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

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TABLE OF CONTENTS

List of Abbreviations

Abbreviation and Terminology	Terms
ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
APOA-I or APOA1	Apolipoprotein A-I
APOA-V or APOA5	Apolipoprotein A-V
APOB	Apolipoprotein B
APOB-100	Apolipoprotein B 100
APOB-48	Apolipoprotein B 48
APOC2	Apolipoprotein C2
APOC3	Apolipoprotein C3
CI	Confidence Interval
COVID	Coronavirus disease
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
FAS	Full analysis set
FCS	familial chylomicronemia syndrome
FT4	Free thyroid hormone
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment for insulin resistance
ICF	Informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	Interactive Voice/Web Response System
LDL-C	Low density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic resonance imaging
PK	Pharmacokinetics
PPS	Per protocol set
PROS	Patient-reported outcomes analysis set
PT	Preferred term
Q3M	Once every 3 months
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System Organ Class
SS	Safety analysis set
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
TG	Triglyceride(s)
ULN	Upper limit of normal
VAS	Visual analog scale

1 Introduction

Familial chylomicronemia syndrome (FCS) is a severe and ultrarare genetic disease that is typically caused by multiple monogenic mutations, resulting in extremely elevated fasting triglycerides (TG). VSA001 (ARO-APOC3), developed by Arrowhead, 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.

This study is a phase 3 study to evaluate the efficacy and safety of VSA001 injection in Chinese adults with familial chylomicronemia syndrome, it sponsored and conducted by Visirna Therapeutics Co., Ltd.

This statistical analysis plan (SAP) is the final analysis plan, jointly developed by statisticians, the principal investigator, and the sponsor based on the VSA001-3001 clinical study protocol V3.4 (dated September 2, 2024). It defines the analysis populations relevant to the primary analysis, key variables, and statistical analysis methods, and provides the principles for statistical analysis methods and data handling.

2 Study Design

2.1 Objectives

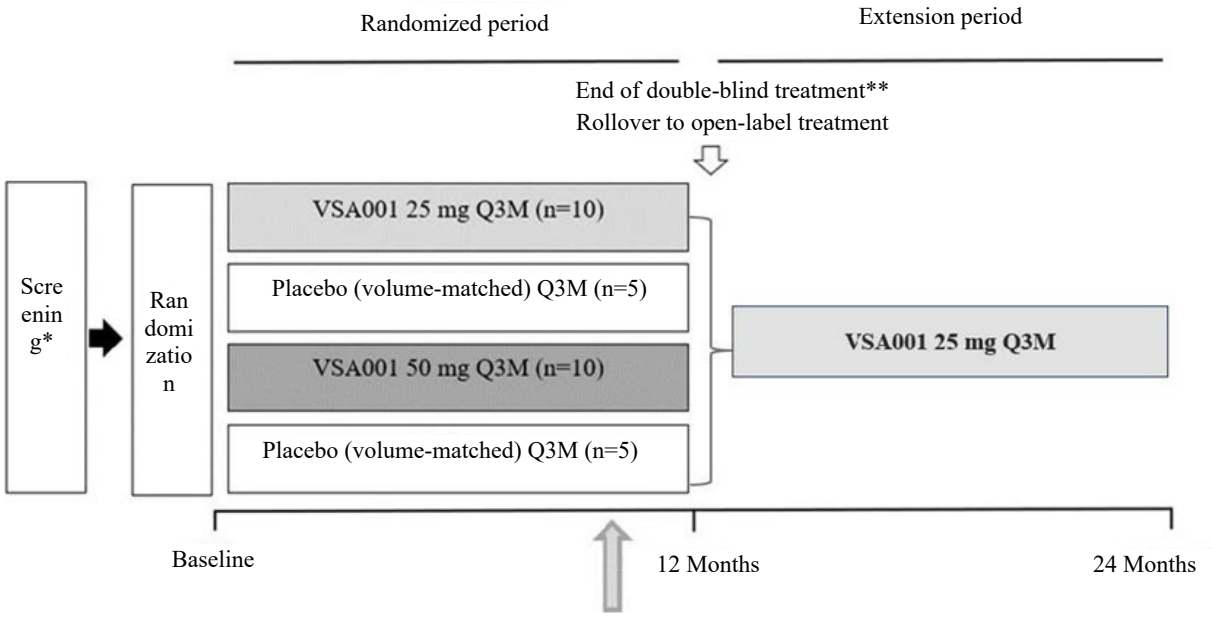
The objectives of this study are to evaluate the efficacy and safety of VSA001 in adults with FCS.

2.2 Overall Design

This is a randomized, double-blind, placebo-controlled, dose-selection phase III clinical study, comprising two parallel dose groups: the 25 mg group and the 50 mg group. Following a once-every-3-month (Q3M) dosing regimen and using the percent change from baseline at Month 10 in fasting serum triglyceride TG as the primary endpoint, the efficacy of VSA001 injection will be evaluated in Chinese adult patients with familial chylomicronaemia syndrome (FCS). 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. The duration of the study is approximately 30 months; the enrollment will last about 6 months, and follow-up will last about 24 months. Taking into account the effects of uncertainties such as competitive enrollment, block randomization, and COVID-19, approximately 36 participants will be enrolled.

This study consists of two periods: the screening period and the treatment period. The treatment period includes the randomized period and the extension period. The study flow chart is as follows (Figure 1):

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

Screening period

Participants who have signed an informed consent form (ICF) previously approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) may initiate 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.

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.

Treatment period

Eligible participants will be randomized and proceed to the treatment period, which consists of two periods: the randomized period and the extension period. No dose escalation or dose reduction will be made during the treatment of the randomized period.

(1) Randomized period

A total of 30 participants will be enrolled in the randomized period. Participants who meet the

inclusion and exclusion criteria will be randomized in a 2:1:2:1 ratio to each dose cohort (VSA001 25 mg, 25 mg volume-matched placebo, VSA001 50 mg, 50 mg volume-matched placebo). An Interactive Web Response System (IWRS) will be used to randomize eligible participants to the active drug or placebo group based on a stratified block randomization algorithm. Stratification factors include:

- TG level at screening (≥ 2000 mg/dL vs < 2000 mg/dL).

The randomized period will last 12 months, during which, participants will receive VSA001 or matched placebo subcutaneously Q3M in a double-blind manner, for a total of 4 doses, as follows:

- 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.

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), as follows:

- 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 investigational product, i.e., starting from Month 12 of the Schedule of Activities.

(2) Extension period

The extension period will last 12 months, during which, participants will receive VSA001 subcutaneously Q3M in an open-label manner, for a total of 4 doses, as follows:

- 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. Accordingly, participants who have received VSA001 25 mg Q3M or 50 mg Q3M during the randomized period will continue the same dose of VSA001 in the extension period. Participants who have received placebo will switch to the corresponding dose of VSA001 based on the initial dosing group to which they are 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 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.

2.3 Schedule of Activities

The schedule of activities is shown below:

Randomized period

Study visit	Screening	Randomized period														
					Month											
					1	2	3	4	5	6	7	8	9	10	11	12[a]
Study day	Day -56 to -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/HCV serology screen	X															
FSH (women not of childbearing potential to confirm postmenopausal status)	X															
Pregnancy test (for women of	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Study visit	Screening	Randomized period														
		Day 1[b]	Day 2	Day 15	Month											
					1	2	3	4	5	6	7	8	9	10	11	12[a]
Study day	Day -56 to -1				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]
childbearing potential)																
Thyroid function test	X															
Routine laboratory tests[h]	X	X		X		X	X			X			X			X
Liver function tests (ALP, ALT, AST, TB), 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													
Diet assessments[o]		X					X			X			X			X
Quality of Life Assessment (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-PAN26)		X					X			X			X			X
Concomitant medications/therapies	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events (including documentation of pancreatitis, abdominal pain or events requiring apheresis)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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.

Extension period

Study visit	Extension period					
	Month					
	13	14	15	18	21	24/EOS[a]
Study day	Day (±10 days)					
	290	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 examinations			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, TB) 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 QLQ-PAN26)						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.

3 Endpoints

3.1 Primary Endpoints

The primary endpoints for this study are as follows:

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

3.2 Secondary Endpoints

3.2.1 Key secondary endpoints

The key secondary endpoints for this study are as follows:

- Percent change from baseline at Months 10 and 12 (geometric mean) 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

3.2.2 Other 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 acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
  2. Serum lipase activity (or amylase activity) ≥3 × ULN
  3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI), or transabdominal ultrasonography.

3.3 Exploratory 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

  HOMA-IR = Fasting glucose (mmol/L) × Fasting insulin (μU/mL)/22.5
- 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, TG <880 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
- Time to first adjudicated acute pancreatitis event

4 Sample Size Estimation

These estimates assume an average of 75%, 80% and 5% reduction from baseline in fasting TG at Month 10 in participants receiving VSA001 25 mg, VSA001 50 mg and placebo, respectively. 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 groups. Assuming a dropout rate of 10% at Month 10, a total of 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.

5 Randomization and Blinding

5.1 Randomization

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). An Interactive Web Response System (IWRS) will be used to randomize eligible participants to the active drug or placebo group based on a stratified block randomization algorithm. The stratification factor is the TG level at screening (≥ 2000 mg/dL vs. < 2000 mg/dL).

5.2 Blinding Method

Randomized period

A double-blind design will be adopted during the randomized period of this study. Within each dose group, treatment assignment (VSA001 vs. placebo) will be blinded. Since injection volumes differ among dose groups, blinding will not be applied between dose groups. To mask the slight color difference between the active drug and placebo, the syringes will be blinded at the pharmacy as described in the Pharmacy Manual, so that the blinded staff and participants will remain blinded to the treatment assignment.

5.2.1 Extension period

In the extension period of the study, participants will receive open-label treatment, but 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.

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.

In addition, considering the risk of unblinding due to TG and lipid parameter results, related parameters will be analyzed at the central laboratory. After completion of the Month 13 visit, the central laboratory will provide available lipid parameter results to the investigator through the Month 24/End-of-Treatment (EOS) Visit.

6 Statistical Hypotheses

For the primary efficacy endpoint and key secondary efficacy endpoints, the statistical hypotheses for each dose (25 mg and 50 mg) are as follows:

H_0: there was no difference between the VSA001 group and the pooled placebo groups in the median of the given variable

H_1: there was difference between the VSA001 group and the pooled placebo groups in the median of the given variable

To control the overall Type I error at a 0.05 level, the sequential strategy would be implemented for comparison for multiplicity following a fixed sequence, that is, the hypothesis testing procedure from the primary endpoint to the key secondary endpoints would use the following fixed-sequence stepping-down procedure, and the key secondary endpoints would be tested sequentially only if the primary efficacy analysis of the primary endpoint proved the results were significantly in favor of the active treatment groups (see Table 1).

Table 1 Sequence of hypotheses testing

Type	**Endpoints**	**Test Sequence**
Primary endpoints	Percent change from baseline at Month 10 in fasting serum TG	1
Key secondary endpoints	Percent change from baseline at Months 10 and 12 (averaged) in fasting serum TG	2
	Percent change from baseline at Month 10 in fasting serum APOC3	3
	Percent change from baseline at Month 12 in fasting serum APOC3	4

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. pooled placebo groups and VSA001 50 mg vs. pooled placebo groups. When performing the efficacy analysis for an endpoint, the adjustment for multiplicity of testing for the comparison between 2 VSA001 treatment groups and pooled placebo groups will be carried out using Holm's procedure. A detailed introduction to the Holm's procedure and reference core code can be found in Section 11.7 and Appendix 12.3.

7 Analysis Populations

Full analysis set (FAS): All randomized participants will be included in the 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 (SS): All randomized participants who have received at least one dose of the investigational product. All safety and tolerability analyses will be performed using this set. Participants will be analyzed according to the treatment they actually receive.

Per protocol set (PPS): Including participants in the FAS set without major protocol deviations that would affect efficacy assessments.

Patient-reported outcomes analysis set (PROS): Including all participants who were randomized and enrolled and received at least one PRO assessment. Participants will be analyzed according to the study treatment assigned at randomization.

Pharmacokinetics analysis set (PKS): All participants who have been randomized and received at least one dose of investigational product and have at least one evaluable plasma concentration data after dosing.

8 Statistical Analysis

8.1 General Principles

The statistical analysis software was SAS® 9.4 or later.

Unless otherwise specified, baseline and efficacy analysis will be summarized and analyzed according to randomized treatment groups (VSA001 25 mg, VSA001 50 mg, and pooled placebo groups) and/or total group. Safety analysis will be descriptively summarized by actual treatment groups (VSA001 25 mg, VSA001 50 mg, and pooled placebo groups) and/or total group.

Unless otherwise specified, all analyses will be conducted for both the randomized period and the extension period.

Unless otherwise specified, placebo in this SAP refers to the pooled placebo groups.

(1) Unless otherwise specified, descriptive statistics will be used for quantitative data. Statistical parameters include number of participants, arithmetic mean, standard deviation, standard error of the mean, median, 25th percentile, 75th percentile, minimum, and maximum. Unless otherwise specified, the arithmetic mean, median, point estimates of statistical hypothesis tests and 95% confidence intervals (CIs) , 25th percentile, and 75th percentile will be rounded to 1 more decimal place than the source data; standard deviation, standard error of the mean, and standard error will be rounded to 2 more decimal places than the source data; minimum and maximum values will retain consistent with the source data. All statistical parameters will be rounded to no more than 4 decimal places.

(2) Descriptive statistics will be used for enumeration data, including the number and percentage of participants (percentage will be rounded to 1 decimal place). If the number of participants is 0, the percentage will not be calculated. Unless otherwise specified, the denominator for calculating the percentage is the total number of participants in the corresponding group of the analysis population.

MedDRA and WHODrug codes generally use the latest dictionary codes, and the specific dictionary version will be based on the actual coding dictionary used in the source data.

For two-sided test of statistical tests, P-value ≤ 0.05 indicates a statistically significant difference (unless otherwise specified). P values will be reported with 4 decimal places. If P value < 0.0001, it will be displayed as "< 0.0001". If P value > 0.9999, it will be displayed as ">0.9999".

Unless otherwise specified, tables are limited to scheduled visits only, while all visits will be presented in listings, including unscheduled visits. If the reason for "not done" or "not assessed" is not collected in the CRF, the listings will only present the results of the visits at which the relevant tests or assessments have been completed.

8.2 Data Processing Rules

Outlier processing rules

If a laboratory test value is recorded as lower (and equal to) or higher (and equal to) than the test range value (such as, <x, ≤x, >x, ≥x), it will be processed as the test range value (i.e. =x) during summary of descriptive statistics, but in listings, it will still be listed as recorded on the eCRF, that is, "<x", "≤x", ">x" or "≥x". In rare cases, some efficacy lab parameters may have a value of 0. If the lower limit of quantitation is available, then half of this limit will be used for the analysis.

Missing and incomplete dates processing rules

For missing dates related to adverse events, previous/concomitant medication, and previous/concomitant non-drug therapy, if it is necessary to compare with the first dose date or informed consent date, and unless otherwise specified, the missing dates should be imputed according to the following method before making any determination:

(1) Missing dates of adverse events (AEs) will be imputed as follows:

- Missing of start date of AE
  - If the year and month are known and differ from the year and month of the first dose, it will be imputed with the first day of the known month;
  - If the year and month are known and the year and month are the same as the year and month of the first dose, the date of first dose will be used for imputation, and it will be assumed by default that the AE occurred after the first dose;
  - If only the year is known and differ from the year of the first dose, it will be imputed with "January 1";
  - If only the year is known and the year is the same as the year of first dose, the date of first dose will be used for imputation, and it will be assumed by default that the AE occurred after the first dose;
  - If year, month and day are all missing, the date of the first dose will be taken as the corresponding start date;

- All other situations will be considered completely missing and no imputation will be performed.

- Missing of end date of AE
  - If the year and month are known, it will be imputed with the last day of the known month;
  - If only the year is known, it will be imputed with "December 31";
  - If the start date imputed is later than the end date, the end date will be taken as the corresponding start date;
  - Other conditions are regarded as missing, and no imputation will be performed.

  If the imputed date is later than the date of death, it will be replaced with the date of death.

(2) Missing date of previous concomitant medication (CM) or previous concomitant non-drug therapy (PR) will be imputed as follows:

- Missing of the start date of previous concomitant medication/previous concomitant non-drug therapy
  - If the year and month were known, it will be imputed with the first day of the known month;
  - If only the year is known, it will be imputed with "January 1";
  - If the year, month, and day are all missing, the start date of the record will not be imputed, and the record should be included in both previous medication and concomitant medication/previous non-drug therapy and concomitant non-drug therapy.

- Missing of the end date of previous concomitant medication/previous concomitant non-drug therapy
  - If the year and month are known, it will be imputed with the last day of the known month;
  - If only the year is known, it will be imputed with "December 31";
  - If the year, month, and day are all missing, and the previous concomitant medication / previous concomitant non-drug therapy is not ongoing, the end date of the record will not be imputed, and the record should be included in concomitant medication/concomitant non-drug therapy.

  If the imputed date is later than the date of death, it will be replaced with the date of death.

(3) Other missing dates will not be imputed.

Imputation of missing/incomplete dates is only used for edit check and calculation; in listings,

the original collected data will still be displayed.

8.2.1 Analysis visits

Analysis visit window is defined based on scheduled study day, as detailed in Table 2. Within an analysis visit window, if a scheduled visit occurs, then the measurement from this scheduled visit will be used as the measurement for the visit window. If unscheduled visit occurs within an analysis visit window, the measurement from the visit closest to the scheduled study day within the analysis visit window will be used. If there are more than one measurement with equal distance to the scheduled study day, the last one will be used. If no visits occur within an analysis visit window, the measurement for this visit will be treated as missing. For visits due to early termination of treatment or study discontinuation, it will be treated as analysis visit +1 if more than one visits are measured within one analysis visit window.

Table 2 Derivation rules for analysis visits

Visits	Study day	Analysis window (study day)
Randomized period (D1)	1	1
Randomized period 1 month	30	(Post Day 1, 45]
Randomized period 2 months	60	(45, 75]
Randomized period 3 months	90	(75, 105]
Randomized period 4 months	120	(105, 135]
Randomized period 5 months	150	(135, 165]
Randomized period 6 months	180	(165, 195]
Randomized period 7 months	210	(195, 225]
Randomized period 8 months	240	(225, 255]
Randomized period 9 months	270	(255, 285]
Randomized period 10 months	300	(285, 315]
Randomized period 11 months	330	(315, 345]
Randomized period 12 months	360	(345, 375]
Extension period 13 months	390	(375, 405]
Extension period 14 months	420	(405, 435]
Extension period 15 months	450	(435, 465]
Extension period 18 months	540	(465, 585]
Extension period 21 months	630	(585, 675]
Extension period 24 months	720	(675, 765]

For the participants experiencing acute pancreatitis during the randomized period and transitioned to the extension period, analysis visits window for the extension period is defined based on the study day in extension period, as detailed in Table 3.

Table 3 Rules for deriving analysis visits per study day in extension period

Visits	Study day in extension period	Analysis window (study day in extension period)
Month 12	1	Extension day 1

Visits	Study day in extension period	Analysis window (study day in extension period)
Month 13	30	(Post extension day 1, 45]
Month 14	60	(45, 75]
Month 15	90	(75, 135]
Month 18	180	(135, 225]
Month 21	270	(225, 315]
Month 24	360	(315, 405]

8.2.2 Definition

(1) Triglycerides (TG) baseline

Triglycerides baseline was defined as the geometric mean of the results of the Day 1 (pre-dose) assessment and the last assessment prior to the first dose (excluding the day of the first dose). If any one of the two assessment results was missing, the other non-missing value would serve as baseline.

(2) Other baselines

Except for the baseline TG definition mentioned above, in this study, the baseline for other assessment parameters is defined as the last non-missing value prior to (or on) the first dosing date.

(3) Baseline in extension period

In the analysis for extension period, the baseline is defined as the last non-missing value before (or on) the first dosing date of active drug (i.e., VSA001). For participants who have received placebo during the randomized period, the baseline is defined as the last non-missing value before (or on) the first dosing date of active drug. For participants who have received active drug during the randomized period, the baseline is defined as the last non-missing value before (or on) the first dosing date of active drug in the randomized period.

(4) New Onset Diabetes Mellitus (NODM)

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

(5) Worsening of preexisting diabetes mellitus

Worsening of preexisting diabetes mellitus is identified and evaluated by the following:

- Worsening of HbA1c that is considered clinically significant by the investigator to modify or change the anti-diabetic regimen.
- An adverse event of hyperglycemia or hyperglycemic complication occurs after the first

dosing.

8.2.3 Treatment group

There are two study treatments in this study: one active drug (VSA001) and one placebo, both to be administered by SC injection. In the randomized period, the analysis will include three treatment groups: VSA001 50 mg group, VSA001 25 mg group, and pooled placebo groups. In the extension period, the analysis will include two treatment groups: VSA001 50 mg group and VSA001 25 mg group.

For the FAS, treatment group assignment is based on randomization. For the PPS and SS, treatment group assignment is based on the actual treatment received.

8.2.4 Other definitions

(1) Conversion between study day and year: Study year = Study days/365.25, rounded to 2 decimal places;

(2) Conversion between study day and month: Study month = Study days/30.4375, rounded to 2 decimal places.

8.3 Study Population

8.3.1 Participant disposition

Descriptive statistics will be used to summarize all participant screening data, including the number of screened participants, number and reasons for screen failures, and the number and percentage of successfully randomized participants.

Descriptive statistics will be used to summarize the disposition of all randomized participants by treatment group, including entry into each analysis set, unblinding and rollovering to open-label treatment due to acute pancreatitis, and to summarize the number and percentage of participants who have completed treatment, discontinued treatment (with reasons), completed the study, and discontinued the study (with reasons) by randomized and extension periods, respectively.

Participant disposition will be visualized using a flowchart.

Descriptive statistics will be used to summarize the division of datasets and to summarize reasons for participant exclusion from each analysis set.

The screening results of all participants will be listed.

Specific reasons for screen failures not meeting inclusion/exclusion criteria will be listed.

Disposition for randomized participants will be listed.

Participant dataset division and reasons for exclusion from each analysis set will be listed.

8.3.2 Protocol deviations

Protocol deviation will be discussed and finalized at the Data Review Meeting prior to database lock (DBL).

The number of participants with each type of major protocol deviation and the corresponding percentage will be summarized by treatment group using descriptive statistics, and a listing will be provided to present protocol deviation details for each participant by treatment group by treatment group.

8.4 Demographics and Baseline Information

Analysis of demographics and baseline characteristics was performed based on FAS with descriptive statistics for each treatment group and overall.

8.4.1 Demographics

Based on the FAS, descriptive statistics will be used to summarize participant age (years), gender, FSH result, reproductive status, race, ethnicity, height (cm), weight (kg), body mass index (BMI) (kg/m^2), and BMI classification by treatment group.

Demographic information for enrolled participants will be listed by treatment group.

8.4.2 Baseline disease characteristics

Based on the FAS, the baseline fasting serum TG, baseline fasting serum TG classification (≥ 2000 mg/dL and < 2000 mg/dL), stratification factors (based on IWRS), baseline APOC3, baseline LDL-C, baseline TC, baseline HDL-C, baseline non-HDL-C, baseline VLDL-C, baseline LP[a], presence of concomitant diabetes mellitus, baseline HbA1c, baseline HbA1c classification (< 5.7%, 5.7% to 6.5%, and ≥ 6.5%), baseline lipid-lowering drugs, baseline diabetes mellitus status, baseline antidiabetic drugs, whether FCS supportive genetic testing performed, history of recurrent acute pancreatitis not caused by alcohol or gallstones, history of recurrent hospitalization for severe abdominal pain without other identifiable cause, history of pancreatitis during childhood/adolescence, history of diseases other than FCS, surgical history, allergy history, smoking status, whether alcohol consumption is controlled within moderate limits, history of substance abuse, history of ASCVD-related conditions, baseline ejection fraction, baseline Child-Pugh liver function classification, and baseline New York Heart Association (NYHA) functional classification will be summarized by treatment group using descriptive statistics.

Baseline characteristics of participants will be listed by treatment group.

8.4.3 Non-FCS history

Non-FCS history will be coded using the MedDRA Drug Dictionary.

Descriptive statistics will be used to summarize the number and percentage of participants by treatment group, system organ class (SOC), and preferred term (PT).

Non-FCS history information of participants will be listed by treatment group.

8.4.4 Surgical history

Surgical history will be coded using the MedDRA Drug Dictionary.

Descriptive statistics will be used to summarize the number and percentage of participants by treatment group, system organ class (SOC), and preferred term (PT).

Surgical history information of participants will be listed by treatment group.

8.4.5 10-year ASCVD risk assessment

Descriptive statistics will be used to summarize the results of the 10-year ASCVD risk assessment, including presence of ASCVD-related medical history, classification as a population with elevated 10-year ASCVD risk, and 10-year cardiovascular event risk (%) by treatment group.

Results of the 10-year ASCVD risk assessment will be listed by treatment group.

8.4.6 Baseline virus serology test

Virus serology test includes hepatitis B surface antigen (HbsAg), hepatitis C virus antibody (HCVAb).

Descriptive statistics will be used to summarize baseline virus serology results by treatment group.

Participants serology test results will be listed by treatment group.

8.4.7 Baseline thyroid function test

Thyroid function test includes thyroid-stimulating hormone (TSH) and free thyroxine (FT4).

Descriptive statistics will be used to summarize baseline thyroid function test results by treatment group, including quantitative results and clinical evaluation.

Participant thyroid function test results will be listed by treatment group.

8.5 Previous/Concomitant Drug Therapy

Previous/concomitant medications were coded using the WHO Drug Dictionary.

If the drug start date or end date is earlier than the first dosing date of the investigational product, it will be classified as previous medication.

If the drug start date or end date is later than the first dosing date of the investigational product, or if the start date is earlier than the first dosing date but the end date is on or after the first dosing date, or if the start date is earlier than the first dosing date and the medication is ongoing, or if there is no clear evidence indicating that the medication ended prior to the first dosing date of the investigational product, it will be classified as concomitant medication.

If the start date is missing, it will be classified as both previous and concomitant medication.

For the extension period study, the first dosing date in the extension period will be used for the classification.

Descriptive statistics will be used to summarize the number and percentage of participants receiving previous/concomitant medications (sorted in descending order of the total number of participants under the ACT2/PN, or in alphabetical order in case of the same number of participants) by treatment group, treatment subgroup (ACT2), and drug preferred name (PN).

Participants previous/concomitant medication use will be listed by treatment group.

8.6 Previous/Concomitant Non-drug Therapy

Previous/concomitant non-drug therapy will be coded using the MedDRA Drug Dictionary.

If the non-drug therapy start date or end date is earlier than the first dosing date of the investigational product, it will be classified as previous non-drug therapy.

If the non-drug therapy start date or end date is later than the first dosing date of the investigational product, or if the start date is earlier than the first dosing date but the end date is on or after the first dosing date, or if the start date is earlier than the first dosing date and the therapy is ongoing, or if there is no clear evidence indicating that the therapy ended prior to the first dosing date of the investigational product, it will be classified as concomitant non-drug therapy.

If the start date is missing, it will be classified as both previous and concomitant non-drug therapy.

For the extension period study, the first dosing date in the extension period will be used for the classification.

Descriptive statistics will be used to summarize the number and percentage of participants receiving previous/concomitant non-drug therapy and previous/concomitant apheresis-related non-drug therapy (sorted in descending order of the total number of participants under the SOC/PT, or in alphabetical order in case of the same number of participants) by treatment group, system organ class (SOC) and preferred term (PT).

Participants previous/concomitant non-drug therapy will be listed by treatment group.

8.7 Efficacy Analysis

Except for the analysis methods described below, efficacy analysis results of participants will be listed by treatment group.

8.7.1 Primary efficacy endpoint analysis

The primary efficacy endpoint of this study was percent change from baseline at Month 10 in fasting serum TG level, and fasting serum TG level at Month 10 was the geometric mean of 2

measurements taken during Month 10, or one measurement if only one valid measurement was available during Month 10.

Analysis of the primary efficacy endpoint was performed only during the randomized period.

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

- **Primary estimand**

I. Clinical concerns

In Chinese participants with FCS, regardless of treatment discontinuation for any reason/concomitant medications/rescue medications/changes in background therapies/other intercurrent events, how much difference there is between the test group (VSA001 25 mg or VSA001 50 mg Q3M) and the control group (placebo Q3M) in the median percent change from baseline at Month 10 in fasting serum TG.

II. Definition of estimand

The estimand was defined as follows:

(1) Target population: adult participants with FCS who meet the eligibility criteria.

(2) Treatment: this was a double-blind trial adopting the following treatment regimens:

- Test group 1: VSA001 25 mg Q3M;
- Test group 2: VSA001 50 mg Q3M;
- Control group: placebo Q3M.

(3) Target variable: percent change from baseline at Month 10 in fasting serum TG.

(4) Intercurrent events and handling strategies:

Table 4 Intercurrent events and handling strategies of primary estimand

Intercurrent events	Handling strategies	Considerations
Early termination	Therapeutic strategy	Reflecting the clinical practice, data continued to be collected after occurrence of the intercurrent event and was included in analysis
Use of concomitant therapy	Therapeutic strategy	Use of concomitant therapies reflected the treatment practice; data continued to be collected after occurrence of the intercurrent event and was included in analysis
Use of rescue medications	Therapeutic strategy	Use of rescue medications reflected the treatment practice; data continued to be collected after occurrence of the intercurrent event and was included in analysis
Change of background treatment	Therapeutic strategy	Change of background therapies reflected the treatment practice; data continued to be collected after occurrence of the intercurrent event and was included in analysis

(5) Population-level summary: difference in median percent change from baseline in

treatment and control groups.

III. Analysis of estimands

(1) Primary analysis

As TG and its percent change from baseline did not meet the assumptions for hypothesis test of normality, the primary efficacy analysis was performed using a non-parametric test method, where continuity-corrected Wilcoxon (Mann-Whitney) rank sum test of the significance of the difference in median between groups (active treatment groups and placebo group) was performed, and the Hodges-Lehmann method was used to estimate the differences in median between groups and their 95% confidence intervals.

The primary analysis was performed based on FAS; on the basis of the handling strategy for intercurrent events, missing fasting serum TG at Month 10 was imputed mainly based on the Pattern Mixture Models (PMM) according to the following rules:

For participants who discontinued the randomized period and who do not have Month 10 TG measurements, the missing data imputation method will use participants in the same treatment group who discontinued the randomized period and have Month 10 TG measurements. If there are no or very few participants in the same treatment group who discontinued the randomized period and have Month 10 TG measurements, missing Month 10 TG values will be imputed as follows:

For the VSA001 groups, assuming that the efficacy would be diluted after withdrawing treatment, such participants would exhibit the same disease evolution pattern as participants in the control group; assuming that such missing was Missing Not at Random (MNAR), only the baseline TG values in the test group (excluding post-treatment data) and data in the placebo group would be used for imputation. For the placebo group, a multiple imputation method assuming Missing at Random would be used for missing TG values at Month 10.

Based on each imputed dataset, the continuity-corrected Wilcoxon rank-sum (Mann-Whitney) test will be used to separately assess the statistical significance of median differences between each active treatment group and the placebo group. The Hodges-Lehmann method will be used to estimate the inter-group median differences and their corresponding 95% CIs. These results will be pooled according to Rubin’s rules, and the modified Mogg and Mehrotra (2007) procedure will be applied (refer to Section 11.4 for implementation code; refer to Section 11.1 for the implementation code for pooling Hodges-Lehmann estimates and CIs). The sequential testing order between the two active dose groups and the placebo group will follow the Holm procedure to control the overall Type I error.

Details of the primary imputation method for PMM are provided in Appendix 12.1.

(2) Sensitivity analysis

For the primary analysis of the primary efficacy endpoint, sensitivity analysis (with estimand

definitions consistent with the primary analysis) will be conducted within the FAS to assess the robustness of the primary efficacy endpoint results:

Table 5 Sensitivity analysis of primary estimand

Sensitivity analysis	Handling methods of missing values	Statistical analysis methods
Sensitivity analysis 1	No imputation	Wilcoxon rank sum test and truncated Hodges-Lehmann method
Sensitivity analysis 2	No imputation	Wilcoxon rank sum test and Hodges-Lehmann method
Sensitivity analysis 3	No imputation	MMRM
Sensitivity analysis 4*	Same as primary analysis	Analysis of covariance (ANCOVA)

* Sensitivity analysis would be executed only if the data passes the test for normality.

Sensitivity analysis 1:

Pearson's coefficient of skewness will be calculated by treatment group, using Pearson's first coefficient of skewness to assess skewness of the primary endpoint. If the data exhibit a weak mode or multiple modes, Pearson's second coefficient of skewness will be used to assess central tendency. Based on the α-truncated Hodges-Lehmann method (if the data exhibit negative skewness, remove the smallest value; if the data exhibit positive skewness, remove the largest value), the inter-group median differences and their 95% CIs will be estimated.

Pearson's first coefficient of skewness (mode skewness) is defined as:

$$\text{Pearson's coefficient of skewness} = \frac{\text{Arithmetic mean - mode}}{\text{Standard deviation}}$$

Pearson's second coefficient of skewness (median skewness) is defined as:

$$\text{Pearson's coefficient of skewness} = \frac{3 \times (\text{Arithmetic mean - median})}{\text{Standard deviation}}$$

Sensitivity analysis 2:

Based on the unimputed data, the continuity-corrected Wilcoxon rank-sum (Mann-Whitney) test will be used to separately assess the statistical significance of median differences between each active treatment group and the placebo group. The Hodges-Lehmann method will be used to estimate the inter-group median differences and their corresponding 95% CIs (refer to Section 11.1 for implementation code of the Wilcoxon rank-sum test and the Hodges-Lehmann method).

Sensitivity analysis 3:

Based on unimputed data, a mixed-effects model for repeated measures (MMRM) will be used to calculate the least squares means (LS means) for each treatment group along with their 95% CIs, as well as the LS mean differences, 95% CIs, and P values for each active treatment group

versus the control group. In the MMRM, the covariance matrix will be calculated based on restricted maximum likelihood estimation (REML), where the covariance structure will be designated as unstructured (UN); the degree of freedom will be estimated using Kenward-Roger approximation; if the model is not convergent under the UN structure, the surrogate covariance structure will be used for processing based on the actual data.

Sensitivity analysis 4:

Based on imputed data, an analysis of covariance (ANCOVA) model will be applied to calculate the LS means and their 95% CIs for each treatment group, as well as the LS mean differences, 95% CIs, and P values for each active treatment group versus the control group (refer to Section 11.6 for implementation code).

(3) Supplemental analysis

In addition to the primary analysis and sensitivity analysis, the following supplementary analysis will be performed (the supplementary estimand is defined as the same as for the primary estimand):

Table 6 Supplemental analysis of primary estimand

Supplemental analysis	Analysis Populations	Handling methods of missing values	Target variables	Statistical analysis methods
Supplemental analysis 1	PPS	Same as primary analysis	Same as primary analysis	Wilcoxon rank sum test and Hodges-Lehmann method
Supplemental analysis 2	PPS	No imputation	Same as primary analysis	Wilcoxon rank sum test and Hodges-Lehmann method

Supplemental analysis 1:

The statistical analysis method based on PPS population is the same as that for the primary analysis.

Supplemental analysis 2:

The statistical analysis method based on PPS population is the same as that for sensitivity analysis 2.

(4) Subgroup analysis

Subgroup analysis will be performed for the following subgroups by the method for the primary analysis of the primary endpoint:

- TG stratification in IWRS system (< 2,000 mg/dL, ≥ 2,000 mg/dL)
- Gender (male, female)
- BMI (<25 kg/m^2、>= 25 kg/m^2)

- LDL-C (< baseline median, ≥ baseline median)
- FCS-supporting genetic testing (Yes, No)

8.7.2 Key secondary efficacy endpoint analysis

The key secondary efficacy endpoints for this study included (for randomized period only):

1) Percent change from baseline at Months 10 and 12 (geometric mean) in fasting serum TG;

The calculation formula of the endpoint is shown as follows:

$$\frac{\sqrt{\text{TGm10} \times \text{TGm12}} - \text{TG baseline}}{\text{TG baseline}} \times 100$$

TGm10 represented the geometric mean of 2 measurements taken during Month 10, or one measurement if only one valid measurement was available during Month 10; TGm12 represented the fasting serum TG at Month 12.

2) Percent change from baseline at Month 10 in fasting serum APOC3;

3) Percent change from baseline at Month 12 in fasting serum APOC3.

- **Each key secondary estimand**

I. Clinical concerns

In Chinese participants with FCS, regardless of treatment discontinuation for any reason/concomitant medications/rescue medications/changes in background therapies/other intercurrent events, how much difference there is between the test group (VSA001 25 mg or VSA001 50 mg Q3M) and the control group (placebo Q3M) in the median of each key secondary efficacy endpoints.

II. Definition of estimand

The estimand was defined as follows:

(1) Target population: adult participants with FCS who meet the eligibility criteria.

(2) Treatment: this was a double-blind trial adopting the following treatment regimens:

- Test group 1: VSA001 25 mg Q3M;
- Test group 2: VSA001 50 mg Q3M;
- Control group: placebo Q3M.

(3) Target variable: same as key secondary efficacy endpoints.

(4) Intercurrent events and handling strategies:

Table 7 Intercurrent events and handling strategies of each key secondary estimand

Intercurrent events	Handling strategies	Considerations

Early termination	Therapeutic strategy	Reflecting the clinical practice, data continued to be collected after occurrence of the intercurrent event and was included in analysis
Use of concomitant therapy	Therapeutic strategy	Use of concomitant therapies reflected the treatment practice; data continued to be collected after occurrence of the intercurrent event and was included in analysis
Use of rescue medications	Therapeutic strategy	Use of rescue medications reflected the treatment practice; data continued to be collected after occurrence of the intercurrent event and was included in analysis
Change of background treatment	Therapeutic strategy	Change of background therapies reflected the treatment practice; data continued to be collected after occurrence of the intercurrent event and was included in analysis

(5) Population-level summary: difference in median percent change from baseline in treatment and control groups.

III. Analysis of each key secondary estimand

(1) Primary analysis

The primary analysis method for each secondary estimand was the same as for the primary analysis of the primary estimand (any missing value would first be imputed before deriving the mean).

(2) Sensitivity analysis

Sensitivity analysis for each secondary estimand are as follows (any missing value will first be imputed before deriving the mean):

Table 8 Sensitivity analysis of each key secondary estimand

Sensitivity analysis	Handling methods of missing values	Statistical analysis methods
Sensitivity analysis 1	No imputation	MMRM
Sensitivity analysis 2*	Same as primary analysis	Analysis of covariance (ANCOVA)

* Sensitivity analysis would be executed only if the data passes the test for normality.

(3) Supplemental analysis

The supplemental analysis method for each secondary estimand was the same as for the supplemental analysis of the primary estimand (any missing value would first be imputed before deriving the mean).

8.7.3 Analysis of other secondary efficacy endpoints and exploratory efficacy endpoints

Based on PKS, tests for other secondary endpoints and exploratory efficacy endpoints were all exploratory and would be summarized using descriptive statistics.

Continuous variable endpoints would be analyzed using the analysis of covariance (ANCOVA)

model. The normality assumption would be tested using the residual method. If normality assumption was not met, a non-parametric analysis method consistent with the primary analysis would be used to estimate the difference between groups in the median and its 95% confidence interval based on the Hodges-Lehmann method. Some blood lipid parameters would also be analyzed using Mixed Model for Repeated Measures (MMRM).

Binary efficacy endpoints related to TG (e.g., proportion of participants achieving fasting serum TG <500 mg/dL) would be analyzed, using the logistic regression model with treatment group and TG baseline value as covariates, at each scheduled assessment time point.

For the incidence of positively adjudicated events of acute pancreatitis, the intergroup odds ratio corrected for the randomization strata would be calculated using the stratified CMH method, and the 95% confidence interval (Wald method) and P value would also be calculated. The VSA001 25 mg dose group and VSA001 50 mg dose group would be pooled into the VSA001 group for analysis.

For other categorical endpoints (e.g., hospitalization rate for abdominal pain), the intergroup odds ratio corrected for the randomization strata would be calculated using the stratified CMH method, and the 95% confidence interval (Wald method) and P value would also be calculated.

Kaplan-Meier curves for time to the first adjudicated acute pancreatitis event would be plotted.

8.8 Safety Analysis

Safety analysis, which was performed based on the Safety Set (SS), included drug exposure and compliance, adverse events, summary of death, laboratory tests (including hematology, blood chemistry, coagulation function, urine routines, microscopic urinary sediment, urinalysis, blood glucose, serum insulin and C-peptide, glycosylated hemoglobin, liver function test, and serum pregnancy test), physical examination, vital signs, and 12-lead electrocardiogram (ECG).

8.8.1 Drug exposure and compliance

The summary of drug exposure and compliance will be performed based on the SS.

(1) Duration of drug therapy

The time of exposure to drug is defined as the interval between the time of the first dose and the time of last exposure, i.e.:

Time of exposure to drug (day) = date of the last dose + 90 - date of the first dose + 1,

Time of exposure to drug (months) = time of exposure to drug (days)/30.4375 (calculated to 2 decimal places),

The time of exposure to drug in the randomization period will be calculated using the date of the last dose in the randomization period. The time of exposure to drug in the extension period will be calculated using the date of the first dose of active drug. The date of the last dose is the date of the last dose in the extension period.

(2) Planned cumulative number of injections, actual cumulative number of injections and compliance

Planned cumulative number of injections is defined as the planned number of injections specified by the protocol. It is 4 in the randomization period.

The actual number of injections is the sum of actual number of injections for the participant.

Compliance (%) = Actual cumulative number of injections/planned cumulative number of injections × 100%.

The actual number of injections, time of exposure (months), classification of time of exposure (months), overall compliance, and classification of overall compliance will be summarized by treatment group using descriptive statistics.

The distribution and administration of the drug to participants at each visit, the exposure to drug of participants, and the compliance will be listed by treatment group.

8.8.2 Adverse event

A treatment-emergent adverse event (TEAE) was defined as an AE or worsening of a pre-existing condition that occurred after treatment with the investigational product (IP). The TEAE reporting period begins after the first dose and extends until 6 months after the last dose or the EOS visit is complete, whichever is later. Unless otherwise specified, all the following AEs will be statistically described based on TEAEs, and non-TEAEs will be only presented in listings.

According to the criteria for causality between the drug and AEs, the relationship between AEs and the investigational product will be classified into three categories: unrelated, possibly related, and probably related. Related to the investigational product is defined as possibly related and probably related.

The severity of AEs will be graded using NCI-CTCAE V5.0 as: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death). If the severity is missing, it will not be imputed.

Adverse events of special interest (AESI) include: hypersensitivity/anaphylaxis, injection site reactions, and potential hepatotoxicity events.

All adverse events will be coded using MedDRA coding system.

The number of participants experiencing AEs and the severity of AEs based on System Organ Class (SOC) and Preferred Term (PT) will be summarized by treatment group using descriptive statistics. For calculation of the incidence of AEs, each participant will be counted at most once per SOC and per PT. In case of multiple occurrences of the same AE in the same participant, the occurrence of the worst severity would be counted in summarizing its severity (AEs were sorted in descending order of the total number of participants under the SOC/PT, or in

alphabetical order in case of the same number of participants experiencing different AEs).

TEAEs of suboptimal glycemic control are adverse events in Standardized MedDRA Queries (SMQs) (see Appendix 12.2 for details).

Adverse events will be summarized in the same way as above, including:

- Treatment-emergent adverse event (TEAE);
- Treatment-related adverse event (TRAE);
- Treatment-emergent serious adverse event (TESAE);
- Treatment-related serious adverse event;
- Treatment-related acute pancreatitis;
- Treatment-emergent adverse event leading to temporary discontinuation;
- Treatment-emergent adverse event leading to permanent treatment discontinuation;
- Treatment-emergent adverse event leading to death;
- Treatment-emergent adverse event of special interest;
- Treatment-emergent adverse event of special interest - hypersensitivity/anaphylactic reaction;
- Treatment-emergent adverse event of special interest - injection site reaction;
- Treatment-emergent adverse event of special interest - potential hepatotoxicity;
- TEAEs of suboptimal glycaemic control.

The AEs in participants who transfer from 50 mg dose group to 25 mg dose group will be analyzed separately.

List of AEs of participants was presented.

8.8.3 Summary of death

Death and cause of death, number and percentage of participants who receive autopsy will be summarized by treatment group using descriptive statistics.

The information on death of participants in each treatment group will be listed by treatment group.

8.8.4 Laboratory tests

The glycemic status at baseline is defined as the following:

- Diabetes: HbA1c ≥6.5% at baseline;
- Prediabetes: 5.7%≤ HbA1c<6.5% at baseline;

- Normoglycemia: HbA1c <5.7% at baseline.

The actual values and changes from baseline in HbA1c and fasting blood glucose will be statistically described by visit according to baseline glucose status. The number and percentage of participants who meet the following glycosylated hemoglobin will be summarized:

- Receiving diabetes medications at baseline;
- HbA1c ≥ 6.5% at any visit after baseline (not applicable to participants with diabetes at baseline);
- TEAEs indicating worsening of diabetes;
- New diabetes medication added;
- New diabetes as determined by the Medical Monitor (not applicable to population with diabetes at baseline), mainly based on participants who have HbA1c < 6.5% on Day 1 or participants who have not received any diabetes medications before screening, and then HbA1c is > 6.5% for 2 consecutive times and/or new diabetes medications are started in randomization period.

Actual values of HbA1c, fasting blood glucose, HOMA-IR, and C-peptide and their changes from baseline were described statistically for the following populations.

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

In addition, the numbers and percentages of participants meeting the following were summarized for the above populations:

- HbA1c >10% at any post-baseline visit;
- An increase from baseline with HbA1c >2% at any post-baseline visit;
- Participants with HbA1c >7.5% at baseline and HbA1c increased by >1% from baseline at least 2 post-baseline visits.

Line charts of changes at different visits in mean (±SEM) changes from baseline in HbA1c and fasting blood glucose were plotted by group.

Laboratory tests include: Hematology, blood chemistry, coagulation function, urine routines, urinary sediment microscopy, urinalysis, liver function, blood glucose, serum insulin, C-peptide, and glycosylated hemoglobin.

The entire study period is defined as all visits after baseline. The worst results (abnormal with clinical significance > abnormal without clinical significance > normal > not tested) at each visit (including unscheduled visits) will be used for clinical evaluation.

The test results of quantitative laboratory tests (hematology, blood chemistry, coagulation function, urinalysis, liver function) and changes from baseline at each visit after baseline will be summarized by treatment group using descriptive statistics.

Clinical evaluation results of laboratory test items (hematology, blood chemistry, coagulation function, urine routines, urinary sediment microscopy, urinalysis, liver function, blood glucose, serum insulin, C-peptide, glycosylated hemoglobin) at each visit after administration (including the whole study period) will be summarized by treatment group and visit in cross-classification tables.

Feasible test items will be summarized in cross-tables according to CTCAE criteria.

In addition, liver function abnormal will be summarized according to the following categories:

- Creatine kinase > 5 × ULN
- Creatine kinase > 10 × ULN
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN
- ALT or AST > 5 × ULN
- Total bilirubin > 2 × ULN
- (ALT or AST >3 × ULN) and (total bilirubin >2 × ULN or International Normalized Ratio (INR) >1.5)
- Creatinine >2 mg/dL or 50% increase from baseline in percent change.

Laboratory test results of participants in each treatment group will be listed by treatment group.

Abnormal laboratory test results of participants in each treatment group will be listed by treatment group.

8.8.5 Pregnancy test

Blood pregnancy test results of participants in each treatment group will be listed by treatment group.

8.8.6 Signs and symptoms of pancreatitis and medical treatment records

Signs and symptoms of pancreatitis and medical treatment records of participants in each treatment group will be listed by treatment group.

8.8.7 Alcohol consumption

The information on alcohol consumption of participants in each treatment group will be listed by treatment group.

8.8.8 Vital signs

The entire study period is defined as all visits after baseline. The worst results (abnormal with

clinical significance > abnormal without clinical significance > normal > not tested) at each visit (including unscheduled visits) will be used for clinical evaluation.

Test results of vital signs (systolic blood pressure, diastolic blood pressure, body temperature, heart rate, respiratory rate, body weight, BMI), changes from baseline and percent changes from baseline at each visit after administration will be summarized by treatment group using descriptive statistics.

Clinical evaluation results of vital signs at each visit after administration (including entire study period) will be summarized by treatment group in cross-classification tables.

Participants vital signs test results will be listed by treatment group.

8.8.9 12-Lead electrocardiograms

TThe entire study period is defined as all visits after baseline. The worst results (abnormal with clinical significance > abnormal without clinical significance > normal > not tested) at each visit (including unscheduled visits) will be used for clinical evaluation.

The test results of 12-lead ECG (heart rate, PR interval, QRS interval, QT interval) at each visit and each time point and the changes from baseline at each visit and each time point after administration will be summarized by treatment group using descriptive statistics. The maximum QTcF > 450 ms, > 480 ms, > 500 ms after baseline, maximum increase from baseline in QTcF of > 30 ms, > 60 ms will be descriptively summarized by treatment group, visit and planned test time point.

Clinical evaluation results in 12-lead ECG at each visit and each time point before and after administration will be summarized in cross-classification tables.

12-Lead ECG test results of participants will be listed by treatment group.

8.8.10 Physical examinations

Physical examination results (except for other sites) will be summarized by treatment group using descriptive statistics.

Participants physical examination results will be listed by treatment group.

8.8.11 Other examinations

Other examination results of participants in each treatment group will be listed by treatment group.

8.9 Immunogenicity Analysis

The immunogenicity test results at each visit will be summarized by treatment group using descriptive statistics.

Participants immunogenicity test results will be listed by treatment group.

8.10 Patient-Reported Outcome (PRO) Analysis

8.10.1 European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

The EQRTC QLQ-C30 consists of 30 scoring items, which can be grouped into 15 scales (dimensions): including: 5 functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning), 3 symptom scales (fatigue, pain, nausea, vomiting), 1 general health status, and 6-single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). The scoring method for each scale (dimension) is as follows:

Table 9 Scoring method for EQRTC QLQ-C30 scales (dimensions)

Scale (dimension)	Code	Properties	Number of items	Item range (R)	Original score (RS)*
Physical functioning	PF	Functional	5	3	$(Q_1 + Q_2 + Q_3 + Q_4 + Q_5)/5$
Role functioning	RF	Functional	2	3	$(Q_6 + Q_7)/2$
Emotional functioning	EF	Functional	4	3	$(Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$
Cognitive functioning	CF	Functional	2	3	$(Q_{20} + Q_{25})/2$
Social functioning	SF	Functional	2	3	$(Q_{26} + Q_{27})/2$
General health status	QL		2	6	$(Q_{29} + Q_{30})/2$
Tiredness	FA	Symptomatic	3	3	$(Q_{10} + Q_{12} + Q_{18})/3$
Nausea and vomiting	NV	Symptomatic	2	3	$(Q_{14} + Q_{15})/2$
Pain	PA	Symptomatic	2	3	$(Q_9 + Q_{19})/2$
Polypnoea	DY	Symptomatic	1	3	Q_8
Insomnia	SL	Symptomatic	1	3	Q_{11}
Loss of appetite	AP	Symptomatic	1	3	Q_{13}
Constipation	CO	Symptomatic	1	3	Q_{16}
Diarrhoea	DI	Symptomatic	1	3	Q_{17}
Financial difficulties	FI	Symptomatic	1	3	Q_{28}

Note: *Qxx represents the xx^{th} question in the questionnaire.

In the process of calculating the original score above, the denominator is the number of non-empty items required for the current dimension. If 50% or more of the items are missing, the original score will be set to be blank.

The standardized score (SS) will be calculated using the following formula:

Functional: SS=[1-(RS-1)/R]*100,

Symptom: SS = (RS-1)/R*100,

General health status: SS =(RS-1)/R*100.

Where, R is the full range of scores for each scale or item and RS is the original score for each scale (dimension). The higher the standardized scores of functional scales and general health status, the better the quality of life of the participant; the higher the standardized scores of symptom scales, the worse the quality of life of the participant.

If the original score is missing, the main imputation method for missing values is as follows:

1) If there are non-missing records before and after the current visit, it will be imputed with the mean of the two most recent records before and after the current visit. If the non-missing record before the current visit is baseline, it will be imputed according to 2).
2) If there is no valid record before the current visit (non-missing record after baseline), it will be imputed with the recorded value closest to and after the current visit; if the baseline value is missing, it will not be imputed.
3) If there is no non-missing record after the current visit, it will be imputed with the worst condition of the participant after baseline.
4) Baseline values will not be used to impute missing values after baseline

Multiple imputation will be used as a secondary imputation method for missing values.

The original scores for each dimension of EQRTC QLQ-C30 at baseline and each post-treatment visit and their changes from baseline will be summarized by treatment group using descriptive statistics.

Using the Mixed Model for Repeated Measures (MMRM), the original scores, least squares mean changes from baseline and their 95% CIs, and the least squares mean differences between groups and their 95% CI and corresponding P values at each post-treatment visit for each dimension of the EQRTC QLQ-C30 were summarized by treatment group. Specifically, in the MMRM, the covariance matrix was calculated based on restricted maximum likelihood estimation (REML), where the covariance structure was designated as unstructured (UN); the degree of freedom was estimated using Kenward-Roger approximation; if the model was not convergent under the UN structure, the surrogate covariance structure would be used for processing based on the actual data. Model-based analysis was performed separately without imputation or using the primary imputation or multiple imputation method.

The original evaluation results of EQRTC QLQ-C30 of participants of each treatment group will be listed by treatment group. The scoring results of EQRTC QLQ-C30 scales of participants of each treatment group will be listed by treatment group.

8.10.2 Quality of Life Questionnaire for Pancreatic Carcinoma (EORTC QLQ-PAN26)

The EQRTC QLQ-PAN26 scale consists of 26 scoring items, which can be grouped into 17 scales (dimensions), including: 2 functional scales, 5 symptom scales, and 10 single-item symptom scales. The scoring method for functional scales and symptom scales are as follows:

Table 10 Scoring method for EQRTC QLQ-PAN26 scales (dimensions)

Scale (dimension)	Code	Properties	Number of items	Item range (R)	Original score (RS)
Pancreatic pain	PP	Symptomatic	4	3	$(Q_{31} + Q_{33} + Q_{34} + Q_{35})/4$
Gastrointestinal symptoms	DS	Symptomatic	2	3	$(Q_{36} + Q_{37})/2$
Liver Symptoms	LI	Symptomatic	2	3	$(Q_{44} + Q_{45})/2$
Altered bowel habit	BO	Symptomatic	2	3	$(Q_{46} + Q_{47})/2$
Body image	BI	Symptomatic	2	3	$(Q_{48} + Q_{49})/2$
Satisfaction with health care	SA	Functional	2	3	$(Q_{53} + Q_{54})/2$
Sexual function	SX	Functional	2	3	$(Q_{55} + Q_{56})/2$

In the process of calculating the original score above, the denominator is the number of non-empty items required for the current dimension. If 50% or more of the items are missing, the original score will be set to be blank.

The standardized score (SS) will be calculated using the following formula:

Functional: SS=[1-(RS-1)/R]*100,

Symptom: SS = (RS-1)/R*100.

Where, R is the full range of scores for each scale or item and RS is the original score for each scale (dimension). The higher the standardized scores for symptom scales and functional scales, the better the quality of life of the participant; the higher the standardized score for satisfaction with health care of the functional scale, the worse the quality of life of the participant.

If the original score is missing, the main imputation method for missing values is as follows:

1) If there are non-missing records before and after the current visit, it will be imputed with the mean of the two most recent records before and after the current visit. If the non-missing record before the current visit is baseline, it will be imputed according to 2).
2) If there is no valid record before the current visit (non-missing record after baseline), it will be imputed with the recorded value closest to and after the current visit; if the baseline value is missing, it will not be imputed.
3) If there is no non-missing record after the current visit, it will be imputed with the worst condition of the participant after baseline.

4) Baseline values will not be used to impute missing values after baseline

The original scores for each dimension of EQRTC QLQ-PAN26 at baseline and each post-treatment visit and their changes from baseline will be summarized by treatment group using descriptive statistics.

Using the Mixed Model for Repeated Measures (MMRM), the scores, least squares mean changes from baseline and their 95% CIs, and the least squares mean differences between groups and their 95% CI and corresponding P values at each post-treatment visit for each dimension of the EQRTC QLQ-PAN26 were summarized by treatment group. Specifically, in the MMRM, the covariance matrix was calculated based on restricted maximum likelihood estimation (REML), where the covariance structure was designated as unstructured (UN); the degree of freedom was estimated using Kenward-Roger approximation; if the model was not convergent under the UN structure, the surrogate covariance structure would be used for processing based on the actual data. Model-based analysis was performed separately without imputation or using the primary imputation or multiple imputation method.

The original evaluation results of EQRTC QLQ-PAN26 of participants of each treatment group will be listed by treatment group. The scoring results of EQRTC QLQ-PAN26 scales of participants of each treatment group will be listed by treatment group.

8.10.3 EuroQoL 5-Dimension Questionnaire (EQ-5D-5L)

The EQ-5D-5L questionnaire contains 5 dimensions (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) and a 100-point EQ-5D visual analogue scale (EQ VAS). Each dimension contains 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to do).

EQ-5D-5L score utility index of participants will be summarized using a corrected multiplicative model MULT8 algorithm applicable to the Chinese population (Luo et.al. 2017). The calculation method as follows:

$$y = \alpha + \sum_l \left(\sum_d \beta_d \chi_{dl}\right) L_1 + e$$

$$= \alpha + (\beta_{MO}\chi_{MO2} + \beta_{SC}\chi_{SC2} + \beta_{UA}\chi_{UA2} + \beta_{PD}\chi_{PD2} + \beta_{AD}\chi_{AD2})\, L_2$$

$$+ (\beta_{MO}\chi_{MO3} + \beta_{SC}\chi_{SC3} + \beta_{UA}\chi_{UA3} + \beta_{PD}\chi_{PD3} + \beta_{AD}\chi_{AD3})\, L_3$$

$$+ (\beta_{MO}\chi_{MO4} + \beta_{SC}\chi_{SC4} + \beta_{UA}\chi_{UA4} + \beta_{PD}\chi_{PD4} + \beta_{AD}\chi_{AD4})\, L_4$$

$$+ (\beta_{MO}\chi_{MO5} + \beta_{SC}\chi_{SC5} + \beta_{UA}\chi_{UA5} + \beta_{PD}\chi_{PD5} + \beta_{AD}\chi_{AD5})\, L_5$$

$$+ e$$

Where, MO indicates mobility, SC indicates self-care, UA indicates usual activities, PD indicates pain or discomfort, and AD indicates anxiety or depression. d indicates the dimension, l indicates the evaluation result of a dimension, and χ_{dl} indicates a dummy variable of

dimension *d* at level *l*.

When calculating an utility index, according to the choices of each dimension, utility index = 1 - sum of weights for all dimension values. If EQ-5D-5L score of a participant at a visit is 13254, the utility index of the participant at the visit is 1-(0.116 + 0.045 + 0.302 + 0.215) = 0.322. Coefficients for each dimension are given in Table 3.

Table 11 Weights of dimensions and levels of EQ-5D-5L

Dimension 1	Weight	Dimension 2	Weight	Dimension 3	Weight	Dimension 4	Weight	Dimension 5	Weight
MO1	0	SC1	0	UA1	0	PD1	0	AD1	0
MO2	0.066	SC2	0.048	UA2	0.045	PD2	0.058	AD2	0.049
MO3	0.158	SC3	0.116	UA3	0.107	PD3	0.138	AD3	0.118
MO4	0.287	SC4	0.210	UA4	0.194	PD4	0.252	AD4	0.215
MO5	0.345	SC5	0.253	UA5	0.233	PD5	0.302	AD5	0.258

In the process of calculating the utility indexes above, if 50% or more of the items above are missing, the utility index will be set to be blank. The higher the utility index, the worse the quality of life of the participant; the higher the EQ VAS score, the better the quality of life of the participant.

If the utility index or EQ VAS score is missing, the missing value will be imputed by the following method:

1) If there are non-missing records before and after the current visit, it will be imputed with the mean of the two most recent records before and after the current visit. If the non-missing record before the current visit is baseline, it will be imputed according to 2).
2) If there is no valid record before the current visit (non-missing record after baseline), it will be imputed with the recorded value closest to and after the current visit; if the baseline value is missing, it will not be imputed.
3) If there is no non-missing record after the current visit, it will be imputed with the worst condition of the participant after baseline.
4) Baseline values will not be used to impute missing values after baseline.

The utility indexes of EQ-5D-5L score and EQ VAS score at baseline and each post-treatment visit and their changes from baseline will be summarized by treatment group using descriptive statistics.

Using the Mixed Model for Repeated Measures (MMRM) (with treatment group, analysis visit, treatment group-by-analysis visit interaction and baseline value as independent variables), the utility indexes of EQ-5D-5L score and EQ VAS score at baseline and each post-treatment, least squares mean changes from baseline and their 95% CIs, and the least squares mean differences

between groups and their 95% CI and corresponding P values were summarized by treatment group. Specifically, in the MMRM, the covariance matrix was calculated based on restricted maximum likelihood estimation (REML), where the covariance structure was designated as unstructured (UN); the degree of freedom was estimated using Kenward-Roger approximation; if the model was not convergent under the UN structure, the surrogate covariance structure would be used for processing based on the actual data. Model-based analysis was performed separately without imputation or using the primary imputation or multiple imputation method.

EQ-5D-5L scoring results of participants of each treatment group will be listed by treatment group.

8.11 Pharmacokinetic Analysis

Based on the PKS, the test results of drug concentrations at each visit and each sampling time point will be summarized by treatment group using descriptive statistics. The concentrations below or equal to the lower limit of quantitation (BQL) will be treated as “zero”.

Participants drug concentration test results will be listed by treatment group.

The drug concentrations of each group will be statistically described by scheduled visits and sampling time points.

9 Supplemental Explanation of Statistical Analysis Methods

1) Due to the significant variability of TG, the protocol specifies that "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". The arithmetic mean mentioned above was uniformly updated to "geometric mean" in the SAP to better reflect the true level of TG in a participant over a certain period of time.
2) Patient-reported outcome can reflect how patient's feelings and mainly focuses on participantive measurement. Compared with the protocol, a PROS is added to the SAP to analyze the data in the quality of life evaluation scale.
3) Given that this product has the potential to reduce triglycerides, and high triglyceride levels are closely associated with the occurrence and severity of acute pancreatitis, "Time to first adjudicated acute pancreatitis event” is added as an exploratory endpoint in the SAP to further evaluate the potential benefits of this product in reducing the risk of acute pancreatitis.

10 Template of Statistical Analysis Form

Template of statistical analysis form will be provided as separate files. During the analysis process, minor updates may be made to the TFL template to make the analysis results clearer or easy to interpret. These updates will not require amendment to the SAP. However, if there are changes to the original statistical analysis methods, the SAP will need to be amended.

11 REFERENCES

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

2) Luo et.al. Estimating an EQ-5D-5L Value Set for China. VALUEINHEALTH 20(2017)662–669

12 Reference SAS Code for Statistical Analysis

12.1 Reference core code for Wilcoxon test and Hodges-Lehmann estimation

```
proc npar1way data=datain HL alpha=0.05;
class TRTN;
var PCHG;
run;
```

Notes:

1) Each participant in **datain** contains only 1 record of the current analysis endpoint (if any).

12.2 Imputation of missing value of PMM framework: Reference core codes under missing not at random assumption in VSA001 group

```
proc mi data=dsin out = dsout nimpute = 100 seed = 20250225;
where trtpn in (1 2);
VAR BASE MX;
FCS;
transform log(BASE) log(MX) ;
run;
```

Notes:

1) dsin is the missing data of MX endpoint measure in the placebo group and VSA001 group. BASE is the baseline variable of the corresponding endpoint measure. MX is the measured value of the endpoint measure at Month X;

2) It will be imputed only with baseline values of the treatment group and the data of the

placebo group for VSA001 25 mg and VSA001 50 mg dose groups separately.

12.3 Imputation of missing value of PMM framework: Reference core codes under missing at random assumption in placebo group

```
proc mi data= dsin out = dsout nimpute=100 SEED= 20250225;
VAR BASE M1 M2 M3 M4 M5 M6 M7 M8 M9 M10;
FCS;
transform log(BASE) log(M1) log(M2) log(M3) log(M4) log(M5) log(M6) log(M7) log(M8) log(M9) log(M10) ;
run;
```

12.4 Reference core codes incorporated based on Rubin's rule

```
proc mianalyze data= HodgesLehmann ;
by trtpn;
modeleffects SHIFT;
stderr STDERR;
run;
```

12.5 Mixed model for repeated measures (MMRM) reference core code

```
proc mixed data=dsin;
class SUBJID trtpn(ref='1') AVISITN STRA;
model PCHG=STRA BASE TRTPN AVISITN TRTPN*AVISITN /solution residual cl ddfm=kr;
repeated AVISITN/subject=subjid type=XX r rcorr;
lsmeans trtpn*AVISITN/diff pdiff cl;
run;
```

Notes:

1) For the covariance structure, priority should be given to UN. If the model fails to converge under the UN structure, alternative covariance structures should be used for processing based on the actual data.

12.6 Reference core codes for analysis of covariance (ANCOVA)

```
proc glm data=dsin order =data plots=none;
by _imputation_;
```

```
class SUBJID trtpn(ref='1');

model PCHG=BASE TRTPN /solution;

lsmeans trtpn/diff pdiff stderr cl;

ods output MODELANOVA = ANOVA2 LSMEANS = LSMEANS2 LSMEANCL = LSMEANSCL2 LSMEANDIFFCL = LSDIFF2 estimates=contrast2;

output out=new r=resid;

run;
```

Notes:

1) The dsin input dataset is that after imputation.

12.7 Reference core codes for P values adjusted by Holm's procedure

```
proc multtest inpvalues(raw_p) =dsin out =dsout holm;

run;
```

13 APPENDIX

13.1 Primary Analysis Imputation Method for Missing Month 10 TG with A Pattern Mixture Model

Scenario I:

For participants who discontinued the randomized period and who do not have Month 10 TG measurements, the missing data imputation method will use participants in the same treatment group who discontinued the randomized period and have Month 10 TG measurements. Missing Month 10 TG data will be imputed using PROC MI procedure with a multivariate imputation by fully conditional specification methods to create 100 datasets. The covariates include: treatment group, baseline fasting serum TG, and fasting serum TG from Month 1 to Month 10.

The core reference SAS code is as follows:

```
proc mi data= dsin out = dsout nimpute=100 SEED=20250225;

VAR BASE M1 M2 M3 M4 M5 M6 M7 M8 M9 M10;

FCS;

transform log(BASE) log(M1) log(M2) log(M3) log(M4) log(M5) log(M6) log(M7) log(M8) log(M9) log(M10) ;

run;
```

Notes:

1) The dsin input dataset is that after imputation.

Scenario II:

If there are no or very few participants in the same treatment group who discontinued the randomized period and have Month 10 TG measurements, missing Month 10 TG values will be imputed as follows:

For the VSA001 groups, assuming that the efficacy would be diluted after withdrawing treatment, such participants would exhibit the same disease evolution pattern as participants in the control group; assuming that such missing was Missing Not at Random (MNAR), only the baseline TG values in the test group (excluding post-treatment data) and data in the placebo group would be used for imputation. Refer to the code in Section 11.2. For the placebo group, a multiple imputation method assuming Missing at Random would be used for missing TG values at Month 10. Refer to the code in Section 11.3.

After imputation step, percentage change in TG will be calculated and each of the 100 multiply imputed datasets for FAS patients will be analyzed by either PROC NPAR1WAY procedure (primary) or PROC MIXED procedure (sensitivity). The estimate and standard error for treatment effect from the analysis will be analyzed by PROC MIANALYZE to obtain the overall estimate of treatment difference, as well as the confidence interval and P-value. The test statistics for making inference will be based on the method provided by Rubin and a modified macro from Mogg and Mehrotra (2007), refer to the code in Section 11.4.

13.2 SMQ of Suboptimal Glycemic Control of the Project - List of Standardized Queries

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

13.3 Introduction to Holm's Procedure

Holm's procedure is a modification method for multiple testing of statistics in a step-down manner (step-up P values) based on Bonferroni method. In this method, after calculating the P values of hypothesis tests, the P values are ranked in ascending order, denoted as $P_1 < P_2 < ... < P_m$, and their corresponding null hypotheses are H_{01}, H_{02},...H_{0m}; then the P values are compared with the corresponding αi in ascending order, and H_{0i}, $1 \leq i \leq m$, are tested in turn. In the first step, starts with the minimum P value, and perform testing of the null hypothesis H_{01}. If $P_1 > \alpha_1$ (= α/m), the null hypothesis H_{01} will not be rejected, and the tests of all remaining hypotheses will be stopped. If $P_1 \leq \alpha 1$, H_{01} will be rejected, and H_{A1} will be established. Proceed to the next step of hypothesis test. $\alpha_2 = \alpha/(m-1)$ is for the second hypothesis test. Compare the P value of this hypothesis test with α_2. If $P_2 > \alpha_2$, stop the remaining hypothesis tests; otherwise, H_{A2} is established, and proceed to the next hypothesis test. More generally, when testing the i^{th} null hypothesis H_{0i}, if $P_i > \alpha_1$ (=α/(m – i+1)), stop the test and accept H_{0i},..., H_{0m}; otherwise, reject H_{0i} (and accept H_{Ai}), and proceed to the next hypothesis test.