X															
Medical history (including genotype)	X	X														
Physical examinations	X	X		X			X			X			X			X
Single 12-lead ECG[f]	X									X			X			X
Triplicate 12-lead ECG[g]		X					X									
HBV and HCV serology screening	X															
FSH (women not of childbearing potential to confirm postmenopausal status)	X															
Pregnancy test (for women of childbearing potential)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid function test	X															

Visit	Screening	Randomized period															
					Month												
					1	2	3	4	5	6	7	8	9	10	11	12[a]
Study Day	Day -56 to Day -1	Day 1[b]	Day 2	Day 15	Day (±5 days)						Day (±10 days)		Day (±5 days)		±10 days	±5 days
					30	60	90[b]	120	150	180[b]	210	240	270[b]	300	330	360[b]
Routine laboratory tests[h]	X	X		X		X	X			X			X			X
Liver function tests (ALP, ALT, AST, TBL), blood glucose, and CBC[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
APOC3 and lipid parameters[j]	X	X			X	X	X	X	X	X	X	X	X	X[k]	X	X
Child-Pugh score	X[l]															
Anti-Drug Antibody		X			X		X			X			X			X
Sparse-PK Sampling[m]		X					X									
IP administration[n]		X					X			X			X			X
Follow-up 24 h post-dose			X													
Dietary assessment[o]		X					X			X			X			X
Quality of Life Assessment (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQPAN26)		X					X			X			X			X
Concomitant medications/therapies	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total cholesterol; BP = blood pressure; ECG = electrocardiogram; EORTC QLQ = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol 5-dimension instrument; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; IP = investigational product; PK = pharmacokinetics.

a. If a participant discontinues study participation early, then the Month 24 assessments (see **Schedule of Activities: Extension period**) should be completed at the time of early discontinuation, if possible.

b. Assessments completed on dosing days are to be done pre-dose, and Day 1 assessments will be used as baseline, unless otherwise specified. Urine pregnancy tests on Day 1 and subsequent dosing visit days will be performed pre-dose and must be negative.

c. It is recommended that all enrolled participants maintain on a diet of ≤ 20 g of fat per day from the start of screening and throughout the study. The special diet of

patients will be determined by the PI.

d. Assessments of all eligibility criteria (including laboratory values) must be completed within 56 days prior to Day 1, and all laboratory tests at screening and Day 1, except for coagulation, will be performed by the central laboratory.
e. Height (cm) at screening visit only; weight (kg) at all indicated visits.
f. Single 12-lead ECG will be performed in the supine position after the participant has rested comfortably for 5 min. ECGs will be collected prior to any blood draws.
g. Triplicate 12-lead ECG will be performed using validated ECG services equipment approximately time-matched to whole blood PK collections for all participants: ECG assessments should be done within -30 min prior to the pre-dose PK blood collections, and within 30 min before the 2-hour and 4-hour post-dose PK blood collections.
h. Blood and urine samples will be collected at screening after obtaining informed consent. Routine laboratory tests (blood chemistry, coagulation, urinalysis, and HbA1c) after Day 1 will be performed in the laboratory of the site. At study visits with blood draws for clinical laboratory tests or lipid parameter measurements, participants will have fasted for at least 10 hours prior to blood draw unless otherwise specified. HbA1c will be continuously assessed during the study, and the results will be used to determine whether treatment should be discontinued for the participants according to the criteria for treatment discontinuation (Appendix 5); samples collected on Month 2 (Day 60) will be analyzed for HbA1c only.
i. Liver function, blood glucose, and CBC tests after Day 1 will be performed in the laboratory of the study. Any elevation in ALP, ALT, AST, or TBL test results will be evaluated and followed by the laboratory of the site as described in the consensus guidelines for suspected drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis, and participants will have fasted for at least 10 hours prior to blood draw. The CBC will be used to monitor platelet counts. Only liver function, blood glucose, and CBC within 28 days prior to randomization will be accepted for the review of eligibility criteria.
j. Whole blood for pharmacodynamic (PD) analysis will be drawn after the site has confirmed the participant has maintained a stable diet for ≥4 weeks and stable background medications. These samples will be transported to the Sponsor's designated central laboratory for APOC3 and lipid parameter measurements. Only lipid parameters (TG, LDL-C, TC, non-HDL-C, HDL-C, VLDL-C, LP[a]) are required at screening, i.e., APOC3 testing is not required. At baseline (Day 1) and subsequent visits, lipid testing parameters will include TG, LDL-C, TC, non-HDL-C, HDL-C, VLDL-C, APOB-48, LP[a], APOB-100, total APOB, APOC-III, APOC-II, APOA-I, and APOA-V. Lipid parameter testing must be done after the participant has fasted for ≥10 hours before collection at each study visit.
k. At Month 10, collect lipids twice, 2 to 7 days apart, for calculation of study endpoints.
l. Child-Pugh score will be determined based upon clinical evaluations by the Investigator and pre-dose Day 1 baseline laboratory values.
m. Sparse PK sampling plan: All participants who have signed the informed consent for PK sampling will have whole blood for plasma PK samples drawn within 30 min pre-dose and at 4 hours (±30 min) post-dose at Day 1 and Month 3 after study treatment administration (VSA001 or placebo).
n. Prior to each dosing, the Investigator must make assessments based on the participant's most recent available laboratory test results (including but not limited to urine pregnancy, liver function, and HbA1c) and clinical condition to confirm eligibility for dosing. At Month 12, all participants will receive the first open-label dose of VSA001 at the dose corresponding to their study treatment dose in the randomized period (remain blinded to the initial treatment assigned in the randomized period until the last participant finishes the assessments in the randomized period. Thus, participants who received VSA001 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (i.e., VSA001 25 mg Q3M or 50 mg Q3M). All participants in the open-label period will receive VSA001 25 mg Q3M after approval of the new version of the protocol (V3.4).
o. Diet will be recorded on at least 3 of the past 5 days before the study visit.

Schedule of Activities: Extension period

Visit	Extension period					
	Month					
	13	14	15	18	21	24/EOS[a]
Study Day	Day (±10 days)					
	390	420	450[b]	540[b]	630[b]	720[b]
Dietary counseling/maintain diet	X	X	X	X	X	X
Review with participant signs and symptoms of pancreatitis and when to seek medical care	X	X	X	X	X	X
Weight			X	X	X	X
Vital signs (BP, temperature, respiratory rate, heart rate)			X	X	X	X
Physical examination (symptom-directed)			X	X	X	X
Single 12-lead ECG[c]			X	X	X	X
Pregnancy test (for women of childbearing potential)	X	X	X	X	X	X
Routine laboratory tests[d]	X	X	X	X	X	X
Liver function tests (ALP, ALT, AST, TBL) and CBC[e]	X	X	X	X	X	X
APOC3 and lipid parameters[f]	X	X	X	X	X	X
Anti-Drug Antibody			X	X		X
IP administration[g]			X	X	X	
Dietary assessment[h]			X	X	X	X
Quality of Life Assessment (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQPAN26)						X
Concomitant medications/therapies	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain, or events requiring apheresis)	X	X	X	X	X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; BP = blood pressure; ECG = electrocardiogram; EORTC QLQ = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EOS = end of study; EQ-5D-5L = EuroQol 5-dimension instrument; IP = investigational product.

a. If a participant discontinues study participation early, then the Month 24 assessments should be completed at the time of early discontinuation, if possible.
b. Safety assessments completed on dosing days are to be done pre-dose, unless otherwise specified.
c. Single 12-lead ECG will be performed in the supine position after the participant has rested comfortably for 5 min. ECGs will be collected prior to any blood draws.
d. Routine laboratory tests (blood chemistry, coagulation, urinalysis, blood glucose, and HbA1c) will be performed in the laboratory of the site. At study visits with blood draws for clinical laboratory tests or lipid parameter measurements, participants will have fasted for at least 10 hours prior to blood draw unless otherwise specified. HbA1c will be continuously assessed during the study, and the results will be used to determine whether treatment should be discontinued for the

participants according to the criteria for treatment discontinuation (Appendix 5); samples collected at Months 13 and 14 will be analyzed for HbA1c only.

e. Any elevation in ALP, ALT, AST, or TBL test results will be evaluated and followed by the laboratory of the site as described in the consensus guidelines for suspected drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis. The CBC will be used to monitor platelet counts.
f. Samples for APOC3 and lipid parameter measurements will be transported to the Sponsor's designated central laboratory for testing. Lipid parameter testing must be done after the participant has fasted for ≥10 hours before collection at each study visit.
g. Prior to each dosing, the Investigator must make assessments based on the participant's most recent available laboratory test results (including but not limited to urine pregnancy, liver function, and HbA1c) and clinical condition to confirm eligibility for dosing.
h. Diet will be recorded on at least 3 of the past 5 days before the study visit.

1. Table of Contents, List of Tables, and List of Figures

Table of Contents

List of Tables

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2. List of Abbreviations and Definition of Terms

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

Table 1: Abbreviations

Abbreviations	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
APOA-I or APOA1	Apolipoprotein A-I
APOA-V or APOA5	Apolipoprotein A-V
APOB	Apolipoprotein B
APOB-100	Apolipoprotein B-100
APOB-48	Apolipoprotein B-48
APOC2	Apolipoprotein C2
APOC3	Apolipoprotein C3
ARO-APOC3	Short name for ARO-APOC3 Injection
ARO-APOC3 Injection	Clinical drug product solution ready for SC injection
ASCVD	Arteriosclerotic cardiovascular disease
AST	Aspartate aminotransferase
CECT	Contrast-enhanced computed tomography
cGMP	Current Good Manufacturing Practice
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID	Coronavirus Disease
CRA	Clinical Research Associate
CRO	Contract research organization
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
DNA	Deoxyribonucleic acid
DSC	Data Safety Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of study
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
ET	Early Termination

Abbreviations	Definition
FAS	Full analysis set
FCS	Familial chylomicronemia syndrome
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPIHBP1	Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1
HbA1c	Glycated haemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	Heart rate
HTG	Hypertriglyceridaemia
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDL-C	Intermediate-density lipoprotein cholesterol
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
kDa	Kilodalton
LISR	Local injection site reactions
LDL-C	Low-density lipoprotein cholesterol
LMF1	Lipase maturation factor 1
LPL	Lipoprotein lipase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NAG	N-Acetylgalactosamine
NCA	Noncompartmental Analysis
NHV	Normal healthy volunteers
NLME	Nonlinear mixed effects
NOAEL	No observed adverse effect level
Non-HDL-C	Non-high-density lipoprotein cholesterol

Abbreviations	Definition
NYHA	New York Heart Association
OTC	Over-the-counter
PD	Pharmacodynamics
PFS	Prefilled Syringe
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred term
Q3M	Once every 3 months
QTcF	QT interval corrected by Fridericia's formula
RISC	Ribonucleic acid-induced silencing complex
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interference
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SHTG	Severe hypertriglyceridaemia
siRNA	Small interfering ribonucleic acid
SOA	Schedule of activities
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TRAE	Treatment-related adverse event
TRL	Triglyceride-rich lipoprotein
ULN	Upper limit of normal
VAS	Visual analogue scale
VLDL-C	Very low density lipoprotein cholesterol
WNL	Within normal range

3. Introduction

3.1. Overview of Disease Background

3.1.1. Familial chylomicronemia syndrome

Familial chylomicronemia syndrome (FCS) is a severe and ultrarare genetic disease, with an estimated prevalence of approximately 1 in 1,000,000. FCS is often caused by various monogenic mutations (e.g., null mutations in the genes coding for lipoprotein lipase [LPL], glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 [GPIHBP1], apolipoprotein C2 [APOC2], apolipoprotein A5 [APOA5], or lipase maturation factor 1 [LMF1]). FCS generally results in extremely high fasting TG levels (above 900 mg/dL), ranking the first 0.1% of the TG levels. Such severe elevations lead to various serious signs and symptoms including acute pancreatitis (which can be fatal), chronic daily abdominal pain, type 2 diabetes mellitus, hepatic steatosis, and cognitive issues (aka “brain fog”). In recent years, a stepwise calculation method- and scoring-based approach has been proposed for clinical diagnosis of FCS (Falko 2018; Stroes 2017; Moulin 2018). Genetic testing has gradually become a common test in the clinical care of patients with dyslipidaemia. FCS is one of the blood lipid abnormalities for which genetic testing may be clinically useful; however, no clinical practice guidelines have been available for genetic testing for patients who may have inherited dyslipidaemia (Brown 2020). Currently, there are very limited treatment choices that can adequately treat FCS. Only one antisense oligonucleotide inhibitor of apolipoprotein C3 (APOC3) was approved for marketing in Europe and Brazil.

The only effective treatment is a diet extremely low in fat (about 20 g per day). This diet does not normalize TG levels but reduces the risk of pancreatitis. However, diet compliance is one of the major barriers to reducing the risk of pancreatitis. Generally, the available therapies lower TG levels through the LPL pathway which usually causes dysfunction in FCS patients, making these therapies mostly ineffective. FCS patients are also at a risk of significantly increased TG levels after meals (usually > 500 mg/dL), generally leading to severe abdominal pain and a risk of postprandial pancreatitis, which usually requires hospitalization. Pancreatitis is one of the major complications of FCS that can be life-threatening; it is induced by digestion of TG in a large number of chylomicrons by pancreatic lipase. Pancreatitis is estimated to have a mortality of 10% for each episode and can lead to other life-threatening conditions such as sepsis, acute respiratory distress syndrome, hypovolaemic shock, and renal failure.

Acute pancreatitis is a condition known to be associated with severe hypertriglyceridaemia (SHTG, including FCS), and is characterized by severe, persistent upper abdominal pain and increased serum lipase and/or amylase. It can lead to organ failure, frequent emergency clinic visits, hospitalization, chronic abdominal pain, and even death. Recurrence of acute pancreatitis can cause chronic pancreatitis, resulting in pancreatic failure and chronic abdominal pain, as well as associated pancreatic endocrine dysfunction (e.g., diabetes mellitus). The mortality rate associated with acute pancreatitis attacks ranges from 3% (mild cases) to 30% (severe cases).

Hypertriglyceridaemia (HTG)-associated acute pancreatitis has higher morbidity and mortality than pancreatitis of other etiologies (FDA 2018). The risk of acute pancreatitis increases with increasing serum TG levels, and the incidence of acute pancreatitis increases by 3% to 4% for every 100 mg/dL (1.13 mmol/L) increase in TG levels (Gelrud 2017; Scherer 2014).

3.1.2. Apolipoprotein C3

APOC3 is an 8.8 kilodalton (kDa) protein component of triglyceride-rich lipoproteins (TRLs) such as very-low-density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL-C), chylomicrons, high-density lipoprotein cholesterol (HDL-C), and remnant particle lipoproteins. APOC3 is mainly synthesized in hepatocytes (about 80% in hepatocytes and 20% in intestinal cells), and its key function is to inhibit LPL-mediated hydrolysis of TG on TRLs on the surface of capillary endothelial cells of muscle and adipose tissues. APOC3 also delays clearance of lipoprotein remnants by the liver by inhibiting hepatocyte receptor-mediated uptake. APOC3 functions as a key regulator of fasting and postprandial plasma TG levels (Crosby 2014).

Studies in transgenic mice overexpressing APOC3 and *APOC3*-knockout mice suggest that APOC3 would delay *in vivo* VLDL-C hydrolysis and may delay the catabolism of TRL residues in liver and other tissues (Aalto-Setala 1992; Aalto-Setala 1996; Gerritsen 2005; Jong 2001; Khetarpal 2015). Plasma TG, VLDL-C, and IDL-C were significantly lower, and TG clearance was higher in the *APOC3*-knockout rabbit model than in wild-type animals. Both aortic and coronary atherosclerosis were significantly reduced in gene-knockout rabbits compared to wild-type controls (Yan 2020).

Two reports concurrently published in 2014 used complementary genetic methods to demonstrate that *APOC3* functional deletion mutations were closely associated with reduced TG and reduced incidence of coronary artery disease, while marked hepatic steatosis was not observed (Crosby 2014; Jorgensen 2014). Compared with non-carriers, patients with *APOC3* homozygous deficiencies had an 88% reduction in APOC3 and a 59% reduction in TG (Lek 2016; Saleheen 2017). In addition, patients with *APOC3* homozygous deficiencies ("human knockout") did not appear to present adverse phenotypes (Lek 2016; Proctor 2003). Given the important role of APOC3 in serum TG level modulation and its hepatocyte primary source of synthesis, it is an ideal target for hepatocyte targeted ribonucleic acid interference (RNAi) mediated gene silencing.

Reducing APOC3 through a hepatocyte-targeting RNAi strategy may reduce circulating TG, potentially benefiting multiple patient populations including FCS patients, who remain at a high risk of high TG-induced pancreatitis after receiving the current standard of care.

3.2. Overview of VSA001 Development

Below is a brief overview of the available information for VSA001 (ARO-APOC3); a comprehensive review of available data (i.e., a review prior to the start of the study) is included

in the Investigator's Brochure (IB).

3.2.1. Mechanisms of Action and Therapeutic Rationale

VSA001 (ARO-APOC3) acts through the mechanism of RNAi. RNAi-based therapeutics have the potential to silence the expression of any specific target gene. RNAi is a naturally- occurring phenomenon by which siRNAs trigger a sequence- specific down- modulation of gene expression. RNAi-triggering molecules are synthetic oligonucleotides intended to silence the expression of specific genes in a targeted manner (Fire 1998). The RNAi trigger is a short, double-stranded siRNA conjugated to an N-acetyl galactosamine (NAG) targeting moiety, acting as a ligand for the highly expressed, hepatocyte-specific asialoglycoprotein receptor. Available nonclinical and clinical pharmacokinetic (PK) data show rapid absorption and clearance of all NAG conjugated triggers from the blood stream within 24 to 48 hours post-SC administration.

VSA001 is a synthetic, hepatocyte-targeted, double-stranded RNAi trigger designed to specifically silence messenger RNA (mRNA) transcription of the *APOC3* gene using the RNA interference (RNAi) mechanism. Preclinical distribution studies show that VSA001 is distributed to the liver, where the trigger molecule is taken up by hepatocytes via receptor-mediated endocytosis. Introduction of the double-stranded RNAi trigger into the cytoplasm of hepatocytes results in its association with the protein components of the RNA-induced silencing complex (RISC), resulting in "on-target" highly sequence-specific degradation of mRNA complementary to the antisense strand of the RNAi trigger. Active RISC is a multiple turnover enzyme complex; therefore, a single RNAi trigger into RISC can result in the degradation of many mRNA molecules. Prolonged reduction in the expression of the corresponding proteins can provide sustained pharmacological activity for a duration significantly exceeding that of plasma exposure.

It is expected that silencing hepatic *APOC3* and blocking APOC3-mediated lipoprotein lipase (LPL) inhibition with VSA001 can enhance peripheral LPL activity and reduce serum TG. In addition, *APOC3* silencing eliminates steric hindrance of APOC3 on hepatocytes, leading to increased hepatic clearance of TRL.

3.2.2. Preclinical Studies

The sponsor is conducting a comprehensive preclinical program to support SC administration of VSA001 (ARO-APOC3). The studies of potential clinical significance and relevant to this protocol are summarized below.

Proof-of-concept studies in animal models support the use of siRNA targeting *APOC3* as a potential treatment option for SHTG and FCS. The results of potential clinical significance and relevant to this protocol are summarized below. Details regarding preclinical pharmacology, PK, and toxicology results are provided in the Investigator’s Brochure (IB).

- Preclinical pharmacology of ADS-005, the active pharmaceutical ingredient (API) in

VSA001, showed that treatment with ADS-005 in transgenic mice (TgAPOC3) resulted in dose-dependent decreases in liver *APOC3* mRNA level, which was associated with a >90% decrease in serum APOC3. The decreased serum APOC3 was associated with decreased serum lipids (91% maximum mean reduction in TG, 45% maximum mean reduction in total cholesterol, and 64% maximum mean reduction in low-density lipoprotein C [LDL-C]).

- Similar reductions in serum APOC3 were also observed following treatment with ADS-005 in rhesus monkey model of diet-induced dyslipidaemia. VSA001 treatment was well tolerated in toxicology studies in rats and non-human primates.
- Results of the non-Good Laboratory Practice (GLP) *in vitro* toxicology studies suggest that at the ADS-005 concentrations up to 250 μg/mL (far exceeding the expected blood concentration with the clinically used dose).
  - The possibility of ADS-005 exposure inducing a congenital immune system is minimal.
  - There is no possibility of complement activation, mitochondrial toxicity/cytotoxicity, or platelet aggregation in whole blood.
- A set of genotoxicity and safety pharmacology studies recommended by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) showed that ADS-005 was not genotoxic and had no adverse effects on the central nervous, respiratory, or cardiovascular system.
- GLP toxicity studies where rats and cynomolgus monkeys received multiple doses of ADS-005 SC showed that ADS-005 treatment was well tolerated, with a No Observed Adverse Effect Level (NOAEL) of 300 mg/kg for both species.
- In rat and cynomolgus monkey studies, significant histopathologic adverse outcomes were consistent with those observed with other NAG-siRNA drugs for SC administration.

3.2.3. Clinical Studies

A Phase 1 single and multiple ascending dose study (AROAPOC31001) to evaluate the safety, tolerability, PK and pharmacodynamics (PD) of ARO-APOC3 (VSA001) in healthy adult subjects and patients with HTG and chylomicronemia syndrome (CS, including FCS) has been completed. Results of study AROAPOC31001 showed that in healthy participants, ARO-APOC3 treatment reduced serum TG, LDL-C, and apolipoprotein B (APOB), and increased HDL-C by reducing production of APOC3 in liver through the action of RNAi. The 10, 25, 50 and 100 mg doses all showed sustained PD activity, lasting for more than 3 months. Except for mild, transient local injection site reactions (LISRs) and transient, self-limiting alanine aminotransferase (ALT) increased, single and repeat doses of ARO-APOC3 were well tolerated in healthy participants; based on the safety profile of the Phase 1 data, it was considered acceptable to further perform later-phase clinical evaluation. Preliminary data from participants with FCS also suggested significant reductions in APOC3 and TG following repeat doses (at baseline and on Day 29) of AROAPOC3 25 mg and 50 mg. See the IB for more

information on the results of study AROAPOC31001.

Results of the Phase 1 study support the design information for conducting randomized, double-blind, placebo-controlled Phase 2 studies in patients with SHTG (AROAPOC3-2001) and mixed dyslipidaemia (AROAPOC3-2002), as well as an open-label extension study in patients from these studies (AROAPOC3-2003). PK and PD model analysis results of the Phase 1 study support selecting 25 and 50 mg once-every-3-month (Q3M) doses for the Phase 3 clinical study in FCS patients. In addition, the completed Phase 1 clinical study included a small proportion (12.5%) of Asian participants to compare for any differences in PK, PD, or safety of ARO-APOC3 (VSA001) in Asian and non-Asian participant subgroups, showing that there were no significant differences between the two subgroups, as specified in the ARO-APOC3 Ethnic Sensitivity Assessment Report (version 1.0, dated September 21, 2022).

The AROAPOC3-2001 study is a completed phase IIb, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ARO-APOC3 (VSA001) in adult patients with SHTG. Participants were randomized in a 3:1 ratio to either ARO-APOC3 10 mg, 25 mg, or 50 mg dose group or placebo group to receive two subcutaneous doses on Day 1 and at Week 12, respectively. A total of 229 participants were randomized in the study and a total of 226 participants were included in the final analysis set at EOS. During the study period, a total of 171 participants (75.7%) experienced at least one TEAE. Overall, the most commonly reported TEAEs were poor glycemic control, COVID-19, upper respiratory tract infection and headache. ARO-APOC3 was generally well tolerated and all doses demonstrated acceptable safety and tolerability profiles. The incidence of TEAEs was generally balanced between ARO-APOC3 and placebo. The proportion of participants who experienced SAEs was higher in the placebo group (16.4%) than in the ARO-APOC3 groups (3.6% to 12.5%). No SAEs reported were considered by the investigator or sponsor to be related to ARO-APOC3 treatment. In contrast, the SAEs were considered related to the basic pathology and comorbidities of the participant population/study participants. There was a modest numerical increase in HbA1c levels in all ARO-APOC3 treatment groups compared with placebo, mostly driven by diabetics with poor glycemic control at baseline, predominantly those who received the 50 mg dose. Although all doses of ARO-APOC3 showed increased HbA1 levels compared with placebo, the ARO-APOC3 25 mg dose was associated with a lower magnitude of effect on HbA1c levels as well as better glycemic control compared with the ARO-APOC3 10 and 50 mg doses.

3.3. Potential Risks for Study Participation

3.3.1. Embryo-fetal

Limited GLP toxicology and clinical studies related to reproductive toxicity have been available. Therefore, eligible participants (men and women, including their partners) enrolled in this study must agree to use highly effective contraceptive methods or exercise abstinence (only acceptable if the method is in line with the participant's normal lifestyle) during the study (Appendix 1).

3.3.2. Hepatic function

The target organ of VSA001 (ARO-APOC3) is liver. Literature on siRNA describes ALT changes associated with the off-target effect of microRNA in hepatocytes induced by the siRNA seed region (Janas 2018). Screening was performed for the presence of potential messenger RNA (mRNA) and microRNA homologies in the siRNA sequences of VSA001 sense and antisense strands, where sequences with homology were not considered. Therefore, such off-target effects are not expected to occur.

However, transient mild to moderate ALT increased was occasionally observed in study AROAPOC31001 (see the IB for details), which was not accompanied by International Normalized Ratio (INR) or total bilirubin (TBL) increased. To reduce this risk, a fixed stop rule for ALT and aspartate aminotransferase (AST) increased is included in this study protocol (Appendix 2). Blood samples will be collected as specified in the Schedule of Activities (SOA), and liver function and any potential liver injury will be evaluated. The Data Safety Committee (DSC) will regularly review all available safety data, including laboratory data (Section 5.4.1).

3.3.3. Injection Site AEs

Other modified siRNA candidate drugs for SC administration evaluated in clinical studies were associated with mild to moderate LISRs (e.g., pain and erythema) (Appendix 3). Commonly reported in study AROAPOC31001 were mild injection site adverse events (AEs). In this study, measures such as rotating the injection site and allowing VSA001 solution to recover to room temperature before injection will be taken to minimize LISRs.

3.3.4. Poor glycemic control

Interim analyses for the two Phase 2 clinical trials in patients with SHTG (AROAPOC3-2001) and mixed dyslipidaemia (AROAPOC3-2002) noted unbalanced changes in glycosylated haemoglobin (HbA1c) over time, mainly presented as significantly increased HbA1c in participants in the ARO-APOC3 treatment group compared to the placebo group. These changes were mainly observed in participants who had diabetes at baseline and were observed to be the most significant in the subset of participants treated with the highest dose of ARO-APOC3 (50 mg). Based on these observations, the rules for treatment discontinuation and safety precautions for all ongoing ARO-APOC3 clinical studies have been updated. In the extension period (AROAPOC3-2003) to the aforementioned two Phase 2 clinical trials, assessment at the 50 mg dose level has been stopped, and participants who have been enrolled to receive or have already received the 50 mg dose will switch to the 25 mg dose for the next scheduled dose according to the study Schedule of Activities.

This study is a phase III clinical study to evaluate the efficacy and safety of VSA001 in FCS patients, which is consistent with the overseas phase III clinical study in FCS patients (AROAPOC3-3001 study). The data from the AROAPOC3-3001 randomized double-blind study are summarized as follows: ARO-APOC3 25 mg Q3M and 50 mg Q3M both resulted in

great reductions in triglycerides, and approximately 80% of participants in both dose groups achieved 50% reduction in triglycerides. Compared to placebo, 25 mg and 50 mg doses of VSA001 provided similar efficacy results. The incidence of TEAEs was generally balanced between the ARO-APOC3 groups and the placebo group. No death occurred during the study period; the incidences of SAEs and Grade ≥ 3 TEAEs were higher in the placebo group than in the VSA001 groups. The observed TEAEs generally showed no dose dependence. Based on the analysis results of the phase III global FCS study (AROAPOC3-3001) of this product, the proposed market dose is 25 mg.

The study will continue to evaluate the dose of 50 mg in FCS participants in the randomized treatment period, but the evaluation frequency of HbA1c will be increased (Schedule of Activities: Randomized period; Schedule of Activities: Extension Period). In addition, relevant criteria for treatment discontinuation are established (Appendix 5). All participants in the open-label period will receive VSA001 25 mg Q3M in the extension period (after approval of protocol V3.4).

3.3.5. Benefit-risk Assessment

To date, VSA001 (ARO-APOC3) has demonstrated an acceptable benefit-risk profile, yet further clinical studies with longer exposure periods are warranted. Results of the Phase 1 study AROAPOC31001 showed that treatment with ARO-APOC3 10-100 mg resulted in significant and durable reductions in serum APOC3 compared to placebo in healthy participants and patients with HTG and chylomicronemia (including FCS).

Silencing APOC3 resulted in reductions in serum TG and other lipid parameters. In normal healthy volunteers (NHVs) receiving a single dose of ARO-APOC3, serum APOC3 decreased in a dose-dependent manner by up to 94% from baseline. In addition, TG (by up to -66%) and non-HDL-C (by up to -31%) were also reduced, and HDL-C (by up to +74%) was increased, with the dose effect generally associated with the decreased serum APOC3 in participants in the active drug group. In NHVs receiving repeated doses of ARO-APOC3, APOC3 (by up to -94%), TG (by up to -75%) and non-HDL-C (by up to -39%) continued to decrease, and HDL-C (by up to +75%) increased. These responses continued until Week 16 (12 weeks after the last dose).

In patients with HTG and/or chylomicronemia receiving repeated doses of ARO-APOC3, compared to single dose, ARO-APOC3 produced similar or even greater effects at similar doses. Decreases in APOC3 (by up to -98%), TG (by up to -87%), and non-HDL-C (by up to -55%) and increases in HDL-C (by up to +120%) were observed. The effects of ARO-APOC3 treatment on these and other key lipid parameters continued until Week 16 (12 weeks after the last dose).

ARO-APOC3 treatment was generally well tolerated. No deaths or discontinuations from study due to AE were reported during the studies. Three participants reported 3 serious adverse events (SAEs), all of which were considered to be unrelated to the investigational product, and all the

participants completed study. There is no clear evidence that the frequency or severity of AEs would increase with dose. The reporting rate of treatment-emergent adverse events (TEAEs) was similar in the pooled placebo group and ARO-APOC3 treatment group. Most TEAEs were unrelated to study treatment, and no participants withdrawn from study due to TEAE. Overall, the AEs observed in this Phase 1 study were typical AEs expected to be observed in follow-up for a group of normal participants over the same time period. The most commonly reported drug-related AE was LISRs, which were all mild. Injection site AEs are expected based on the similar results reported in other clinical studies of siRNA for SC administration. Overall, there were no clinically significant trends in adverse laboratory test results. No clinically significant adverse changes or outcomes of particular concern were observed in electrocardiography (ECG), vital signs, or physical examination, either.

Unbalanced changes in HbA1c as treatment prolonged were observed in the interim analyses for the overseas Phase 2 clinical studies (AROAPOC3-2001 and AROAPOC3-2002) of ARO-APOC3, with HbA1c observed to be significantly increased in participants with diabetes in the ARO-APOC3 treatment group compared to the placebo group, particularly in participants in the 50 mg dose group. The data from the AROAPOC3-3001 randomized double-blind study in FCS patients are summarized as follows: ARO-APOC3 25 mg Q3M and 50 mg Q3M both resulted in great reductions in triglycerides, and approximately 80% of participants in both dose groups achieved 50% reduction in triglycerides. Compared to placebo, 25 mg and 50 mg doses of ARO-APOC3 provided similar efficacy results. The incidence of TEAEs was generally balanced between the VSA001 groups and the placebo group. No death occurred during the study period; the incidences of SAEs and Grade ≥ 3 TEAEs were higher in the placebo group than in the ARO-APOC3 groups. The observed TEAEs generally showed no dose dependence. Based on the analysis results of the Phase III global FCS study (AROAPOC3-3001) of this product, the proposed market dose of VSA001 is 25 mg. In FCS participants of the study (VSA001-3001 study), on the premise of increasing the evaluating frequency of HbA1c and establishing relevant criteria for treatment discontinuation, the 25 mg and 50 mg dose groups will continue to be evaluated during the randomized treatment period. In addition, all participants in the open-label period will receive VSA001 25 mg Q3M in the extension period (after approval of protocol V3.4).

4. Study Objectives and Endpoints

4.1. Objective

The primary objective of this study is to evaluate the efficacy and safety of VSA001 in adults with FCS.

4.2. Endpoints

4.2.1. Primary endpoint

The primary endpoint for this study is as follows:

- Percent change from baseline at Month 10 in fasting serum TG

4.2.2. Key secondary endpoints

The key secondary endpoints for this study are as follows:

- Percent change from baseline at Months 10 and 12 (averaged) in fasting serum TG
- Percent change from baseline at Month 10 in fasting serum APOC3
- Percent change from baseline at Month 12 in fasting serum APOC3

4.2.3. Secondary endpoints

The following secondary endpoints are for the randomized period only, except as noted.

- Percent change from baseline at Month 10 in fasting serum non-high density lipoprotein cholesterol (non-HDL-C) and HDL-C
- Percent change from baseline at Month 12 in fasting serum TG, non-HDL-C, and HDL-C
- Proportion of participants achieving fasting serum TG of <500 mg/dL at Month 10
- Proportion of participants achieving fasting serum TG of <500 mg/dL at Month 12
- Change and percent change from baseline at each scheduled assessment in fasting serum TG up to Month 12
- Incidence of TEAEs in the participants (either period)
- Incidence of positively adjudicated events of acute pancreatitis (either period)
  Note: Any AEs and SAEs reported by the investigator during the study that are consistent with acute pancreatitis events will be adjudicated by the blinded Data Safety Committee based on the Atlanta Classification for Acute Pancreatitis 2013 for fulfillment of any 2 of the following 3 criteria:
  1. Abdominal pain consistent with symptoms of acute pancreatitis (acute episodes of persistent, severe upper abdominal pain often radiating to the back)
  2. Serum lipase activity (or amylase activity) ≥3 × ULN
  3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) or transabdominal ultrasonography

4.2.4. Exploratory endpoints

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

- Change and percent change from baseline at each scheduled assessment in fasting serum lipid parameters (total cholesterol, low-density lipoprotein cholesterol [LDL-C], HDL-C, non-HDL-C, VLDL-C, total apolipoprotein B [APOB], APOB-48, lipoprotein(a) [LP(a)], APOB-100, APOC2, APOC3, apolipoprotein A-I [APOA1], and apolipoprotein A-V [APOA5]), with all values drawn after at least a 10-hour fast.

- Changes from baseline at each scheduled assessment in fasting serum blood glucose, glycated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide
- Change and percent change from baseline at each scheduled assessment in TG, APOC3, non-HDL-C, and HDL-C (extension period only)
- Proportion of participants reaching TG of <500 mg/dL at each scheduled assessment
- Incidence of hospitalizations for abdominal pain
- Participant incidence of emergent apheresis
- PK parameters of VSA001
- Incidence of anti-drug antibodies (ADA) to VSA001
- Change from baseline at each scheduled assessment in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 score
- Change from baseline at each scheduled assessment in EORTC QLQ-PAN26 score
- Change from baseline at each scheduled assessment in EuroQol 5-dimension instrument (EQ-5D-5L) score

5. Investigational Plan

5.1. Overall study design

5.1.1. Overview of study design

This is a randomized, double-blind, placebo-controlled, dose-finding clinical trial that will include 2 parallel dose groups: 25 mg and 50 mg. Following a once-every-3-month dosing regimen and using the percent change from baseline at Month 10 in fasting serum TG as the primary endpoint, the efficacy of VSA001 in patients with FCS will be evaluated. At the same time, the occurrence of safety events in the participants during the treatment period will be collected, and the optimal dose for Chinese patients with FCS will be explored based on the benefit-risk assessment.

This study will be conducted in adult participants with FCS. participants who have signed the Informed Consent Form (ICF) previously approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) may enter screening, during which eligibility assessments will be completed. At the same time, a stable diet, lifestyle and medication scheme will be maintained at the Principal Investigator (PI)'s discretion and based on the local standard of care during this period. All other eligibility criteria assessments and review of laboratory test values must be completed within 8 weeks prior to Day 1.

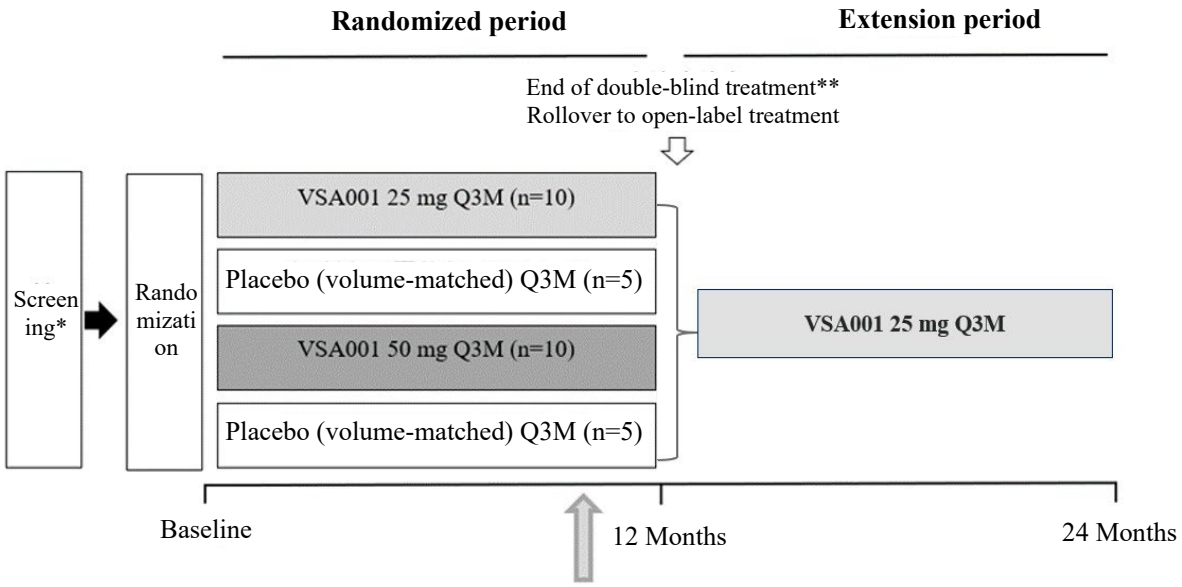
During the randomized period, approximately 30 participants (meeting all eligibility criteria during the screening period) will be randomized in a double-blinded manner to receive SC administration of either VSA001 or matching placebo once every 3 months (Q3M; Figure 1), for a total of 4 doses. Blinding will be preserved during randomized period; however, treatment

unblinding may occur, at the PI's or medical monitor's discretion, when deemed necessary for treatment of an adverse event (AE) or for a safety event-related decision or a decision to be made regarding trial continuation in an individual participant.

Early in the extension period of the study, participants will remain blinded to the treatment assignment for the randomized period and will start to receive open-label VSA001 at the same dose as the study treatment dose that they received during the randomized period. Thus, participants who received VSA001 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (i.e., VSA001 25 mg Q3M or 50 mg Q3M). Based on the analysis results of the Phase 3 global FCS study (AROAPOC3-3001) of this product, the proposed market dose of VSA001 is 25 mg. In the extension period of the study, after the approval of the protocol (V3.4), all participants should receive treatment with VSA001 25 mg Q3M; participants in the 50 mg group who earlier entered the open-label period will also be switched to the 25 mg treatment group for the next dose.

At the PI's discretion and based on the local standard of care, it is recommended that all enrolled participants maintain a diet containing ≤20 g fat per day from starting screening and throughout the study and maintain a stable treatment regimen throughout the study. The specific diet for a patient will be determined by the PI. Dietary counseling will start during the treatment stabilization period and be performed at each subsequent study visit to promote compliance, and dietary assessments will be performed in accordance with the SOAs (Schedule of Activities: Randomized Period and schedule of activities: extension period) and Section 10.4.

Figure 1: Study Flow Chart



Q3M=once every 3 months

* Stabilization of diet, medications, and laboratory values will be reviewed during screening period

** Participants in the 50 mg group who have entered the open-label period before dose combination will switch to 25 mg at the next treatment visit

For any participant experiencing acute pancreatitis, the participant may be unblinded and transitioned to the open-label treatment period of the study after assessment by the Investigator. This will be documented via the Interactive Web Response System (IWRS).

- If the participant had been assigned to receive placebo, they will be re-assigned to receive open-label treatment with VSA001 if they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and relevant procedures will start from Month 12 of the Schedule of Activities.
- If the participant had been assigned to receive VSA001, they will restore open-label treatment with VSA001 if they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and until at least 3 months have passed since the receiving the last dose of study drug, i.e., starting from Month 12 of the Schedule of Activities.

5.1.2. Informed Consent

Before starting any screening procedure, the PI or designated study doctor will inform the participant of the nature and purpose of the study, including the risks and benefits involved, possible AEs, and the fact that participation in the study is voluntary, and provide a copy of the IRB/IEC-approved ICF for review. Each participant will provide a written Informed Consent Form to participate in the study in the presence of the PI or designated study doctor and confirm receipt of the above information, and the ICF will also be signed and dated by the PI or

designated study doctor. The time that each participant gives informed consent will be recorded in the site source documentation. The PI will retain a signed original of the Informed Consent Form and provide a copy to the participant.

Informed Consent Form will be signed in accordance with the principles of the ICH Good Clinical Practice (GCP) procedures. For all participants considering to participate in the study and be subsequently enrolled or excluded, the PI or medically qualified designee completes recording of whether the participant meets the inclusion criteria. Detail information of screening failures can be recorded using the Study Eligibility Screening Form or Participant Screening Failure Log. The procedures outlined in the SOA (Schedule of Activities: Randomized Period) will be followed. The time restriction for fasting outlined in Section 7.2.1 will be followed.

No study assessment or procedure will be performed until the participant has signed the ICF.

5.1.3. Screening

See Schedule of Activities: Randomized Period for the SOA for screening. Before laboratory assessment of fasting blood lipid parameters judged to be acceptable, it should be confirmed that the diet has remained stable for at least 4 weeks. Enrolled participants will be counseled to remain on a diet comprising ≤20 g of fat per day throughout the study, as per the Principal Investigator's (PI's) discretion and in accordance with the local standard of care The specific diet will be determined by the PI based on each individual's specific diagnosis and medical needs. Dietary assessment and counseling will be initiated during Screening, and dietary counseling will be provided throughout the study to promote compliance. The PI may make dietary changes as appropriate.

Only liver function, blood glucose, and hematology tests within 28 days prior to randomization will be acceptable for assessment of in/exclusion criteria; other eligibility criteria assessments and review of laboratory test values (Section 6) must be completed within 8 weeks prior to Day 1. During Screening and throughout the study, participants' blood lipid parameters will be collected in a fasted state (no food or beverages other than water and essential oral medications allowed for at least 10 hours) to assess the eligibility.

A screening failure refers to where a participant did not enter study despite having given consent to participate in the clinical study. It is required to provide essential information of screening failures and ensure that screening failures are reported in a transparent manner and that questions from regulatory authorities are responded to. At a minimum, demographics, screen failure details, eligibility criteria, and any serious adverse events (SAEs) should be included.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. For each screening/re-screening, a re-screened participant will be assigned a new participant screening number.

5.1.4. Treatment Period

Participants meeting the eligibility requirements at Screening will be enrolled in the study. All dose cohorts will enroll in parallel, and participants will be randomized in a 2:1:2:1 ratio into each dose cohort (VSA001 25 mg dose group, volume-matched placebo group, VSA001 50 mg dose group and volume-matched placebo group).

During the 12-month randomized period (Schedule of Activities: Randomized Period), each participant will receive in a double-blinded manner either the active treatment or placebo by SC injection Q3M, as specified below:

- VSA001 25 mg (n=10) or volume-matched placebo (n=5) Q3M; or
- VSA001 50 mg (n=10) or volume-matched placebo (n=5) Q3M

During the 12-month extension period (Schedule of Activities: Extension Period), each participant will be treated with the active drug (VSA001 25 mg or 50 mg) in an open-label manner Q3M. A discussion of dosing in these study parts is provided in Section 5.3.

Each participant will visit the clinical institution on Day 1 (baseline). Study treatment will be administered on Day 1, which must be within 8 weeks following the start of screening assessments. Upon a participant's arrival at the clinical institution, the PI or designated study staff will meet with the participant to reiterate all the study procedures and encourage the participant to ask any questions, and the participant will be asked questions about protocol compliance and safety monitoring. participants will then return to the clinical trial institution for a visit following the SOA, and each visit typically will last approximately 4 hours, unless additional monitoring is deemed necessary by the PI for safety reasons.

All visits will be conducted at the clinical study site. At the PI's discretion and with prior approval of the sponsor, study assessments may be allowed to be performed at a qualified medical institution in the patient's location during non-treatment visits. Use of a qualified medical institution in the patient's location will depend on the qualifications of the local medical institution (such as a tertiary hospital) and the ability of the PI to adequately monitor the participant's safety. The method and any specific risks associated with it must be clearly outlined in an IEC/IRB-approved ICF when using the service of a local medical institution.

Some participants enrolled in this study may have hepatic enzyme increased at baseline. Instructions for adjusting the treatment for participants with ALT/AST increased are provided in Appendix 2.

The parameters to be assessed and the assessment schedule is presented in the SOA. During the study, participants will receive the following assessments regularly: medical history review, physical examination, vital signs measurement (blood pressure, body temperature, heart rate, respiratory rate), weight measurement, AE monitoring, ECG, pregnancy test (for women of childbearing potential), laboratory assessments, and review of concomitant medications. Blood samples will be collected for plasma concentration analysis of HDL-C, LDL-C, VLDL-C, TG

and other specified lipid or metabolic parameters, hematology, serum lipase and insulin, HbA1c, C-peptide, coagulation, serum biochemistry, and VSA001. Urinalysis will include random urine creatinine and random urine protein. Before blood sampling, the participant will be required to fast overnight for at least 10 hours.

Clinically significant changes (including AEs) will be followed up until the event resolves or is considered to have been medically stable.

5.1.5. PK sample collection

Pre-dose and post-dose PK samples will be collected at Day 1 and Month 3 for all participants. The PK sampling points are within 30 min pre-dose and 4 h±30 min post-dose. If the recommended time window is missed, every attempt will be made to collect this PK sample as soon as possible within the same study visit. Only samples collected from participants receiving active treatment will be included in the PK analysis.

5.1.6. Adverse Event Monitoring

Safety assessments include AEs and serious adverse events (SAEs), physical examinations, vital sign measurements (blood pressure, heart rate, body temperature, and respiratory rate), ECG, clinical laboratory tests, concomitant medications/therapy, and reasons for treatment discontinuation. Safety assessments will be performed at the time points specified in the SOA (from signing Informed Consent Form to the Month 24/End-of-Study [EOS] visit) (Schedule of Activities: Randomized Period and Schedule of Activities: Extension Period). The sponsor will regularly review/monitor the safety data (including safety laboratory results) at least monthly.

A TEAE is defined as an AE or worsening of a pre-existing condition that occurs after treatment with the IP. Reporting and follow-up of TEAEs may continue until the EOS and for up to 6 months following the last dose. All SAEs occurring during the reporting period must be reported to the sponsor using the SAE Report Form immediately upon receipt of the notification, in addition to reporting using the electronic Case Report Form (eCRF). All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. However, the sponsor must be notified immediately if the PI becomes aware of any SAE (including death) at any time after the participant has ended study treatment and considers that there is a reasonable relatedness of the event to the IP. Abnormalities in laboratory or ancillary examinations/tests (e.g., ECG) may be reported as an AE if deemed clinically significant by the PI. Laboratory or ancillary examinations/tests abnormalities not reported as clinically significant are not to be reported as AEs in the study database.

5.1.7. Early Termination

If a participant is discontinued from study prematurely, every reasonable effort should be made for the participant to attend the Month 24/EOS visit within 30 days of making the decision to

discontinue the participant's participation in the study. The reason for early termination from the study will be documented in source documents and eCRF(s). Participants who have discontinued VSA001 treatment due to SAE are encouraged to continue receiving medical monitoring follow-up until the event resolves.

5.2. Number of participants

Thirty participants are expected to be enrolled in this study. Taking into account the effects of uncertainties such as competitive enrollment, block randomization, and COVID-19, approximately 36 participants will be enrolled.

5.3. Treatment Assignment

All dose cohorts will enroll in parallel, and participants will be randomized in a 2:1:2:1 ratio into each dose cohort (VSA001 25 mg dose group, volume-matched placebo group, VSA001 50 mg dose group and volume-matched placebo group).

During the randomized period, each participant will receive in a double-blinded manner either the active treatment or placebo by SC injection Q3M, as specified below:

- VSA001 25 mg (n=10) or volume-matched placebo (n=5) Q3M; or
- VSA001 50 mg (n=10) or volume-matched placebo (n=5) Q3M

During the extension period, each participant will receive active treatment in an open-label manner Q3M, as specified below:

- Early in the extension period of the study, participants will remain blinded to the treatment assignment for the randomized period and will start to receive active drug treatment at the same dose as the study treatment dose that they received during the randomized period. Thus, participants who received VSA001 25 mg Q3M or 50 mg Q3M will continue to receive the same dose. Participants who received placebo will switch to active treatment based on the initial dosing group to which they were assigned (i.e., VSA001 25 mg Q3M or 50 mg Q3M).
- Later in the extension period, after the last participant has completed observations for the randomized period, all participants will be switched to open-label VSA001 treatment Q3M.
- Based on the analysis results of the Phase 3 global FCS study (AROAPOC3-3001) of this product, the proposed market dose of VSA001 is 25 mg. In the extension period of the study, after the approval of this version of protocol (V3.4), all participants will receive treatment with VSA001 25 mg Q3M; participants in the 50 mg group who earlier entered the open-label period will also be switched to the 25 mg treatment group for the next dose.

5.4. Dose Modification Criteria

No such dose modifications as dose escalation or dose reduction will be made.

5.4.1. Data Safety Committee and Safety Criteria for Dose Modification or Discontinuation

A Data Safety Committee (DSC), consisting of the CRO and sponsor medical monitors and investigators, etc., will be formed. The DSC will review the safety data after approximately 10 participants have received at least 1 dose of the IP and half of the total number of participants planned to be enrolled have received at least 1 dose of the IP. The study sponsor may also require the DSC to convene an interim meeting to review the safety data and make suggestions related to the study. The planned safety review will include assessment of important safety events such as AEs and SAEs in the 50 mg versus 25 mg dose groups. Where any potential safety signal is detected, the DSC may be required to review the safety data at other unscheduled meetings. The DSC may also make suggestions to the sponsor regarding any follow-up actions and modifying, terminating, or continuing the study as planned. The DSC will review blinded data at public meetings in the presence of the sponsor. The sponsor will provide up-to-date information on study enrollment and conduct, and will inform the DSC of any study-related information, including safety concerns based on blinded data, that may be relevant to DSC review.

The DSC **may** advise the sponsor to suspend further treatment to allow time for evaluating the safety data and recommending actions to be taken, which may include but are not limited to one of the following:

- Continue without protocol amendment
- Continue after protocol amendment
- Termination of the study
- Suspension of the study
- Other changes

The sponsor or PI may discontinue any participant's participation in the study at any time.

A decision to modify the study or to suspend or permanently discontinue treatment for an individual participant or dose group, or to suspend/permanently stop enrollment, may be made in case of any of the following:

- Any confirmed pregnancy in the study will lead to permanent discontinuation of IP dosing of that participant.
- ALT/AST increased may require interruption of study treatment (Appendix 2).
- For participants requiring extracorporeal blood purification or other emergency interventions to reduce TG, the next dose should be delayed until the PI assesses that the condition has been clinically stable in consultation with the medical monitor.
- For participants who have experienced acute pancreatitis, the next dose should be delayed until the PI assesses that the condition has been clinically stable in consultation with the medical monitor. The PI will assess the patient based on the local diagnostic and treatment criteria and develop the treatment scheme for episodes of acute pancreatitis; this may

include referral to the participant's attending physician or other specialists when necessary. For any participant experiencing acute pancreatitis, the participant may be unblinded and transitioned to the open-label treatment period of the study after assessment by the Investigator. This will be documented via the Interactive Web Response System (IWRS).

- If the participant had been assigned to receive placebo, they will be re-assigned to receive open-label treatment with VSA001 if they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and relevant procedures will start from Month 12 of the Schedule of Activities.
- If the participant had been assigned to receive VSA001, they will restore open-label treatment with VSA001 if they are clinically stable based on the assessment of the Investigator in consultation with the Medical Monitor, and until at least 3 months have passed since the receiving the last dose of study drug, i.e., starting from Month 12 of the Schedule of Activities.

- HbA1c increased meeting the criteria for discontinuation of study treatment (Appendix 5).

5.5. Criteria for Study Termination

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

- It is in the best interest of participants' wellbeing to terminate the study.
- Further conducting the clinical trial will no longer be for scientific purposes.

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

5.6. Discussion of Study Design (Including the Choice of Control Groups)

The primary objective of this study is to evaluate the efficacy and safety of VSA001 in adults with FCS.

For participants diagnosed with FCS based on the study inclusion criteria and confirmed to be receiving a stable diet and stable lipid-lowering and antidiabetic treatment regimens (if applicable, it is allowed to modify the antidiabetic treatment regimen during the study) (Section 5.1.3), all remaining eligibility assessments will be completed within 8 weeks prior to randomization on Day 1. The Treatment Period will begin on Day 1 and last for 24 weeks. Dietary education will start at the beginning of the screening period and be repeated at intervals throughout the treatment period. This approach is expected to minimize the potential impact of dietary changes that may alter TG levels and/or confound the interpretation of study results.

A placebo-controlled design is selected for the randomized period as it is impractical to remain blinded to the active control (no clinical standard of care has been available for the disease). The protocol requires that all participants in the active drug group and placebo group receiving lipid-lowering therapy should keep the treatment regimen stable during the study, despite that

other lipid-lowering therapies would have a limited effect on TG compared to the potent TG-lowering effect of VSA001. For example, SHTG patients treated with ω-3 fatty acids had a placebo-adjusted TG reduction of only 33% (Bays 2011) and patients with mild TG increased treated with gemfibrozil had a TG reduction of 31% (Rubins 1999). Therefore, when VSA001 is used in combination with a best lipid-lowering therapy, additional TG-lowering and lipid-lowering effects are expected. In this Phase 3 study, concomitant use of best statins therapy, niacin, ω-3 fatty acids (prescription or non-prescription) or fibrates or other lipid management regimens is allowed as long as the participant has received a stable regimen for at least 4 weeks prior to screening laboratory assessments and agrees to continue receiving this baseline regimen during study treatment. At randomization, subjects will be stratified by TG level at screening (≥2,000 mg/dL vs. <2,000 mg/dL).

An open-label design without a control group is chosen for the extension period to allow all participants to receive active treatment. The durations of treatment and assessments are intended to ensure adequate exposure to VSA001 to evaluate its efficacy and safety in long-term use.

5.7. Rationale for Dose and Schedule of Administration

In the Phase 1 study evaluating ARO-APOC3 (VSA001) in healthy participants, serum APOC3 and TG following 10, 25, or 50 mg dose continued to decrease until Week 16. Beyond Week 16, these PD parameters gradually increased in some healthy participants, and increased compared to the lowest level after about Week 8 in the 50 mg cohort. A relatively marked dose effect was observed with the HDL-C level, which increased with dose, and HDL-C increased in a dose-dependent manner. While a limited number of participants were enrolled in the Phase 1 study, available data from patients with HTG and chylomicronemia showed that treatment with ARO-APOC3 50 mg on Days 1 and 29 maintained reductions in APOC3 and TG following the second dose until Week 12. Additional analysis of Phase 1 study AROAPOC31001 suggested similar percent reductions from baseline in APOC3 and TG in participants with chylomicronemia without genetically documented FCS and participants with genetically documented FCS.

Dose simulation of serum APOC3 and TG responses using a population PD model developed based on data collected in the Phase 1 study AROAPOC31001 suggested that 100 mg dosing may have provided only a small incremental improvement in reducing TG compared to the 50 mg Q3M dosing regimen. Therefore, limiting the dose below 50 mg Q3M in this Phase 3 study is expected to be favorable for optimizing the benefit-risk ratio for participants with FCS. Direct clinical observations and modeling results also suggested that the duration of ARO-APOC3's effects may be short in participants with chylomicronemia, including FCS, and that patients with FCS may require a higher dose compared to the general population with SHTG. Therefore, a dose lower than 25 mg Q3M is not recommended for patients with FCS. Examination of the limited data from study AROAPOC31001 did not reveal any significant

difference in the safety profile between the 25 mg and 50 mg doses, suggesting that the benefit-risk ratios for the two dose levels could be further studied in more FCS patients. Therefore, the recommended doses to be studied in the randomized double-blind period of this Phase 3 trial are 25 mg Q3M and 50 mg Q3M.

Assuming a weight conversion and an average participant weight of 70 kg, the higher dose 50 mg is about 1/420 of the NOAEL (300 mg/kg) in the 4-week/3-dose GLP toxicology studies in rats and monkeys. In chronic GLP toxicity studies, the NOAEL was 15 mg/kg in rats and 180 mg/kg in monkeys. Assuming a participant weigh of 70 kg, in this study, the safety factor for the proposed 50 mg dose is about 20 when calculated based on the NOAEL for rat and 250 when calculated based on the NOAEL for monkey. Additionally, it should be noted that the dose frequency in this study is Q3M, whereas the dose frequency in chronic toxicology studies (6-month rat and 9-month monkey) was every 4 weeks. Therefore, there was a wide margin of safety between clinical doses and animal toxicology study NOAELs.

It was noted in interim analyses for overseas Phase 2 clinical studies of ARO-APOC3 (AROAPOC3-2001 and AROAPOC3-2002) that among patients with SHTG and mixed dyslipidaemia, HbA1c was significantly increased in participants in the ARO-APOC3 treatment group compared to participants in the placebo group, and these changes were mainly observed in participants who had diabetes at baseline and were observed to be the most significant in the subset of participants treated with the highest dose of ARO-APOC3 (50 mg); corresponding risk control measures have been developed for overseas clinical studies. This study is a Phase III clinical study to evaluate the efficacy and safety of VSA001 in FCS patients, which is consistent with the overseas Phase 3 clinical study in FCS patients (AROAPOC3-3001 study). The data from the AROAPOC3-3001 randomized double-blind study are summarized as follows: VSA001 25 mg Q3M and 50 mg Q3M both resulted in great reductions in triglycerides, and approximately 80% of participants in both dose groups achieved 50% reduction in triglycerides. Compared to placebo, 25 mg and 50 mg doses of VSA001 provided similar efficacy results. The incidence of TEAEs was generally balanced between the VSA001 groups and the placebo group. No death occurred during the study period; the incidences of SAEs and Grade ≥ 3 TEAEs were higher in the placebo group than in the VSA001 groups. The observed TEAEs generally showed no dose dependence. Based on the analysis results of the phase III global FCS study (AROAPOC3-3001) of this product, the proposed market dose is 25 mg. (Appendix 5). All participants in the open-label period will receive VSA001 25 mg Q3M in the extension period (after approval of protocol V3.4).

6. Selection and Withdrawal of Participants

6.1. Participant Inclusion Criteria

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

1. Males or non-pregnant (who do not plan to become pregnant), non-lactating females ≥18

years of age.

2. Able and willing to provide written informed consent prior to the performance of any study-specific procedures.
3. Fasting TG ≥10 mmol/L (~880 mg/dL) at screening, that is refractory to standard lipid lowering therapy (sample drawn after at least the minimum time on stable lipid-lowering regimen described in the protocol). Three repeat tests are allowed to qualify.
4. A diagnosis of FCS based on a documented history of fasting TG levels in excess of 1000 mg/dL (for at least 1 prior occasion) in the absence of clear triggering factors (e.g., alcohol, binge eating, etc.), **and at least one of the following**:
    a. A supportive genetic test (from a source-verifiable medical record or based on screening genotype). Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including LPL, APOC2, APOA5, GPIHBP1, GPD1, or LMF1; or evidence of low LPL activity (<20% of normal) based on source-verifiable documentation; or
    b. Documented history of recurrent episodes of acute pancreatitis, not caused by alcohol or cholelithiasis; or
    c. Documented history of repeated hospitalization for severe abdominal pain with no other explainable causes; or
    d. Documented history of childhood or adolescent pancreatitis; or
    e. Family history of hypertriglyceridemia-induced pancreatitis.
5. Willing to follow dietary counseling as per PI judgment based on local standard of care, consistent with the diet control regimen with an intake of ≤20 g of fat per day during the study.
6. If type 2 diabetes management drugs or other medications specified in the Table 2 (see Section 7.2.3) are being used, the dosing regimen must remain stable until qualified lipid parameters are collected at screening.
7. Participants with a medical history of clinical atherosclerotic cardiovascular disease (ASCVD) or those with elevated 10-year ASCVD risk (e.g., ≥7.5% per American Heart Association/American College of Cardiology risk calculator) must be on appropriate lipid-lowering therapy as per local standard of care (i.e., including moderate to high intensity statin, as indicated) prior to collection of qualifying TG levels.
8. Participants of childbearing potential must agree to use a highly effective form of contraception (Appendix 1)during the study and for at least 24 weeks after the last dose of investigational product. Women of childbearing potential on a hormonal contraceptive must be stable on the medication for ≥ 1 menstrual cycle prior to Day 1 of the study. Males must have agreed to not donate sperms during the study and for at least 24 weeks following the last dose of IP. Note: All laboratory tests (except for coagulation) used as inclusion criteria will be assessed by a central laboratory and may be repeated once

(except for TG), and the repeat value may be used for inclusion purposes. Local laboratory testing may be permitted in limited circumstances and only with prior Sponsor approval.

6.2. Participant Exclusion Criteria

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

1. Current use or use within the last 1 year (before screening) of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule.
2. Diabetes mellitus with any of the following:
    a. Newly diagnosed within 12 weeks of screening;
    b. HbA1c ≥ 9.0% at screening.
3. Active pancreatitis within 12 weeks prior to Day 1.
4. History of acute coronary syndrome events within 24 weeks of Day 1.
5. History of major surgeries within 12 weeks of Day 1.
6. Any of the following abnormal laboratory values at screening:
    a. ALT or AST ≥ 3 × ULN at screening;
    b. Total bilirubin ≥1.5×ULN (if the participant has a prior diagnosis and documentation of Gilbert's syndrome, then total bilirubin must be ≤3 mg/dL at screening);
    c. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 at screening, using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation;
    d. Spot urine protein/spot urine creatinine ratio greater than 3 g/day;
    e. Clinically significant abnormality in prothrombin time, partial thromboplastin time, or INR.
7. Uncontrolled hypertension (blood pressure >160/100 mmHg at screening); if untreated, participant may be rescreened once hypertension is treated and controlled.
8. Use of any of the following:
    a. Systemic use of corticosteroids or anabolic steroids within 4 weeks prior to Day 1 or planned use during the study;
    b. Current use of glucagon-like peptide-1 (GLP-1) receptor agonists or planned use during the study;
    c. Plasma apheresis within 4 weeks prior to Day 1 or planned during the study;
    d. Blood donation of 50 to 499 mL within 4 weeks of collection of qualifying lipid parameter collection or of >499 mL within 8 weeks of qualifying lipid parameter collection.
9. On treatment with human immunodeficiency virus (HIV) antiretroviral therapy (Note: determination of HIV status is not a required study procedure).
10. Seropositive for hepatitis B virus (HBV) or hepatitis C virus (HCV) (hepatitis B surface antigen [HBsAg] and HBV DNA positive, or HCV RNA positive).
11. New York Heart Association (NYHA) Class III or IV heart failure or last known ejection fraction of <30%.

12. Clinical evidence of primary hypothyroidism (screening TSH > ULN and free T4< LLN), primary subclinical hypothyroidism (screening TSH > ULN and free T4 WNL), or secondary hypothyroidism (screening TSH < LLN and free T4 < LLN).
13. History of hemorrhagic stroke within 24 weeks of first dose.
14. History of bleeding diathesis or coagulopathy.
15. Current diagnosis of nephrotic syndrome.
16. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol) for both females and males.
17. History of malignancy within the last 2 years prior to the date of consent requiring systemic treatment except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Currently receiving systemic cancer treatment(s) or, in the PI's opinion, at risk of relapse for recent cancer.
18. 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.
19. Any concomitant medical or psychiatric condition or cognitive disorder caused by serious social situation or any other situation that, in the PI's judgment, would make it difficult to comply with protocol requirements or put the participant at additional safety risk.

Note: All laboratory tests used as exclusion criteria can be repeated once, and the re-test value can be used for exclusion.

6.3. Participant Withdrawal Criteria

Participants will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the PI, medically qualified designee, or sponsor will withdraw a participant from the study, per the following criteria, to protect the participant's health:

- The need to take medication which could interfere with study measurements
- Intolerable/Unacceptable adverse events
- Major violation of or deviation from study protocol procedures
- Noncompliance of participant with the protocol
- Participant is unwilling to proceed or consent is withdrawn
- If in the investigator's judgment withdrawal from study would be in the participant's best interest

Reasons for withdrawal will be documented in the eCRF along with all AEs and necessary treatments and be included in the final Clinical Study Report (CSR).

If a participant has withdrawn from study due to an AE/SAE, the PI or a medically qualified designee will evaluate the emergency nature of the event. If needed for the situation, the PI or medically qualified designee will take appropriate diagnostic and therapeutic measures. If the situation is not an immediate emergency, the PI, or medically qualified designee, at the clinical

study facility will attempt to contact the Medical Monitor or medically qualified designee for consultation. Provision of medical assistance, diagnosis, or advice to participants will not be stopped due to failure to contact the medical monitor. The participant will be encouraged to remain available for follow-up medical monitoring. The sponsor will be notified as soon as possible of any participant withdrawals.

7. Treatment of Participants

7.1. Description of study drug

There will be 2 study treatments, i.e., 1 active drug and 1 placebo (control), both to be administered by SC injection.

Investigational product: VSA001 Injection, to be administered SC. The active pharmaceutical ingredient contained in VSA001 is a synthetic, double-stranded siRNA duplex conjugated to a NAG-targeting ligand to facilitate hepatocyte delivery.

Control drug: The control drug is placebo: normal saline (0.9%) administered SC, volume-matched to the corresponding VSA001 dose volume.

See Section 8 for more information on study drug materials and management.

7.2. Restrictions and Concomitant Medications

7.2.1. Fasting

Participants will fast for at least 10 hours prior to blood draw on the day of dosing or any other date on which blood is drawn for measurement of lipid parameters, unless otherwise specified.

7.2.2. Drug Abuse or Alcohol

Participants 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, participants will be instructed to avoid frequent alcohol intake during the study (not more than 14 units per week [1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol]). Participants must avoid drug abuse (e.g. MDMA [methylenedioxymethamphetamine], cocaine, cannabis, ketamine) throughout the study.

7.2.3. Concomitant medications

Use of best statins therapy, niacin, ω-3 fatty acids (prescription or non-prescription) or fibrates or other lipid management regimens is allowed if the participant has received treatment with a stable regimen for a duration specified in Table 2 prior to eligibility screening laboratory assessments and agrees to maintain the stable regimen during study treatment. Adjustments to medication regimens during the study, including lipid-lowering and diabetes mellitus therapies, are only allowed if, at the discretion of the PI, they are needed to provide adequate supportive care. These changes must be recorded in the eCRF no later than the next study visit. Participants

will be instructed to provide the PI with the specific information (indication, dose and date of administration) if they have used any medications, and this information will be recorded in the eCRF. The medical monitor or designee should be notified before any change is made to a participant's prescribed lipid-lowering therapy. Information of any extracorporeal blood purification during the study will be recorded in the eCRF.

Table 2: Restricted Concomitant Medications

Restricted background medications	Duration of receiving a stable regimen prior to eligibility screening laboratory assessments
Lipid-lowering therapies (including statins)	>4 weeks
• Fibrates	>6 weeks
• PCSK9 Inhibitors	>8 weeks
Beta-blockers, thiazide diuretics	>4 weeks
Tretinoin	>8 weeks
Atypical antipsychotics	>12 weeks
Diabetes mellitus medications	>12 weeks
Oral estrogens, tamoxifen, raloxifene	>16 weeks
Immunosuppressants	>24 weeks

7.2.4. Central laboratory lipid examinations

Central lab results may unblind the treatment assignment for VSA001. Central lab results for fasting serum TG and other lipid parameters (LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, APOB-48, LP [a], APOB-100, total APOB, APOC-III, APOC-II, APOA-I, and APOA-V) will not be reported to the PI, and will remain blinded from Day 1. After Day 1, PI should not have local non-protocol tests of these lipid parameters performed for the participant from the first dose of IP to the Month 13 visit for the participant.

Between the Month 10 and Month 13 visits, if a baseline LDL-C ≥130 mg/dL (≥3.37 mmol/L) in a participant has increased by ≥25% from baseline at 2 consecutive visits, the participant's LDL-C values will be unblinded for the remainder of the study, and the central lab will notify the PI to perform medical follow-up. Between the Month 10 and Month 13 visits, if a baseline LDL-C <130 mg/dL (<3.37 mmol/L) in a participant has increased later to ≥130 mg/dL (≥3.37 mmol/L) at 2 consecutive visits, the central lab will notify the PI to perform medical follow-up. For all such cases, the PI will contact the participant to provide appropriate medical follow-up, which includes dietary and medication compliance counseling, and may also include adjusting the participant's lipid-lowering regimen based on the country-specific guidelines (e.g., starting statins therapy or increasing the dose of statins therapy for a previously treated participant).

If any participant has been noted with TG increased by >40% from baseline or absolute TG >4,000 mg/L (45 mmol/L) during treatment, the central lab will immediately notify the PI, who will determine appropriate monitoring and follow-up.

After completing the Month 13 visit until the Month 24/EOS visit, the central lab will provide the PI with available results of the lipid parameters for each participant.

7.2.5. Notifying attending physician

The PI or designee is responsible for notifying the participant's local attending physician, with the participant's consent, that the participant has been participated in the trial, sending correspondence describing the trial nature, treatments, expected benefits or AEs, as well as the concomitant medications that should not be used.

7.3. Treatment compliance

All study treatments 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 and time of study treatment administration will be recorded on the eCRF on dosing days.

7.4. Principle of treatment discontinuation

Any confirmed pregnancy in the study will lead to permanent discontinuation of IP dosing of that participant.

A decision to suspend dosing in an individual participant **may** be indicated based on any of the following:

- A need for apheresis or other emergent interventions indicated to lower TG
- In participants with normal AST and ALT on Day 1, treatment emergent elevations ≥3× ULN at least possibly related to IP per Investigator must be confirmed by repeat blood draw within 72 hours of initial results. For participants with any of the following results, refer to Appendix 2 for the specific instructions on treatment discontinuation or interruption:
  - ALT or AST ≥5×ULN (according to Appendix 2: permanently discontinue IP dosing for the participant; according to the SOA: allow the participant to continue attending study follow-up visits until EOS visit)
  - ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN
  - ALT or AST ≥3 × ULN with new-onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
  - ALT or AST ≥3×ULN with INR >1.5 emerging during treatment (must be confirmed repeatedly) that cannot be explained by any other reasonable reasons*

  * For example, presence of Gilbert's syndrome or hemolytic disease: re-test in case of baseline direct bilirubin >0.5 mg/dL.
- Some participants enrolled in this study may have transaminases increased at baseline. In participants with elevated AST or ALT on Day 1, treatment emergent elevations >2× baseline at least possibly related to IP per Investigator must be confirmed by repeat blood draw within 72 hours of initial results, as follows. For participants with any of the

following results, refer to Appendix 2 for the specific instructions on treatment discontinuation or interruption:

- ALT or AST ≥300 U/L (according to Appendix 2: permanently discontinue IP dosing for the participant; according to the SOA: allow the participant to continue attending study follow-up visits until EOS visit)
- ALT or AST ≥2 × ULN with new-onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
- ALT or AST ≥ 2 × ULN and total bilirubin ≥ 2 × ULN
- ALT or AST ≥2×baseline value with INR >1.5 emerging during treatment (must be confirmed repeatedly) that cannot be explained by any other reasonable reasons*

* For example, presence of Gilbert's syndrome or hemolytic disease: re-test in case of baseline direct bilirubin >0.5 mg/dL.

Instructions for adjusting the treatment for participants with ALT/AST increased are provided in Appendix 2.

- At the investigator's discretion, any participant with poorly controlled diabetes may return to the study site or go to a medical institution recognized by the sponsor and investigators before the next scheduled dose for an unscheduled visit to evaluate the changes in HbA1c, so as to determine whether treatment can be continued. IP treatment should be discontinued if the participant meets the following criteria:
  - HbA1c measurement >10% at the last visit before the next dose, or
  - HbA1c increased by >2% from baseline at the last visit before the next dose, or
  - Baseline HbA1c >7.5% and increased by >1% from baseline at both two study visits (the last visit being the one before the next dose)

Instructions for adjusting the treatment for participants with HbA1c increased are provided in Appendix 5.

7.5. Randomization and Blinding

7.5.1. Randomization

All potential participants who sign an informed consent at screening will receive a number (i.e., a screening number). For participants who are deemed eligible, this screening number will become the participant's permanent study ID number.

Eligible participants will be allocated a unique randomization number, in accordance with the randomization schedule. Participants will be randomized in a 2:1:2:1 ratio into each dose cohort (VSA001 25 mg dose group, volume-matched placebo group, VSA001 50 mg dose group and volume-matched placebo group) Treatments will be administered per the randomized sequence generated by an Interactive Web Response System (IWRS). Active drug treatment or placebo will be assigned using a block randomization method. At randomization, subjects will be stratified by TG level at screening (≥2,000 mg/dL vs. <2,000 mg/dL).

7.5.2. Blinding

The treatment assignment (active drug vs. placebo) will be blinded for this clinical study. Assignment of dose groups will not be blinded as different required injection volumes are prescribed for different dose groups. Thus, participants will receive treatment with the active drug or placebo injection matching the dose group they are assigned to (Section 8.5). To mask the slight color difference between the active drug and placebo, the syringes will be blinded at the pharmacy as described in the Investigational Product Management Manual, so that the blinded staff and participants will remain blinded to the treatment assignment. During the extension period, participants will receive open-label treatment, yet will at the early stage remain blinded to the treatment they were initially assigned to in the randomized period.

Blinding of IP/placebo assignment is critical to the integrity of this clinical study. It is expected that in most cases, AEs can be properly managed without requiring unblinding. However, in the event of any medical emergency, if knowledge of the treatment assignment for an individual participant is deemed critical to the wellbeing and management of the participant, the PI or documented designated treating physician may unblind the treatment assignment. For non-emergencies, the investigator should contact the responsible medical monitor to discuss the participant's situation and the requirement for unblinding. Unblinding will be performed only for the specific participant being discussed on. Information of unblinding will be recorded in the electronic data capture system. The medical monitor should be notified immediately.

The randomization scheme will exercise strict access permission. Staff involved in IP dispensing will be responsible for ensuring compliance with the randomization scheme. Non-blinded clinical study monitors (CRAs) will verify whether the randomization was correct.

If the PI considers, based on the severity of an AE, it necessary to immediately know the identify and dose of the product concerned, unblinding will be completed in the IWRS system. Only designated non-blinded pharmacists, PI, and co-investigators may have access to unblinding for medical emergencies in the IWRS. The medical monitor should be notified in a timely manner.

Where a participant requires emergency unblinding (the PI and medical monitor have/have not had discussion before unblinding), the PI may also need to complete the Study Site Unblinding Report Form to document the medical rationale for the need for unblinding and then forward the form to the medical monitor.

A discussion on blinding the central lab test results of TG and blood lipid parameters is provided in Section 10.1.

7.6. Drug Therapy after the End of Study

This clinical study ends when the participants have completed the End of Study visit (EOS) at Months 24. Participants in the open-label treatment period can discuss with the investigator to choose to continue treatment with the study drugs VSA001 or other treatments. If the

participant chooses to continue the study drug, after assessment by the sponsor, he/she may continue to receive the study drug until the study drug is available or another treatment is recommended by the clinician. This period is drug therapy after the end of study, and diagnosis and treatment will be performed according to clinical routines, and the sponsor will not collect relevant data. If the participant experiences an AE in the period of continuing administration, he/she should actively report it to the investigator. The study team will document and process all unsolicited AEs to ensure participant safety is properly managed.

8. Study Drug Materials and Management

8.1. Study Drugs

The sponsor is responsible for supplying VSA001 and a detailed instruction on the preparation of VSA001 before injection, as specified in the Investigational Product Management Manual. Therefore, VSA001 will be supplied in a single sterile 2 mL vial or prefilled syringe containing VSA001. The correct dose of VSA001 will be prepared by the pharmacy before dosing for a participant. The placebo (0.9% normal saline) will be provided by the sponsor.

8.2. Study Drug Packaging and Labeling

8.2.1. Vial

VSA001 will be supplied in Type 1 2.0 mL sterile glass vials (0.7 mL nominal volume, 0.5 mL extractable volume).

Strength	200 mg/mL
Appearance	Clear, colorless to yellow solution
Inactive ingredients	0.5 mM sodium dihydrogen phosphate, 0.5 mM disodium hydrogen phosphate, and water for injection
Transportation and storage	Cold storage (2-8 ℃)

8.2.2. Prefilled Syringe

The 50 mg dose will be provided in a single-dose PFS. Each PFS contains 50 mg of ADS-005/1 mM aqueous phosphate buffer. The packaging system for VSA001 Injection PFS is a 1 mL long Type I clear glass syringe with a 29 Gauge staked needle and rigid needle shield and a bromobutyl FluoroTec coated plunger. The final assembly of the syringe includes a standard plunger rod and finger flange. Each PFS will be individually packaged in a carton.

Strength	200 mg/mL
Syringe volume	0.25 mL
Appearance	Clear, colorless to yellow solution
Inactive ingredients	0.5 mM sodium dihydrogen phosphate, 0.5 mM disodium hydrogen phosphate, and water for injection
Transportation and storage	Cold storage (2-8 ℃)

The 25 mg dose will be provided in a single-dose PFS. Each PFS contains isotonic saline for 25 mg of ADS-005. The packaging system for VSA001 Injection PFS is a 1 mL long Type I

clear glass syringe with a 29 Gauge staked needle and rigid needle shield and a bromobutyl FluoroTec coated plunger. The final assembly of the syringe includes a standard plunger rod and finger flange. Each PFS will be individually packaged in a carton.

Strength	50 mg/mL
Syringe volume	0.50 mL
Appearance	Clear, colorless to yellow solution
Inactive ingredients	0.9% sodium chloride and water for injection
Transportation and storage	Cold storage (2-8 ℃)

8.3. Storage of Study Drug

VSA001 will be supplied by the sponsor and labeled with the drug name, batch number, expiration date (as applicable) and storage conditions. The IP will be labeled in accordance with the current Good Manufacturing Practice (cGMP)/GCP.

IP supplies will be securely stored at the clinical study site under appropriate conditions. The IP must be stored under physical conditions meeting the IP-specific requirements in a secure area accessible only by PI-authorized personnel.

8.4. Study Drug Preparation

VSA001 will be prepared by the pharmacist or qualified staff at the clinical study site according to the Investigational Product Management Manual. Sterile techniques will be used to ensure sterility of the solution to be injected. The preparation time of the active drug must be recorded and tracked to demonstrate stability of the drug prepared. See the Investigational Product Management Manual for more specific information.

The sponsor will provide the PI with an adequate quantity of clinical drugs. The PI must ensure that the IP provided by the sponsor is correctly received by the non-blinded responsible person, recording all the drug shipping receipts in an appropriate drug accountability form prepared by the clinical study site pharmacy, and that the drugs are stored under the recommended storage conditions in a secure area. The PI is also responsible for ensuring that the non-blinded responsible person would not compromise the integrity of the packaged study drugs prior to dispensing.

Only participants enrolled in the study may receive IP, in accordance with all applicable regulatory requirements. An authorized and trained staff member at each clinical study site will dispense the IP per predefined drug dispensing requirements. Drug dispensing will be rechecked by a second site staff.

8.5. Administration

IP will be administered by appropriately trained clinical study site staff.

Vials will be administered as single SC doses (Table 3). The injection site will be marked and photographed for subsequent observation. The abdomen is the preferred place for the injection.

Optional additional sites are the upper arms and thighs (inner).

Table 3: Injection Number and Volume Per Dose Cohort

VSA001 dose [a]	Concentration	Total injection volume	Injection number per dose	Total number of study injections
25 mg	200 mg/mL	0.13 mL	Single	8
50 mg	200 mg/mL	0.25 mL	Single	8

a The injection volume of the placebo (normal saline) is matched to VSA001 for the first 4 study injections.

Each dose of active drug (VSA001) or placebo (0.9% normal saline) will be administered SC by appropriately trained and qualified clinical staff designated by the PI. Injections will be made into the SC tissue at an appropriate site (e.g., abdomen, thigh, upper arm). The abdomen is the preferred place for the injection. There should be different injection sites (multiple injections at the same accurate site are not allowed, yet alternative injections at different sites in the abdomen are allowed). The injection site location is to be recorded in the eCRF. Before dosing, the IP vial must be allowed sufficient time to recover to room temperature. Do not inject into areas of active skin diseases or lesions such as sunburn, rash, inflammation, or skin infection. The injection volume for each site should not exceed about 0.25 mL.

PFS is a ready-to-use injection that will be injected SC by an investigator or appropriately trained and qualified clinical staff designated by the investigator. Injections will be made into the SC tissue at an appropriate site (e.g., abdomen, thigh, upper arm). The abdomen is the preferred place for the injection. There should be different injection sites (multiple injections at the same accurate site are not allowed, yet alternative injections at different sites in the abdomen are allowed). The injection site location is to be recorded in the eCRF. Before dosing, the PFS must be allowed sufficient time to recover to room temperature. Do not inject into areas of active skin diseases or lesions such as sunburn, rash, inflammation, or skin infection. See the Investigational Product Management Manual for more information. In the open-label period, the sponsor will provide PFSs to the patients after obtaining the relevant approval and completing the import.

8.6. Study Drug Accountability

All material supplied is for use only in this clinical study and should not be used for any other purpose. In accordance with all applicable regulatory requirements, designated site staff will be responsible for IP accountability and reconciliation and maintenance of related records throughout the course of the study. This person will document the amount of IP received from the sponsor and the amount administered to participants. Non-blinded CRAs will perform initial and ongoing IP container and placebo accountability. Non-blinded CRAs will protect the integrity of blinded assignment and not participate in data review for study participants. Used VSA001/placebo containers will be stored isolated by participant and be provided to non-blinded CRAs during IP and placebo reconciliation.

The Drug Dispensing Record must be kept up to date and will contain the following

information:

- Participant identification information of dispensed drug
- The date(s), quantity, batch number(s) and expiration dates of the IP dispensed to the participant.

The date and time of dispensing and preparation will be retained to support IP dosing. Authorized pharmacists or qualified staff, who are non-blinded personnel, will be informed of participants' treatment assignment (i.e., active drug or placebo). The pharmacy will dispense the IP, and the study site will provide the study drug only to participants enrolled in this study in accordance with the study protocol and procedures specified in the Investigational Product Management Manual. Each participant will be given only the IP as assigned by the IWRS. Study drug dosing will be recorded in the eCRF. During the study, the inventory must be available for inspection by the CRA. At the end of the study, the medications supplied will be collected by the study monitor or be returned to the sponsor or the sponsor-designated warehouse by the PI or designee.

8.7. Study Drug Handling and Disposal

For this study, used and partially used drug containers will be retained for a period sufficient for accountability, and will be retained, collected or destroyed by the sponsor as per the relevant regulations.

9. PK Assessments

9.1. PK Assessments

9.1.1. Sample Collection

Plasma PK samples for VSA001 analysis will be collected by venipuncture before IP dosing and 4 hours after IP dosing at Day 1 and Month 3 for all participants (20 in the active drug group and 10 in the placebo group).

9.1.2. Sample Analysis

Whole blood will be collected and handled in accordance with the Central Lab Manual. Plasma samples will be analyzed using cross-validated methods. The criteria for repeated analysis defined in the corresponding internal procedures will be followed. Validation studies (designed to determine the validity, including the accuracy, precision, reproducibility, specificity, recovery, and freezing stability of the analytical method) conducted by the designated bioanalysis laboratory will be provided in the final report as an appendix.

10. Assessment of Efficacy

Efficacy assessments will be performed at post-IP dosing time points outlined in the SOA (Schedule of Activities: Randomized Period and Schedule of Activities: Extension Period).

Efficacy assessments are required to be performed at the study site at the treatment visits, Month 10 visit, and Month 24/EOS visit.

10.1. Serum Triglycerides and Other Lipid Parameters

Blood samples for lipid parameters will be collected from participants by venipuncture. The actual blood collection time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections for the actual time of sample collection will be incorporated at the time of data analysis. Blood samples will be collected at time points outlined in the SOA. The actual sample times (time 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 samples taken outside of the set sampling times.

Fasting serum TG and other lipid parameters will be collected at the screening visit and on Day 1 prior to dosing after at least a 10-hour fast (only 7 items will be detected during the screening period: TG, LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, and LP[a]; on Day 1 and at subsequent visits, 14 items will be detected: TG, LDL-C, total cholesterol, non-HDL-C, HDL-C, VLDL-C, APOB-48, LP[a], APOB-100, total APOB, APOC3, APOC2, APOA1 and APOA5). The Day 1 values will be used as each participant's baseline value for data analysis purposes (except fasting serum TG).

After completion of the Month 13 visit, the central laboratory will provide available lipid parameter results to the PI through the Month 24/EOS Visit.

10.2. Glucose Metabolism

Serum samples will be collected at screening and on Day 1 after at least 10 hours of fasting and prior to dosing. The Day 1 values will be used as each participant's baseline value for data analysis purposes. After Day 1, fasting serum blood glucose, HbA1c, insulin and C-peptide will be measured as per the SOA and assessed by a local laboratory.

10.3. Acute Pancreatitis Events

All treatment-emergent AEs and SAEs reported by the Investigator through Month 24/EOS that are consistent or possibly represent an event of acute pancreatitis will be adjudicated according to the 2013 Revision of the Atlanta Classification Criteria for Acute Pancreatitis, and should meet 2 of the following 3 criteria:

1. Abdominal pain consistent with symptoms of acute pancreatitis (acute episodes of persistent, severe, upper abdominal pain often radiating to the back);
2. Serum lipase activity (or amylase activity) ≥3 × ULN;
3. Characteristic findings of acute pancreatitis on upper abdominal computed tomography (CT), magnetic resonance imaging (MRI), or transabdominal ultrasonography. Note:

Consult a specialist if necessary.

10.3.1. Detecting and Reporting Pancreatic Events

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

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

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

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

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

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

10.4. Diet

Participant diet will be recorded as per the SOA. At these study visits, the participant will be

asked to report their dietary management of FCS for at least 3 of the past 5 days.

10.5. Patient-Reported Outcomes

Participants will complete the EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-PAN26 questionnaires as per the SOA.

10.5.1. EuroQoL 5-Dimension Questionnaire

The EQ-5D-5L comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman 2011). Each dimension has 5 levels: no problems, slight problems, moderate problems, sever problems, and extreme problems. The EQ-5D-5L also includes a visual analog scale (VAS) to record the participant's self-rated health, where the endpoints are labeled "The best health you can imagine" and "The worst health you can imagine". The VAS can be used as a quantitative measure of health outcome that reflects the participant's own judgment.

10.5.2. EORTC QLQ-C30 Questionnaire

The EORTC QLQ-C30 instrument consists of 30 questions: 28 questions about specific aspects of quality of life, and 2 questions about overall health and overall quality of life. It has been translated into 100 languages and validated. The EORTC QLQ-C30 was initially developed and validated in patients with lung cancer (Aaronson 1993), and subsequently shown to be useful for the assessment of quality of life in patients with chronic pancreatitis (Fitzsimmons 2005) and in patients with LPL deficiency (Johnson 2015).

10.5.3. EORTC QLQ-PAN26 Questionnaire

The EORTC QLQ-PAN26 instrument consists of 26 items related to disease symptoms, treatment side effects, and specific emotional issues such as abdominal pain, gastrointestinal symptoms, or anxiety. It focuses on patient-reported outcomes among patients with pancreatic cancer (Fitzsimmons 1999) and was subsequently shown to be useful for the assessment of quality of life in patients with chronic pancreatitis (Fitzsimmons 2005) and in patients with LPL deficiency (Johnson 2015).

11. Assessment of Safety

11.1. Safety Parameters

Safety assessments will be performed at the time points outlined in the SOA (Schedule of Activities: Randomized Period and Schedule of Activities: Extension Period).

A comprehensive safety assessment, including blood and urine tests, is required at the study site at dosing visits, the Month 10 visit, and the Month 24/EOS visit.

11.1.1. Demographics/Medical History

Participant demographics (e.g., date of birth, race and ethnicity, sex) and medical history will

be collected during the screening period. Medical history will include medication use over the previous 30 days, including vitamins, OTC medications, prescription drugs, drug abuse or supplements, and alcohol and tobacco use.

11.1.2. Vital Signs

Systolic/diastolic blood pressure (mmHg), body temperature (degrees Celsius [°C]), heart rate (beats/minute), and respiratory rate (breaths/minute) will be obtained after the participant is semi-supine or sitting for at least 3 minutes. Vital signs will be obtained prior to venipuncture and other invasive procedures.

11.1.3. Physical Examination

A complete physical examination will be performed at screening, including height (centimeters, without shoes) and weight (kilograms, without shoes). At all other time points outlined in the SOA, a symptom-directed physical examination will be performed as indicated.

11.1.4. Electrocardiogram

Standard single 12-lead ECG, which will be recorded at Screening and the time points outlined in the SOA, can be performed on local ECG equipment.

Triplicate 12-lead ECG measurements approximately time-matched to PK blood collections will be obtained using validated ECG services equipment from a study site at Day 1 and Month 3 (before dosing, 2 hours after dosing, and 4 hours after dosing). Any abnormal and clinically significant ECGs, as per the PI's medical judgment, will be repeated in triplicate, with each measurement approximately 1 minute apart. For all triplicate ECGs, the ECGs must be acquired using the same ECG services equipment and results should be interpreted at a central laboratory.

The participant should be supine or semi-supine for at least 5 minutes before each ECG is obtained. ECGs will be performed prior to venipuncture and any other invasive procedures. More details of ECG collections are available in SOA.

The electrophysiological parameters assessed will be heart rate (HR), PR interval, QRS duration, QT interval, and Fridericia-corrected QT interval (QTcF) among other ECG parameters.

11.1.5. Laboratory Assessments

Blood and urine samples will be collected at the study site and shipped to the central laboratory for laboratory tests, PK, PD (APOC3), ADA and lipid parameter analysis during the screening period and on Day 1.

Blood and urine samples will be collected for the laboratory tests detailed below, to establish baseline data and eligibility for enrollment, and subsequent safety laboratory assessments will be conducted in the laboratory of each study site. Each participant is allowed to undergo a second blood draw for laboratory tests during the screening period to establish eligibility. The

results will be assessed by the PI or medically qualified designee before study enrollment. Any abnormality in laboratory values deemed clinically significant by the PI or a medically qualified designee (i.e., those that would jeopardize the safety of the participant or impact on the validity of the study results), will result in exclusion of that participant.

At all non-dosing post-Day 1 visits, in the event of logistical disruptions (e.g., COVID-related reasons) where a participant does not have direct access to the site, follow-up tests for relevant safety measures may be performed at an alternative location accepted by the sponsor, investigator/study site (e.g., local medical institution, or local laboratory). Samples will be collected with the central laboratory's collection kit through home healthcare service and shipped to the central laboratory for testing of APOC3, blood lipids, and anti-drug antibody.

Any abnormal and clinically significant laboratory result, as per the PI's medical judgment, should be documented as an AE or SAE, if applicable.

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

11.1.5.1. Hematology

The following parameters will be assessed: hemoglobin, red blood cell count, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

11.1.5.2. Blood Chemistry

The following parameters will be assessed: sodium, potassium, chloride, bicarbonate (or carbon dioxide), glucose, urea/urea nitrogen, creatinine, creatine kinase, uric acid, phosphate, total calcium, albumin, globulins, total protein, total bilirubin, amylase, lipase, HbA1c, serum insulin, C-peptide, conjugated bilirubin, gamma-glutamyltransferase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, and C-reactive protein.

11.1.5.3. Coagulation

The following parameters will be assessed: partial thromboplastin time, prothrombin time with INR, and fibrinogen.

11.1.5.4. Urine Testing

The following parameters will be assessed: leukocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose. Urine sediment microscopy will be performed if indicated, including white blood cells, red blood cells, epithelial cells, and bacteria. Random urine creatinine and random urine protein tests will also be performed.

11.1.5.5. Virus Serology

The following parameters will be assessed: HBsAg, HBV DNA and HCV antibody, and HCV RNA screening. If necessary, counseling services concerning HBsAg, hepatitis C and their subsequent results will be provided to participants by the PI or medically trained designee.

11.1.5.6. Pregnancy Screen

Postmenopausal status will be confirmed by follicle-stimulating hormone (FSH) level consistent with postmenopausal state. Blood (screening period) and subsequent urine qualitative pregnancy tests will be conducted for women of childbearing potential (for those with negative blood pregnancy tests).

11.1.6. Anti-Drug Antibodies

Serum samples will be used to assess anti-drug antibody, blood samples will be collected at the study site and shipped to the central laboratory for testing.

11.1.7. Early Termination Procedures

If a participant discontinues from the study prematurely, every reasonable effort will be made to perform the early termination visit within 30 days of the decision to terminate the participant's study participation. The reason for early termination from the study will be documented in source documents and eCRF(s). Procedures as outlined for Month 24/EOS in the SOA (Schedule of Activities: Extension Period) will be completed. Participants who discontinue the study due to SAE will be encouraged to continue to remain available for follow-up for medical monitoring until resolution.

11.2. 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 post-dose will be considered treatment-emergent. The PI and clinical facility staff are responsible for detection, recording, and reporting of pregnancy and appropriate follow-up. Any known pregnancy that occurs within 24 weeks after the last dose of IP should be reported by the participant to the PI. Information regarding any reported pregnancy should be collected up to 1 year after birth or until the end of the pregnancy.

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Events

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

Treatment-emergent AEs will be defined as AEs with onset after administration of the study

drug, or when a preexisting medical condition increases in severity or frequency after study drug administration.

Adverse events will not include:

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

11.2.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., screening, treatment, or follow- up), and at any dose of the IP or placebo, that fulfills one or more of the following:

- Results in death
- Is immediately life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the participant 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.)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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

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

Abnormal assessments (e.g., 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

clinically significant (CS) are not reported as AEs 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.

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

Any preexisting conditions or signs and/or symptoms present in a participant prior to the start of the study (i.e., 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 post-dose will be considered treatment-emergent. All AEs must be recorded irrespective of whether they are considered drug-related. Reporting and follow-up of TEAEs may continue until the EOS and for up to 6 months following the last dose.

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

11.5. Recording Adverse Events

When an AE occurs, it is the responsibility of the PI (or medically qualified designee) to review all documentation (e.g., hospital disease course records, laboratory and diagnostic reports) relative to the event. The PI or a medically qualified designee will record the AE on the AE page of the eCRF. Additional reporting requirements for an AE meeting serious criteria are discussed in Section 11.8.

The PI or medically qualified designee will establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In all cases, the diagnosis should be reported as an event rather than an individual sign/symptom. It is not acceptable for the PI to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE page of the eCRF.

11.5.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) include hypersensitivity/anaphylaxis, injection site reactions, and potential hepatotoxicity events. The PI and designated clinical staff are responsible for detecting, recording, and reporting these events. AESIs that occur after the first dose of IP will be considered treatment-emergent. AESIs should be recorded on a specially designated eCRF. A list of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms or search strategies for the AESI categories is provided in Appendix 3.

The criteria used for the assessment or grading of the AESIs are provided below.

A. **Hypersensitivity/Anaphylaxis:** The assessment of hypersensitivity and anaphylaxis will be based on the Sampson criteria (refer to Appendix 3).

B. **Injection site reactions:** LISRs are graded based on the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 5.0):
   - Mild: Tenderness with or without associated symptoms (e.g., warmth, erythema, itching), mild pain, and mild erythema
   - Moderate: Pain with associated phlebitis or lipodystrophy and edema
   - Severe: Tissue ulceration or necrosis with associated severe tissue damage or if operative intervention is indicated.

C. **Potential hepatotoxicity events:** abnormal liver function tests that may indicate potential hepatotoxicity events are graded based on the latest version of CTCAE Version 5.0. Specifically, laboratory test results that indicate an increase in the level of ALT and AST in a blood specimen are graded as follows:
   - Grade 1: If normal at baseline, >ULN-3.0 × ULN; if abnormal at baseline, 1.5-3.0 × the baseline value
   - Grade 2: If normal at baseline, >3.0-5.0 × ULN; if abnormal at baseline, >3.0-5.0 × the baseline value
   - Grade 3: If normal at baseline, >5.0-20 × ULN; if abnormal at baseline, >5.0-20 × the baseline value
   - Grade 4: If normal at baseline, >20 × ULN; if abnormal at baseline, >20.0 × the baseline value

11.6. Evaluating Adverse Events

11.6.1. 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 CTCAE (Version 5.0) and assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the participant, 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. Symptomatic; noninvasive medical intervention indicated.
- **Severe:** An event that prevents normal everyday activities but not immediately life-threatening.
- **Life-threatening:** An event that places the participant at immediate risk of death or disabling.
- **Death:** An event that results in death.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category

utilized for rating the severity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" if it meets one of the predefined outcomes described in Section 11.2.1.2.

11.6.2. Assessment of Causality

The PI (or medically qualified designee) is obligated to assess the relationship between IP and the occurrence of each AE/SAE. The PI (or medically qualified designee) will use clinical judgment to determine the causal relationship. Other plausible causes will be considered and investigated, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP. The PI (or a medically qualified designee) will also consult the IB in the determination of his/her assessment.

There may be situations where an SAE has occurred and the PI has minimal information to include in the initial SAE report. However, the PI (or medically qualified designee) must assess causality for every event prior to transmitting 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 result of causality assessment is one of the criteria used when determining whether to report to the regulatory authorities as required.

The PI (or a medically qualified designee) will provide the assessment of causality using 3 possible categories: Not Related, Possibly Related, or Probably Related.

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

- An unreasonable temporal relationship between the administration of the product and the onset of the AE (e.g., the event occurred either before, or too long after the administration of the product, but is considered product-related)
- A causal relationship between the product and the AE is biologically implausible (e.g., death from a traffic accident)
- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event)

An AE will be considered "possibly related" when an event follows a reasonable temporal sequence from administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals, or an event that follows a known or expected response pattern to the drug but that could have been produced by a number of other factors.

An AE will be considered "probably related" when an event follows a reasonable temporal sequence from administration of the IP, unlikely to be attributed to concurrent disease or other drugs or chemicals. Other examples include an event that follows a known or expected response pattern to the IP, or that is confirmed by stopping or reducing the dosage of the IP and that could not reasonably be explained by known characteristics of the participant's clinical state.

11.7. Follow-up of Adverse Events

After the initial AE, the PI is required to proactively follow each participant and provide further information on the participant'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 participant is lost to follow-up. Once resolved, the appropriate AE page and SAE report form of the eCRF will be updated (if the event is serious). The PI, or medically qualified designee, will ensure that follow-up includes any supplemental investigations that 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 (or a medically qualified designee).

11.8. Prompt Reporting of Serious Adverse Events

Any AE meeting serious criteria (i.e., SAE) must be reported promptly to the Sponsor's designated Pharmacovigilance Contract Research Organization (CRO), and IRB/IEC in accordance with applicable local/institutional requirements.

11.8.1. Completion and Transmission of the Serious Adverse Event Reports

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

The PI (or medically qualified designee) will always provide an assessment of causality at the time of the initial report as described in Section 11.6.2. However, as new information becomes available, causality may be modified.

Email transmission of the SAE report form is the preferred method 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. Notification by telephone does not replace the need for the PI, or medically qualified designee, to complete and sign the SAE report form within the outlined specified 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 participant's health or well-being will be reported to the Sponsor emergency contact listed in the Protocol.

11.8.2. Pregnancy Reporting

Pregnancy occurring in a participant or in the female partner of a male participant during the study must be reported on a pregnancy reporting form or on an SAE form to the designated Pharmacovigilance CRO immediately and not later than 24 hours of initially becoming aware of the pregnancy by the PI.

Any known pregnancy that occurs within 24 weeks after the last dose of IP should be reported by the participant to the PI.

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

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

11.8.3. Serious Adverse Event Reports to the IRB

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 IEC/IRB.

11.8.4. 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 11.8.1. Prompt notification of SAEs by the PI is essential so that the Sponsor may comply with its regulatory obligations.

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

11.8.5. Post-study Adverse Events

A post-study AE is defined as any event that occurs outside of the AE detection period defined in Section 11.4. Investigators are not obligated to actively seek AEs in former study participants. However, if the PI learns of any SAE at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the PI will promptly notify the Sponsor.

11.8.6. Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly (refer to Section 11.6).

12. Statistics

12.1. General Considerations

Statistical analyses and descriptive summaries will be presented for primary, secondary, and exploratory endpoints using appropriate methods. Any proposed amendments to the Statistical Analysis Plan (SAP) will only occur prior to database lock. Descriptive statistics will be presented for all analyses unless otherwise specified. For continuous variables, data will be summarized as number (n), mean, median, standard deviation, minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percents. Data will be analyzed by treatment group (VSA001 25 mg, VSA001 50 mg, or pooled placebo).

Additional details of all planned analyses for this study will be provided in the SAP.

12.2. Analysis Populations

The analysis sets for this study are defined as follows:

- Full Analysis Set (FAS): All randomized participants will be included in FAS. All efficacy analyses will be performed using the FAS. Participants will be analyzed according to the study treatment assigned at randomization.
- Safety Analysis Set: All participants who received at least 1 dose of IP. All safety and tolerability analyses will be performed using this set. Participants will be analyzed according to the treatment they received.
- Per-Protocol set: All randomized participants who completed the study without any major protocol deviations.
- PK Analysis Set: All participants who have been randomized and received at least one dose of study drug and have at least one evaluable plasma concentration data after dosing.

12.3. Sample Size Considerations

Participants will be randomized in a 2:1:2:1 ratio into VSA001 25 mg dose group and volume-matched placebo group, VSA001 50 mg dose group and volume-matched placebo group. The two placebo groups will be pooled for statistical analysis, i.e., the randomization ratio of treatment groups to pooled placebo group is 1:1:1.

The significance of the median difference in percent change from baseline in TG at Month 10 between each active treatment group and placebo group will be judged using the Wilcoxon (Mann-Whitney) rank-sum test with correction for continuity. Type I errors will be controlled using Holm's method.

These estimates assume an average of 75% and 80% reduction from baseline in fasting TG at Month 10 in participants receiving VSA001 25 mg and VSA001 50 mg, respectively, and a 5% reduction in participants receiving placebo. The standard deviation is assumed to be 40% for all three groups (Witztum 2019), and the level of significance α is set to be two-sided 0.05.

It is expected that 27 participants completing the 10-month follow-up will provide a power of greater than 85% to detect at least one VSA001 group with statistically significant differences versus the pooled placebo group. Assuming a dropout rate of 10% at Month 10, a total of approximately 30 participants would need to be enrolled. Taking into account the effects of uncertainties such as competitive enrollment, block randomization, and COVID-19, approximately 36 participants will be enrolled.

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

12.4. Analysis Methods

The primary analysis will include data from the randomized period. The final analysis will include data from the randomized and extension periods. The primary analysis is planned when all randomized participants complete the randomized period or discontinue from study, whichever is earlier. The final analysis is planned when all participants complete the extension period or discontinue from study, whichever is earlier.

12.4.1. Baseline Data

Demographics will be tabulated by participant and summarized by cohort and treatment group. Eligibility assessments at baseline, including medical/surgical history data, physical examination data (including height and weight) will be listed for each participant.

Medical history will be listed by participant. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and Concomitant Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), and summarized by Anatomic Therapeutic Classification and WHO-DD active ingredients.

12.4.2. Efficacy

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

To strictly control the family-wise Type I error, inferential conclusions about these efficacy endpoints will require statistical significance from both dose levels of the previous one. Within each endpoint, there are two tests, VSA001 25 mg vs. placebo and VSA001 50 mg vs. placebo. When performing the efficacy analysis for an endpoint, the adjustment for multiplicity of testing 2 VSA001 treatment groups vs placebo group will be carried out using Holm's step-

down procedure. The sequence of hypothesis testing is as follows:

Endpoints	Test Sequence
Percent change in fasting TG at Month 10 (primary endpoint)	1
Percent change in fasting TG at Month 10 and Month 12 (averaged)	2
Percent change in fasting APOC3 at Month 10	3
Percent change in fasting APOC3 at Month 12	4

The primary objective of this study is to evaluate the effect of VSA001 on fasting serum TG levels in adults with FCS. The primary endpoint is percent change from baseline at Month 10 in fasting serum TG levels. The primary analysis of the primary endpoint will evaluate the difference in means between each VSA001 dose cohort and the pooled placebo cohort and will be conducted in all randomized participants (FAS). The estimand of interest is the difference in means of percent change from baseline in fasting TG at Month 10 in adults with FCS (as defined by the inclusion/exclusion criteria), regardless of treatment compliance or other intercurrent events post-baseline.

For endpoint analysis based on Month 10 data, the laboratory value will be the arithmetic mean of two values during Month 10. If only one value is available during Month 10, then this value will be used for endpoint analysis. For data analysis purposes, baseline for fasting serum TG will be defined as the arithmetic mean of Day 1 pre-dose assessment and the last fasting assessment prior to Day 1. If only one pre-dose value is available, the pre-dose value closest to the first dose will be used.

The primary efficacy analysis will use the Wilcoxon (Mann-Whitney) rank-sum test with correction for continuity to determine the significance of the median difference between the active treatment and placebo groups. The median difference between groups and its 95% confidence interval will be estimated using the Hodges-Lehmann method.

Similar to the primary analysis of Month 10 fasting TG (primary endpoint), the Wilcoxon rank-sum test with the Hodges-Lehmann method will be used to test and evaluate the key secondary endpoints listed above, with testing order 2 to 4. Wilcoxon rank-sum test with Hodges-Lehmann method will also be used to test other continuous secondary endpoints but will only be considered exploratory. The same sensitivity analyses of the primary endpoint will be applied to these 3 key secondary endpoints and other secondary endpoints as well.

For the analysis of exploratory endpoints, descriptive summaries will be provided, as appropriate, and any inferential statistics (i.e., p-values) will be considered only as exploratory. Descriptive statistics will be provided for the secondary endpoints.

For long-term efficacy endpoints such as change and percent change from baseline in TG, APOC3, non-HDL-C, and HDL-C and other lipid parameters in the extension period, descriptive statistics will be provided by active dose received. For participants who receive placebo in the randomized period, baseline of long-term endpoints will be re-derived using the value of the last assessment prior to receiving the first dose of active IP in the extension period.

For participants who receive active drug in the randomized period, baseline is the value of last assessment prior to first dose of active IP in the randomized period.

12.4.3. Safety

In general, safety analyses will be performed and the results summarized by cohort and treatment group. Adverse events will be coded using the latest version of MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). Overall Summaries of TEAEs will be tabulated by seriousness, severity, and relationship to IP. The incidence and frequency of TEAEs, LISR-related TEAEs, serious TEAEs, and serious TEAEs leading to discontinuation, will be summarized by cohort per SOC, PT, and severity. Drug-related TEAEs will be listed in a similar manner. AEs will also be summarized in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome. The incidence/change of biomarkers will be summarized using descriptive statistics. Shift tables may be provided. 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 participant listings. ECG parameters, changes from baseline, and qualitative assessments will be summarized. Pregnancy and FSH test results will be listed.

For long-term safety endpoints, descriptive statistics will be provided by active dose received similar to long-term efficacy endpoints.

12.4.4. Pharmacokinetics and Pharmacodynamics

For all participants undergoing sparse PK sampling, plasma concentrations of VSA001 will be tested and exposure (C_{max} and AUC [if data permit]) assessed. Detailed analysis plans and results will be reported separately.

Derivative change and percent change from Day will be summarized for fasting APOC3, APOC2, and APOA5.

12.4.5. Immunogenicity (Anti-Drug Antibodies)

The number of participants to test positive for ADA at baseline and post-treatment will be summarized. Maximum ADA titer and range of titer values will be presented. ARO-APOC3 treatment-induced ADA formation, if any, will be analyzed to ascertain if the ADA response duration is transient or persistent using the definitions in the white paper published by Shankar et al. (2014) The effect of ADA formation on VSA001 PK, PD, efficacy, and safety will be analyzed.

13. Direct Access to Source Data/Documents

13.1. Study Monitoring

Visirna is responsible for ensuring that the study is properly conducted in accordance with the protocol and that the data recorded on the eCRFs are valid. Participant confidentiality will be

maintained.

In accordance with applicable regulations, GCP and Visirna procedures, Visirna will be responsible for assigning a clinical research associate (CRA) who will contact the study site to organize a visit prior to participant enrollment to review the protocol and data collection procedures with the study site staff. In addition, the assigned CRA 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 CRA will perform the following:

- 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 the following:

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

The PI allows the CRA direct access to all relevant documents and arranges a time for him/herself or his/her staff to discuss findings and any relevant issues with the CRA.

At the end of the study, the CRA will conduct the following activities in conjunction with the PI or study site staff as appropriate:

- Return of all study data to Visirna
- Data queries
- Accountability, reconciliation, and arrangement for unused IP
- Inventory and final disposition (e.g., destruction, and shipping to repository).
- Review of site study records for completeness

13.2. 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 accordance with the approved protocol and will not arbitrarily implement any deviation from or changes to the study protocol, except where necessary to eliminate an immediate hazard to study participants.

Deviations may result from the action or inaction of the participant, 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 drugs, failure to update the ICF when new risks become known, failure to obtain IRB/IEC approvals for the protocol, and ICF revisions

Protocol deviations impacting participant safety or eligibility will be reported to the Sponsor or contract research organization within 2 business days of occurrence and to the IRB/IEC/regulatory authorities as per local regulatory requirements.

The PI is responsible for ensuring that any known protocol deviations are recorded and reported in accordance with the protocol. The nature and reasons for protocol deviations will be recorded.

13.3. Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the PI or designee will obtain a copy of the certification form for all clinical laboratories (except the central laboratory) used in the study, with the certification number and expiration date. Reference ranges for each clinical laboratory test used in this study will be obtained from the laboratory, which will perform the test for the study. In the event of COVID-related restrictions prohibiting participant site visits, local laboratories with associated local lab reference ranges may be utilized with prior Sponsor approval.

13.4. Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, Visirna 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 the Sponsor as soon as possible following awareness of an impending regulatory inspection. The PI and the 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.

13.5. Institutional Review Board/Independent Ethics Committee Approval

Prior to initiation of the study, written IRB/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 approval letter will be provided to the clinical study site and Visirna prior to study commencement. Any written information or advertisements to be used for patient recruitment will be approved by the IRB/IEC prior to use. A list of the IRB/IEC voting members, their titles or occupations, Federal Wide Assurance number (where applicable) and their institutional affiliations will be requested before study initiation.

Protocol amendments that may impact participant safety or the validity of the study will be approved by the IRB/IEC, following written consent of the Sponsor.

14. Quality Control and Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. For more details on the audit assessment, refer to Section 13.4.

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 the IRB/IEC (as appropriate). The PI must submit written approval to the Sponsor before enrolling any patient/participant into the study.

The PI is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC should approve all advertising used to recruit of patients for the study. As required by the regulations, the IRB/IEC must re-approve the protocol upon receipt of the amendment.

The PI is also responsible for providing the IRB/IEC with records of serious adverse drug reactions reported in any other studies 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/IEC according to 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 requirement(s). The protocol will be submitted for approval to the IRB/IEC, and written approval obtained before patients are enrolled. The composition of the IRB/IEC will also be provided to the Sponsor. If approval is suspended or terminated by the IRB/IEC, the PI will notify the Sponsor immediately.

Where applicable, the clinical study site and Visirna agree to abide by the guidelines for

compensation for injuries resulting from participating in a company-sponsored research project.

15.3. Written Informed Consent

Informed consent should be obtained before the participant participates in the study. The contents and process of obtaining informed consent should be in accordance with all applicable regulatory requirements. Study participation includes all screening procedures, as well as any wash-out of prohibited drugs.

It is the responsibility of the PI or medically qualified designee to obtain a signed informed consent form (ICF) from every patient participating in this study after adequate explanation of the objectives, methods and potential risks of the study. The PI or a medically qualified designee must also explain to the participants 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 (i.e., ICF template) will be provided by the PI or by Visirna.

For this study, each eligible participant will be required to sign an ICF before participation in the study.

All eligible participants will have the study explained by the PI or designee. They will receive a full explanation, in lay terms, of the objectives 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 this study is for research purposes only and is not expected to provide any therapeutic benefit to individuals. During the informed consent process, the PI or designee will also review and discuss with each participant all currently approved therapies for the treatment of FCS that are commercially available in the respective region (if any). It should be pointed out that participants can withdraw from the study at any time without any discrimination. Each participant will acknowledge receipt of this information by giving written informed consent for participation in the study. The participant will be given a copy of the signed ICF to retain.

16. Data Handling and Record Keeping

16.1. Inspection of Records

The Sponsor 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, participant medical records and study source documents, and other records relative to study conduct.

16.2. Retention of Records

Following closure of the study, the PI must maintain site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. When permitted by

laws/regulations or institutional policy, some of these records can be stored in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The PI must assure that all reproductions are legible, are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the PI must ensure that there is an acceptable back-up of reproductions and that an acceptable quality control process exists for making these reproductions.

Visirna 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 laws or regulations, or Visirna standards/procedures; otherwise, the retention period will default to 15 years.

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 IRB/IEC approval letter, letter of constitution of the IRB/IEC, and copies of any other correspondence relevant to the study with the IRB/IEC or regulatory authorities
- The IRB/IEC-approved ICF
- Current curriculum vitae (signed and dated) of the PI and coworkers with major responsibilities in the trial
- Site Signature and Delegation of Responsibility Log
- Financial Disclosure Form(s) (where applicable)
- Blank Case Report Form (CRF)/eCRF
- Signed participant 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, participant CRFs, drug accountability forms, and dispensing records, etc.

17. Publication Policy

No publication of the results shall take place without the written consent of Visirna. Prior to submitting for any publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a “Publication”), the PI shall provide Visirna with a copy of the proposed Publication and allow Visirna a period of at least thirty (30) days [or for abstracts, at least five (5) working days] to review the proposed Publication. Proposed publications shall not include any confidential information of Visirna.

At Visirna’s request, the submission or other disclosure of a proposed Publication will be delayed for a sufficient length of time to allow Visirna to seek patent or similar protection of

any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written study contract for the conduct of the study, which includes publication provisions inconsistent with the statement is executed, that contract's publication provisions shall apply rather than this statement.

17.1. Ownership

All information provided by Visirna, as well as all data and information generated by the study site as part of the study (other than a participant's medical records), are the sole property of Visirna.

All rights, ownership and interests in any inventions, know-how or other intellectual or industrial property rights that are conceived or reduced to practice by the study site staff during or as because of the study are the sole property of Visirna and are hereby assigned to Visirna.

If a written contract for the conduct of the study that includes ownership provisions inconsistent with this statement is executed between Visirna and study site, the contract's ownership provisions shall apply rather than this statement.

17.2. Confidentiality

All information provided by Visirna and all data and information generated by the site as part of the study (other than a participant's medical records), will be kept confidential by the PI and other site staff. The PI or other study site staff may not use such information and data for any purpose other than conducting the study. These restrictions do not apply to: (1) information that becomes publicly available through no fault of the PI or the study site staff; (2) information that must be disclosed to the IRB/IEC in confidence for study evaluation purposes only; (3) information that must be disclosed to provide appropriate medical care to a study participant; or (4) study results that may be published as described in the next paragraph. If a written contract for the conduct of the study that includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

The Sponsor complies with data minimization principles in order to collect and process the minimum amount of personal data necessary for 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 will conduct periodic risk assessments/reviews and, as appropriate, update its information security policies and procedures.

18. References

Aalto-Setala K, Fisher EA, Chen X, Chajek-Shaul T, Hayek T, Zechner R, et al. Mechanism of hypertriglyceridemia in human apolipoprotein (apo) CIII transgenic mice. Diminished very low density lipoprotein fractional catabolic rate associated with increased apo CIII and reduced apo E on the particles. J Clin Invest. 1992;90:1889-1900.

Aalto-Setala K, Weinstock PH, Bisgaier CL, Wu L, Smith JD, Breslow JL. Further characterization of the metabolic properties of triglyceride-rich lipoproteins from human and mouse apoC-III transgenic mice. J Lipid Res. 1996;37:1802-1811.

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365-376.

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

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;108:682-690.

Brown EE, Sturm AC, Cuchel M, Braun LT, Duell PB, Underberg JA, et al. Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. J Clin Lipidol. 2020 Jul-Aug;14(4):398-413. doi: 10.1016/j.jacl.2020.04.011. Epub 2020 May 7. PMID: 32507592.

Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med. 2014;371:22-31.

Falko JM. Familial chylomicronemia syndrome: a clinical guide for endocrinologists. Endocr Pract. 2018 Aug;24(8):756-763. doi: 10.4158/EP-2018-0157. PMID: 30183397.

FDA Meeting Transcript Endocrinologic and Metabolic Drugs Advisory Committee Meeting. May 10, 2018. Available from: https://www.fda.gov/media/116320/download.

Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature. 1998;391:806-811.

Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer. 1999;35(6):939-41.

Fitzsimmons D, Kahl S, Butturini G, van Wyk M, Bornman P, Bassi C, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol. 2005;100:918-926.

Gelrud A, Williams KR, Hsieh A, Gwosdow AR, Gilstrap A, Brown A. The burden of familial chylomicronemia syndrome from the patients' perspective. Expert Rev Cardiovasc Ther. 2017;15:879-887.

Gerritsen G, Rensen PC, Kypreos KE, Zannis VI, Havekes LM, Willems van Dijk K. ApoC-III deficiency prevents hyperlipidemia induced by apoE overexpression. J Lipid Res. 2005;46:1466-1473.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727-1736.

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;46:735-745.

Johnson C, Stroes ES, Soran H, Wierzbicki A, Moulin P, Bruckert E, et al. Issues Affecting Quality of Life and Disease Burden in Lipoprotein Lipase Deficiency (LPLD) - First Step Towards a PRO Measure in LPLD (abstract). Value Health. 2015;18:A707

Jong MC, Rensen PC, Dahlmans VE, van der Boom H, van Berkel TJ, Havekes LM. Apolipoprotein C-III deficiency accelerates triglyceride hydrolysis by lipoprotein lipase in wild-type and apoE knockout mice. J Lipid Res. 2001;42:1578-1585.

Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med. 2014;371:32-41.

Khetarpal SA, Rader DJ. Triglyceride-rich lipoproteins and coronary artery disease risk: new insights from human genetics. Arterioscler Thromb Vasc Biol. 2015;35:e3-9.

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536:285-291.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.

Mogg R, Mehrotra DV. Analysis of antiretroviral immunotherapy trials with potentially non-normal and incomplete longitudinal data. Stat Med. 2007;26:484-497.

Moulin P, Dufour R, Averna M, Arca M, Cefalù AB, Noto D, et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". Atherosclerosis. 2018 Aug;275:265-272. doi:

10.1016/j.atherosclerosis.2018.06.814. Epub 2018 Jun 18. PMID: 29980054.

Proctor SD, Mamo JC. Intimal retention of cholesterol derived from apolipoprotein B100- and apolipoprotein B48-containing lipoproteins in carotid arteries of Watanabe heritable hyperlipidemic rabbits. Arterioscler Thromb Vasc Biol. 2003;23:1595-1600.

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;341:410-418.

Saleheen D, Natarajan P, Armean IM, Zhao W, Rasheed A, Khetarpal SA, et al. Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. Nature. 2017;544:235-239.

Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. J Clin Gastroenterol. 2014;48:195-203.

Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, et al; American Association of Pharmaceutical Scientists. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J. 2014;16:658-673.

Stroes E, Moulin P, Parhofer KG, Rebours V, Löhr JM, Averna M. Diagnostic algorithm for familial chylomicronemia syndrome. Atheroscler Suppl. 2017 Jan;23:1-7. doi: 10.1016/j.atherosclerosissup.2016.10.002. Epub 2016 Dec 18. PMID: 27998715.

Van Horn L, Carson JA, Appel LJ, Burke LE, Economos C, Karmally W, et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement from the American Heart Association. Circulation. 2016;134:e505-e29.

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

Yan H, Niimi M, Matsuhisa F, Zhou H, Kitajima S, Chen Y, et al. Apolipoprotein CIII deficiency protects against atherosclerosis in knockout rabbits. Arterioscler Thromb Vasc Biol. 2020;40:ATVBAHA120314368.

Appendix 1. Contraception

Females not of childbearing potential must be surgically sterilized 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) levels consistent with postmenopausal state based on laboratory reference ranges.

If a participant's urine pregnancy test result is positive, the participant will be referred to her attending physician for follow-up. Female participants with a positive pregnancy test at screening or on Day 1 pre-dose will not be enrolled in the study. Female participants who become pregnant during the study period will no longer receive investigational product (IP) but may continue to participate in study follow-up.

All participants (female participants of childbearing potential with male partners and male participants with female partners of childbearing potential) must consent to use a highly effective form of contraception during the study and for at least 24 weeks after the last dose of study treatment.

The followings are acceptable methods of highly effective contraception:

- Using twice the normal protection of birth control (condom + one other form of highly effective contraception); birth control pills, injectable birth control, birth control patches, vaginal contraceptive ring or contraceptive implant associated with inhibition of ovulation, or intrauterine device; or
- Surgical sterilization as a single form of birth control: i.e., tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy, or equivalent effective surgical form of birth control; or
- True sexual abstinence for the duration of the study and for at least 24 weeks after the last dose of IP is acceptable only when in line with the preferred and usual lifestyle of the participant.

The following methods are not considered "true" abstinence and are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational ammenorrhea methods.

Appendix 2. Liver-related Study Dose Modification and Follow-up Guidelines

Treatment-Emergent ALT/AST	Treatment-Emergent Total Bilirubin (TBL)	Liver Symptoms	Action
If normal at baseline: ALT/AST ≥ 5 × ULN If increased at baseline[a]: ALT/AST ≥ 300 U/L	Normal or increased Participants with Gilbert's syndrome or hemolysis - no change in baseline TBL	None	Discontinue IP. Confirm ALT, AST, ALP, and TBL within 72 hours. Initiate close observation and workup for competing etiologies. [b] Follow-up for symptoms.
If normal at baseline: ALT/AST ≥ 3 × ULN If increased at baseline[a]: ALT/AST ≥ 2 × baseline	Normal Participants 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.
If normal at baseline: ALT/AST ≥ 3 × ULN If increased at baseline[a]: ALT/AST ≥ 2 × baseline	Normal Participants 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 (e.g., rash, > 5% eosinophilia)	Interrupt IP. Confirm ALT, AST, ALP, and TBL within 72 hours. Initiate close observation and workup for competing etiologies. [b] IP therapy can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred. Follow-up for symptoms.
If normal at baseline: ALT/AST ≥ 3 × ULN If increased at baseline[a]: ALT/AST ≥ 2 × baseline	TBL ≥ 2 × ULN or INR increased to > 1.5 (for participants with Gilbert's syndrome or hemolysis - doubling of direct bilirubin if baseline TBL > 0.5 mg/dL)	None	Interrupt IP. Confirm ALT, AST, ALP, and TBL within 72 hours. Initiate close observation and workup for competing etiologies. [b] IP therapy can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. IP cannot be restarted if hepatic decompensation occurred.

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; IP=investigational product; TBL=total bilirubin; ULN=upper limit of normal.

[a] Increased at baseline is defined as ALT ≥ 1.5 × ULN.

[b] Acute and chronic viral hepatitis (hepatitis A-E), cholelithiasis, alcoholism or other drugs (both prescribed and over-the-counter herbs and supplements). If needed, consider consultation with hepatologist for identification of alternative etiologies and follow-up.

Source: Adapted from 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;49:702-713.

Guidelines for Close Observation for Potential Drug-Induced Liver Injury

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

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

Evaluate participants 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 participant is asymptomatic, monitor liver biochemistries once a week until they return to baseline.

Participants who live far from study sites may be evaluated locally for medical history, physical examination, and laboratories, if the results can be transmitted promptly to the Principal Investigator.

Appendix 3. Adverse Events of Special Interest - List of MedDRA Preferred Terms or Search Strategy

Injection Site Reactions:

As determined by the Sponsor's pharmacovigilance personnel, the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms will represent injection site reactions:

Injection site discomfort	Injection site calcification
Injection site discoloration	Injection site cellulitis
Injection site erythema	Injection site dermatitis
Injection site irritation	Injection site erosion
Injection site inflammation	Injection site fibrosis
Injection site induration	Injection site indentation
Injection site pain	Injection site necrosis
Injection site edema	Injection site nodule
Injection site pruritus	Injection site ulcer
Injection site rash	Injection site bruising
Injection site urticaria	Injection site haematoma
Injection site reaction	Injection site hypersensitivity
Injection site swelling	Injection site infection
Injection site abscess	Injection site pallor
Injection site abscess sterile	Injection site paraesthesia
Injection site atrophy	Injection site warmth

Hypersensitivity/Anaphylaxis Events:

A participant is said to have an episode fulfilling Sampson criteria if **at least one of the following** criteria is met:

Criterion 1: The participant experienced an onset of both Condition 1 and Condition 2 within 24 hours post dosing with study drug:

- Condition 1 - a skin or mucous membrane AE
- Condition 2 - a respiratory compromise AE or an end-organ dysfunction/reduced blood pressure AE, or reduced systolic blood pressure under 90 mmHg or greater than 30% decrease from baseline based on the vital signs data

Criterion 2: The participant experienced an onset of any 2 or more conditions within 24 hours post dosing with study drug:

- Condition 1 - a skin or mucous membrane AE
- Condition 2 - a respiratory compromise AE
- Condition 3 - an end-organ dysfunction/reduced blood pressure AE, or reduced systolic blood pressure
- Condition 4 - a gastrointestinal AE

Criterion 3: The participant experienced reduced systolic blood pressure within 24 hours post dosing with study drug, and at least 1 qualifying event. *

*A qualifying event is defined as any of the following occurring during the study, after the first administration of the study drug associated with the current reduced systolic blood pressure event.

- Condition 1 - an event meeting Criterion 1
- Condition 2 - an injection site reaction
- Condition 3 - AE under Anaphylactic reaction Standardized MedDRA Query (SMQ) or the Angioedema SMQ or the Hypersensitivity SMQ considered to be related to the study drug.

Potential Hepatotoxicity Events:

The following Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms may represent hepatic events:

Drug-induced liver injury	Liver injury
Hepatotoxicity	Hepatic enzyme increased
Acute hepatic failure	Alanine aminotransferase abnormal
Ascites	Alanine aminotransferase increased
Hepatic failure	Aspartate aminotransferase abnormal
Hepatic fibrosis	Aspartate aminotransferase increased
Hepatic necrosis	Bilirubin conjugated abnormal
Hepatic steatosis	Bilirubin conjugated increased
Hepatobiliary disease	Hepatic enzyme abnormal
Hepatocellular injury	Hepatic enzyme increased
Hyperbilirubinaemia	Liver function test increased
Jaundice	Transaminases increased
Liver disorder	Hypertransaminasaemia

Appendix 4. Table of Fatty Acid Content of Food

Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)	Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)
1	Wheat flour (standard flour)	1.7	24	Dried bean curd	32.7
2	Wheat flour (strong flour)	1.0	25	Agrocybe aegerita (dried)	1.5
3	Hanging noodles (strong flour)	1.0	26	T. gambasum (dried)	3.6
4	Dragon whiskers noodles (vegetarian/egg)	1.2	27	Pholiota adiposa (dried)	1.8
5	Noodles (cut/cooked)	0.3	28	Collybia albuminosa (dried)	2.1
6	Steamed twisted roll (with milk)	2.1	29	Boletus edulis (dried)	0.9
7	Steamed bun (strong flour)	0.9	30	Suillus bovinus (dried)	1.6
8	Gluten	Unknown	31	Tricholoma matsutake (dried)	1.7
9	Long-shaped rice	0.9	32	Russula sanguinea (dried)	3.8
10	Rice flour	0.7	33	Hohenbuehelia serotina (dried)	0.8
11	Corn kernels (yellow, dry)	0.7	34	Hazel mushroom (dried)	6.1
12	Corn flour (yellow)	1.3	35	Undaria pinnatifida (dried)	1.4
13	Corn grits (yellow)	1.0	36	Kelp	6.0
14	Millet (yellow)	2.6	37	Ficus carica (dried)	3.4
15	Fagopyrum esculentum flour	1.9	38	Pecan (cooked)	61.7
16	Naked oats flour	5.8	39	Chestnuts (cooked)	1.4
17	Soy milk powder (Duoli brand)	4.3	40	Pine nuts (cooked)	38.6
18	Soybean milk powder (Damo brand)	8.6	41	Almonds (cooked, shelled)	52.0
19	Firm tofu	7.5	42	Cashew nuts (cooked, shelled)	48.7
20	Soft tofu	5.4	43	Hazelnut kernel (cooked)	50.6
21	Soybean milk	1.5	44	Pistachio (cooked)	50.7
22	Beancurd skin	21.4	45	Torreya grandis (cooked)	54.5
23	Yuba	25.3	46	Peanuts (roasted, Qinjian brand)	44.0
47	Sunflower seeds (creamy)	51.7	67	Ham core	44.4
48	Sunflower seed (cooked)	46.8	68	Barbecued pork	8.7

Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)	Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)
49	Pumpkin seeds (white, cooked)	50.5	69	Spareribs in soy sauce	25.2
50	Watermelon seeds (black, cooked)	44.0	70	Fragrant leached meat	50.4
51	Pork (front rump, Duroc × Landrace × Yorkshire pigs)	23.0	71	Beef (back, top)	11.4
52	Pork (front rump, excellent hybrid pigs)	27.7	72	Beef (fillet, beef fillet)	4.6
53	Pork (hind rump, Duroc × Landrace × Yorkshire pigs)	8.3	73	Beef (rump)	2.4
54	Pork (hind rump, excellent hybrid pigs)	9.6	74	Beef (shoulder)	29.0
55	Pork (hard rib, Duroc × Landrace × Yorkshire pigs)	52.0	75	Beef (brisket)	26.4
56	Pork (hard rib, excellent hybrid pigs)	49.5	76	Beef (belly, tender loin)	27.9
57	Pork (faux-filet, Duroc × Landrace × Yorkshire pigs)	7.1	77	Beef (eye round, sirloin tip)	1.6
58	Pork (faux-filet, excellent hybrid pigs)	5.8	78	Beef (groin beef)	2.7
59	Porcine skin	26.8	79	Beef (shank)	3.0
60	Pork chop (Duroc × Landrace × Yorkshire pigs)	23.0	80	Omasum (black)	1.5
61	Pork chop (excellent hybrid pigs)	29.8	81	Beef in spiced sauce	9.5
62	Pork stomach	2.8	82	Beef (fragrant)	9.5
63	Pork liver	3.5	83	Beef shank (bay leaf)	5.0
64	Pork tongue (pig's tongue as food)	11.3	84	Sliced dried beef (Changfu brand)	4.9
65	Pork kidney (kidney)	1.3	85	Ham	3.0
66	Ham core with whole lean meat	17.6	86	Sandwich ham	4.0
87	Crispy sausage	21.4	111	Young pigeon (braised in brown sauce)	19.7
88	Hot dog	22.4	112	Milk (Guangming brand)	3.0
89	Ham sausage	13.0	113	Milk (Robust brand)	3.6
90	Luncheon meat	28.4	114	Milk (Sanyuan brand)	3.7
91	Pork floss	9.0	115	Milk (Mengniu/Yili)	3.5
92	Braised pork face	28.0	116	Milk (partially defatted)	1.2
93	Smoked tenderloin	3.5	117	Milk (degreased)	0.2

Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)	Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)
94	Dried pork slices	7.8	118	Milk (fortified with zinc and calcium)	2.9
95	Meat crisp	24.0	119	School milk	2.5
96	Roast mutton (spiced)	4.8	120	Whole milk powder (Sanlu)	28.0
97	Mutton shashlik (raw)	4.3	121	Whole milk powder (Yili)	24.6
98	Donkey meat (spiced)	5.3	122	Low-fat milk powder (Yili)	10.4
99	Venison (sika deer)	1.2	123	Milk powder for middle-aged and elderly	5.5
100	Chicken breast	1.8	124	Yogurt (flavored)	3.0
101	Chicken leg	6.8	125	Yogurt (with fruit tablets)	2.7
102	Chicken wings	10.9	126	Cheese (Guangming brand)	26.8
103	Chicken nuggets (with starch)	8.6	127	Low-fat cheese	11.0
104	Pheasant	1.9	128	Cream	81.3
105	Braised chicken (spiced and boneless)	10.2	129	Full-fat sweetened condensed milk	9.5
106	Roast chicken	16.0	130	Egg (red skin)	8.7
107	Spring chicken (cooked)	17.1	131	Silkie egg (green skin)	8.8
108	Roast duck	23.9	132	Sea duck egg	11.5
109	Preserved goose	20.3	133	Salted duck egg (boiled)	11.2
110	Young pigeon	32.2	134	Grass carp	1.8
135	Silver carp	1.5	158	Black sesame dumplings	Unknown
136	Crucian carp	1.1	159	Fermented glutinous rice	Unknown
137	Hairtail	2.9	160	Pancake	Unknown
138	Yellow croaker (small croaker)	3.6	161	Mooncake	Unknown
139	Mackerel	27.6	162	Spring rolls (vegetarian)	Unknown
140	Double-fin shark	0.1	163	Pizza (cheese)	4.8
141	Fish steak	2.2	164	Sandwich (chicken)	14.9
142	Fish ball	1.2	165	Hot dog (original flavor)	13.7
143	Caviar	6.4	166	Sachima egg crisp	28.8
144	Grass carp (black)	15.3	167	Hamburger (regular, cheese, single patty)	10.9
145	Clove fish (spicy)	25.4	168	Hamburger (double patty)	13.6

Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)	Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)
146	Swordfish (fried)	11.3	169	Fried rice with shrimps	Unknown
147	Fried dace with salted black beans	29.8	170	Breakfast milk	2.9
148	Eel (braised in brown sauce)	6.9	171	Eight treasures congee	Unknown
149	Shrimp paste	5.3	172	Black sesame paste	Unknown
150	Sea crab (small)	0.6	173	Cornmeal	9.1
151	Crab stick	0.3	174	Oatmeal	9.1
152	Clam ball	8.3	175	Braised beef instant noodles	15.8
153	Turtle egg	6.1	176	Fried noodles with sizzling beef	16.6
154	Cuttlefish ring	2.0	177	Fried Chinese leek dumpling	Unknown
155	Cuttlefish ball	4.2	178	Shrimp ravioli	Unknown
156	Chicken liver and vegetable puree (Heinz)	1.6	179	Glutinous rice ball	Unknown
157	Rice flour (high protein, Heinz)	1.7	180	Fried rice with assorted meats	Unknown
181	Biscuit (sandwich)	28.8	205	Stuffed rice nuts	39.6
182	Biscuit (stuffed)	15.0	206	Mini puff	42.6
183	Biscuit (stuffed with sweet crisp)	33.2	207	Popcorn	11.4
184	Biscuit (stuffed with soda)	18.3	208	Fish granules	2.3
185	Biscuit (salty)	24.2	209	Pineapple juice (Taihu brand)	0.2
186	Dumplings	Unknown	210	Grapefruit juice drink	0.3
187	Steamed stuffed bun	Unknown	211	Coconut water drink	1.9
188	Rice cake (egg-milk flavor)	28.3	212	Sour milk drink	1.2
189	Snow rice cake	16.6	213	TANG	1.8
190	Egg roll	33.4	214	Lemon tea	1.4
191	Chocolate pie	13.0	215	Coffee bean	8.3
192	French burritos	32.2	216	Ground coffee	0.4
193	Doritos	23.4	217	Ice cream (strawberry)	3.0
194	Corn crisp	32.8	218	Ice cream (with cream)	12.1
195	Crisps	28.0	219	Popsicle	0.9
196	Onion ring	20.1	220	Milk candy	Unknown
197	Rice crust (bean flavor)	28.9	221	Peanut nougat	Unknown
198	Rice crust (millet)	34.9	222	Green plum with snow-like powder	0.8

Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)	Sr. No.	Food Name	Fatty Acid (g/100 g edible portion)
199	Instant seaweed	2.7	223	Preserved fruit	0.4
200	Mushroom slices	7.0	224	Walnut oil	94.7
201	Potato chips (barbecue flavor)	35.4	225	Peanut oil	95.5
202	Potato chips (spicy)	37.7	226	Sunflower seed oil	95.5
203	Potato rings	40.1	227	Corn germ oil	95.6
204	Strange-flavored chickpeas	9.4	228	Rice bran oil	94.4
229	Camellia oleifera seed oil	95.4	239	Salad dressing	74.7
230	Sesame oil	95.3	240	Strawberry jam	0.8
231	Soybean salad oil	95.5	241	Tomato sauce	0.1
232	Salad oil	95.3	242	Fermented bean curd (white)	7.2
233	Dark soy sauce	0.3	243	Chopped chili pepper	0.4
234	Hoisin sauce	未知	244	Pickled cabbage	1.3
235	Beef paste	未知	245	Chicken powder	4.8
236	Peanut butter	50.5	246	Chicken extract	2.6
237	Peanut butter (with chocolate)	52.7	247	Thousand Island salad dressing	41.1
238	Sesame paste	63.9			

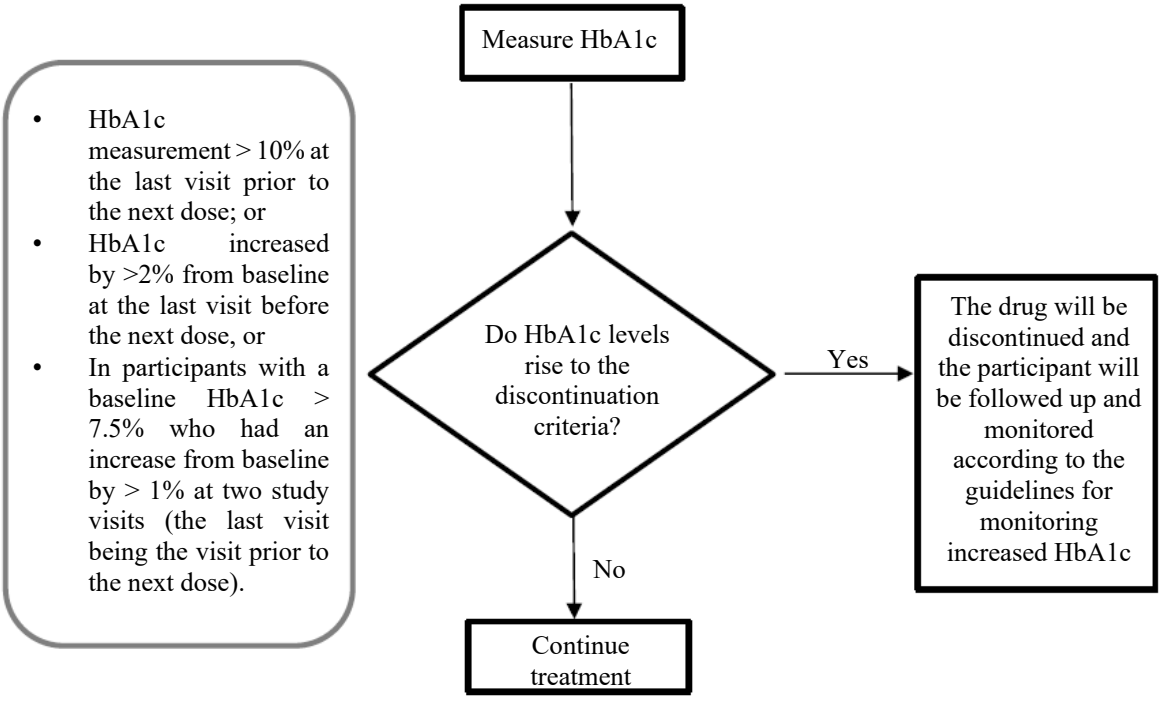
Source: Chinese Food Ingredient List (Standard Version)

Appendix 5. Glycemic Control-related Guidelines

Discontinuation principles related to increased HbA1c:

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

- Glycosylated hemoglobin (HbA1c) measurement > 10% at the last visit prior to the next dose; or
- HbA1c increased by >2% from baseline at the last visit before the next dose, or
- In participants with a baseline HbA1c > 7.5% who had an increase from baseline by >1% at two study visits (the last visit being the visit prior to the next dose).



Relevant monitoring guidelines for increased HbA1c:

- Investigators are encouraged to evaluate diabetes mellitus status and adjust diabetes mellitus management according to clinical practice and diabetes mellitus care guidance.
- At the Investigator's discretion, any participants with inadequately controlled diabetes mellitus may return to the study site or a study facility recognized by the Sponsor and the Investigator for an unscheduled visit prior to the next planned dose to evaluate changes in HbA1c to confirm continued treatment eligibility:
  - If the participant's HbA1c test value is increased by > 2% from baseline, it is necessary to conduct an unscheduled visit within 14 days and optimize hypoglycemic therapy according to clinical practice guidelines
  - After optimized hypoglycemic therapy, HbA1c will be retested within 14 days before the next dose
  - If the HbA1c retest results after optimized hypoglycemic therapy show:

- If the test value is decreased by ≥ 1% from the last time and HbA1c is ≤ 9.5%, the dosing can be continued according to the Schedule of Activities
- If the test value is decreased by ≥ 1% from the last time and HbA1c is still > 9.5%, or if the test value is decreased by < 1% from the last time and HbA1c is ≤ 9.5%, the investigator may discuss subsequent treatment with the medical monitor
- If the test value is decreased by < 1% from the last time and HbA1c is > 9.5%, the dosing should be interrupted once

- If the dosing is interrupted twice, the participant will withdraw from the trial.

Appendix 6. Description of Clinical Laboratory Tests

Blood and urine samples of participants will be collected at the study site and shipped to the designated central laboratory for all laboratory tests, pharmacokinetics (PK), pharmacodynamics (PD, specifically APOC3 protein), anti-drug antibody (ADA) and lipid testing during the screening period and on Day 1 (except coagulation). Safety laboratory testing after Day 1 will be conducted in the laboratory of the study site, and the investigator may add unscheduled visits and laboratory testing during the study according to the specific situation of the participant.

Laboratory	Visits	Testing Item	Data Analysis Institution	Remaining Sample Disposal Institution
Chongqing Denali Medpharma Co., Ltd.	Day 1, Month 3	Sparse PK: Pharmacokinetics samples will be collected pre-dose and post-dose to test blood concentrations of the investigational product	R&G PharmaStudies Co., Ltd.	Chongqing Suxin Medical Waste Treatment Co., Ltd.
	Day 1, Months 1, 3, 6, 9, 12, 15, 18, and 24/or early termination	ADA: Used to observe the immunogenicity of investigational products		
Teddy Clinical Research Laboratory (Shanghai) Limited*	Screening period	• Virology (HBsAg, HBV DNA and HCV antibody, HCV RNA) • Pregnancy screening: FSH (for postmenopausal women), and serum beta-HCG (for women of childbearing age) • C-peptide, insulin, TSH, FT4, blood chemistry, HbA1c, and hematology • Urinalysis, urine sediment microscopy, random urine creatinine, and random urine protein • 7-item lipid test (TG, LDL-C, TC, non-HDL-C, HDL-C, VLDL-C, and LP[a])	R&G PharmaStudies Co., Ltd.	Shanghai Solid Waste Disposal Co., Ltd.*
	Day 1 (baseline)	• C-peptide, insulin, blood chemistry, HbA1c, and hematology • Urinalysis, urine sediment microscopy, random urine creatinine, and random urine protein • APOC3 and lipid parameters (TG, LDL-C, TC, non-HDL-C, HDL-C, VLDL-C, APOB-48, LP[a], APOB-100, total APOB, APOC-III, APOC-II, APOA-I, and APOA-V)		
	At Months 1, 2, 3, 4, 5, 6, 7, 8, 9,	• APOC3 and lipid parameters (TG, LDL-C, TC, non-HDL-C, HDL-C, VLDL-C, APOB-48, LP[a], APOB-100, total APOB, APOC-III,		

	10*, 11, 12, 13, 14, 15, 18, 21, and 24/or early termination	APOC-II, APOA-I, and APOA-V) • Lipid parameter testing must be done after the participant has fasted for ≥ 10 hours before collection at each study visit • At Month 10, blood lipid data will be collected 2 times, 2-7 days apart, for efficacy assessment		
Laboratory of study site	Screening period	Coagulation only	R&G PharmaStudies Co., Ltd.	Medical institutions
	Day 1	Urine pregnancy (for women of childbearing age), coagulation		
	All visits after Day 1	• Routine laboratory tests (kidney function, electrolytes, coagulation, urine tests, blood glucose, HbA1c, insulin, C-peptide, etc.) • Liver function tests (ALP, ALT, AST, TBL), hematology • Urine pregnancy (for women of childbearing age) • Note: For specific details, see the Schedule of Activities (SOC)		

*Among them, samples for APOA-V/APOB-48/APOB-100 will be undertaken by Wuxi Teddy Medical Testing Co., Ltd., a subsidiary of Shanghai Teddylab, while the remaining samples will be disposed of by Wuxi Industrial Waste Safety Disposal Co., Ltd.

All laboratory tests (except for coagulation) used as inclusion criteria will be assessed by a central laboratory and may be repeated once (except for TG), and the repeat value may be used for inclusion purposes. Three repeat TG tests are allowed during screening period to confirm the results. Local laboratory testing may be permitted in limited circumstances and only with prior Sponsor approval.

At all non-dosing post-Day 1 visits, in the event of logistical disruptions (e.g., COVID-related reasons) where a participant does not have direct access to the site, follow-up tests for relevant safety measures may be performed at an alternative location accepted by the sponsor, investigator/study site (e.g., local medical institution, or local laboratory). Samples will be collected with the central laboratory's collection kit through home healthcare service and shipped to the central laboratory for testing of APOC3, blood lipids, and anti-drug antibody (if necessary).