A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ISIS 678354 Administered Subcutaneously to Patients with Severe Hypertriglyceridemia

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This study has been transitioned to CTIS with ID 2024-510696-38-00 check the CTIS register for the current data. Primary objective: To evaluate the efficacy of olezarsen as compared to placebo on the percent change in fasting triglycerides from...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54207

Source
ToetsingOnline

Brief title
ISIS 678354-CS5

Condition

- Metabolic and nutritional disorders congenital
- Lipid metabolism disorders

Synonym
severe high fats (triglycerides) levels, severe hypertriglyceridemia

Research involving
Human

Sponsors and support

Primary sponsor: Ionis Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Ionis Pharmaceuticals;inc.

Intervention

Keyword: ISIS 678354, Olezarsen, Severe Hypertriglyceridemia

Outcome measures

Primary outcome

The primary endpoint is the percent change in fasting triglycerides (TG) from

Baseline at month 6 (average of Weeks 25 and 27) compared to placebo

Secondary outcome

Secondary endpoints include the following:

• Percent change in fasting TG from Baseline at Month 12 (average of Week 51

and Week 53) compared to placebo

• Proportion of patients who achieve fasting TG < 500 mg/dL (5.65 mmol/L) at

Month 6 and proportion of patients who achieve fasting TG < 500 mg/dL at Month

12 compared to placebo

• Proportion of patients who achieve fasting TG < 880 mg/dL (10 mmol/L) at

Month 6 and proportion of patients who achieve fasting TG < 880 mg/dL at Month

12 compared to placebo in the subgroup of patients with baseline TG >= 880 mg/dL

• Proportion of patients who achieve fasting TG < 1000 mg/dL (11.29 mmol/L) at

Month 6 and proportion of patients who achieve fasting TG < 1000 mg/dL at Month

12 compared to placebo in the subgroup of patients with baseline TG >= 1000 mg

• Percent change from Baseline at Month 6 and at Month 12 compared to placebo

in fasting:

o apoC-III

o VLDL-C

o Non-HDL-C

o HDL-C

• Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo in patients with >= 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment. This endpoint will be evaluated in the combined data from this study and ISIS 678354-CS6 (another Phase 3 study in patients with severe hypertriglyceridemia) as the individual studies may not have sufficient sample size to support meaningful conclusions.

• Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo in patients with >= 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment. This endpoint will be evaluated in the combined data from this study and ISIS 678354-CS6 for the same reason as above

• Adjudicated acute pancreatitis event rate during the Treatment Period compared to placebo. This endpoint will be evaluated in the combined data from this study and ISIS 678354-CS6 for the same reason as above.

• Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo. This endpoint will be evaluated in the combined data from this study and ISIS 678354-CS6 for the same reason as above

Additional/Exploratory endpoints:

Change or percent change from Baseline compared to placebo in the following:

• Proportion of patients who achieve various % reductions in fasting TG from

Baseline at Month 6 and proportion of patients who achieve various % reductions in fasting TG from Baseline at Month 12 compared to placebo

• Proportion of patients who achieve various thresholds in fasting TG at Month 6 and proportion of patients who achieve various thresholds in fasting TG at Month 12 compared to placebo

• Proportion of patients who develop fasting TG > 2000 mg/dL (22.6 mmol/L) at Month 6 and proportion of patients who develop fasting TG > 2000 mg/dL at Month 12 compared to placebo in the subgroup of patients with baseline TG <= 2000 mg/dL

• Percent change from Baseline at Month 6 and at Month 12 compared to placebo in fasting remnant cholesterol, TC, LDL-C, apoB, apoB-48, apo E, and apoA-1

• Lipoprotein particle size/number (select sites*)

• Homeostatic Model Assessment of Insulin Resistance (HOMA--IR), Homeostatic Model Assessment of Beta Cell Function (HOMA-B), hemoglobin A1c (HbA1c)

• Fibrosis-4 index (FIB-4 index)

• Inflammatory and exploratory biomarkers in blood related to cardiometabolic diseases

• Patient-reported abdominal pain and other symptoms as measured by the FCS Symptoms module of the FCS Symptoms and Impacts Scale and health-related quality of life (HRQoL) as measured by the PROMIS 29+2 measure, the EQ-5D-5L, the Patient Global Impression of Health and Patient Global Impression of Change in Health measures

• Change in hepatic fat fraction (HFF) from Baseline to Month 12, as measured by MRI, (select sites*)

*To be conducted at a limited number of selected sites

Safety endpoints:

• Event rates of independently adjudicated MACE and the composite of CV death, non-fatal MI, non-fatal ischemic stroke, and arterial revascularization (coronary and non-coronary), and the triple composite of CV death, non-fatal MI, and non-fatal ischemic stroke

• Relationship of triglyceride polygenic risk score with triglyceride lowering and pancreatitis event rate

• Incidence of all-cause ER visits, incidence of all-cause hospitalizations, incidence of ER visits for abdominal pain or hospitalizations for abdominal pain,
and total inpatient days compared to placebo

• PK: Plasma peak and trough exposure; half-life for subjects who will not rollover to the OLE study.

• exposure/response relationship for apoliprotein C-III and triglyceride, and factors affecting pharmacokinetics and -dynamics may be evaluated in this study, or in the future, as part of the population PK/PD and covariate analysis, if deemed appropriate, and results will be reported separately

Study description

Background summary

High levels of fats (triglycerides) in the blood (Severe Hypertriglyceridemia) causes reduced blood flow in the microcirculation. This may affect many organ

systems including the central nervous system, the cardiovascular system, the musculoskeletal system, and the gastrointestinal system. This may also affect a person*s health-related quality of life. People often experience frequent and severe abdominal pain (stomach area), lack of energy and strength, anxiety about potential pain attacks and overall health, difficulty concentrating and are at a higher risk of developing acute inflammation of the pancreas. The pancreas is an organ in the stomach area that helps with digestion and regulates blood sugar. Inflammation of the pancreas causes severe pain in the stomach area, often requires long stays in the hospital, and may result in pancreatic damage and critical illness. Standard therapeutic fat-lowering agents such as statin, ezetimibe, fibrates, fish oils and niacin, may be insufficient in reducing triglycerides in people with severe hypertriglyceridemia.

Apolipoprotein C-III (apoC-III) is found in blood and increases the fat levels in the blood. The study drug, olezarsen, reduces the amount of apoC-III in the blood. This may help people lower the amount of fat in the blood. The study drug could hopefully reduce some of the symptoms you may experience with high fat levels (e.g. inflammation of the pancreas). Health authorities have not approved the study drug for the treatment of severe hypertriglyceridemia and as such can only be used for research. The study drug has previously been tested in humans.

Study objective

This study has been transitioned to CTIS with ID 2024-510696-38-00 check the CTIS register for the current data.

Primary objective: To evaluate the efficacy of olezarsen as compared to placebo on the percent change in fasting triglycerides from Baseline

Secondary objectives:
• Proportion of patients who achieve fasting triglycerides < 500 mg/dL (5.65 mmol/L)
• Proportion of patients who achieve fasting triglycerides < 880 mg/dL (10 mmol/L)
• Proportion of patients who achieve fasting TG < 1000 mg/dL (11.29 mmol/L)
• Percent change from Baseline in fasting apolipoprotein C-III, very-low density lipoprotein cholesterol (VLDL-C), non-high-density lipoprotein cholesterol (HDL-C), and high-density lipoprotein cholesterol (HDL-C)
• Adjudicated acute pancreatitis event rate in patients with >= 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment.
• Adjudicated acute pancreatitis event rate

Other/Exploratory Objectives:
• Proportion of patients with various % reduction in fasting TG from Baseline
• Proportion of patients achieving thresholds in reduction in fasting TG

• Proportion of patients who develop fasting TG > 2000 mg/dL (22.6 mmol/L)
• Percent change from Baseline in fasting remnant cholesterol, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), apolipoprotein 48 (apoB48), apolipoprotein E (apoE), and apolipoprotein A-1 (apoA-1)
• Lipoprotein particle size/number (select sites*)
• Measures of glycemia
• Fibrosis-4 index (FIB-4 index)
• Inflammatory and exploratory biomarkers in blood, related to cardiometabolic diseases
• Patient-reported abdominal pain, other symptoms and health-related quality of life (HRQoL)
• Change in hepatic fat fraction (HFF) (select sites*)
• Major adverse cardiovascular events (MACE)
• Relationship of TG polygenic risk score with TG lowering and pancreatitis event rate
• Incidence of all-cause ER visits, incidence of all-cause hospitalizations, incidence of ER visits for abdominal pain or hospitalizations for abdominal pain, and total inpatient days compared to placebo
• Pharmacokinetics (PK): exposure/response analysis using relevant exposure parameters and biomarkers

* To be conducted at a limited number of selected sites

Study design

This is a multi-center, randomized, double-blind, placebo-controlled study. Eligible patients will enter an approximately 4 to 8-weeks, but no more than 12 weeks, Screening Period that includes an at least 2-week Diet/Life-style Stabilization/Run-in Period and an approximately 2-week Qualification Period. Following qualification, approximately 540 eligible patients will be randomized 1:1 to Cohort A (50 mg) or Cohort B (80 mg) and each cohort further randomized 2:1 to receive olezarsen or placebo in a 53-week Treatment Period. Patients in Cohort A will receive 50 mg of olezarsen once every 4 weeks (Q4W) or matching volume of placebo (0.5 mL) during Weeks 1-49 of the Treatment Period. Patients in Cohort B will receive 80 mg olezarsen once Q4W or matching volume of placebo (0.8 mL) during Weeks 1-49 of the Treatment Period. The 80-mg dose (blinded olezarsen or placebo) may be adjusted to 50 mg Q4W due to tolerability or safety reasons at any point during the study following consultation with the Sponsor Medical Monitor or designee. Randomization will be stratified by (1) TG >= 880 mg/dL (10 mmol) vs. < 880 mg/dL and (2) prior history of pancreatitis (within 10 years prior to Screening). Diet and life-style counseling should commence at the start of the Screening Period and continue to be reinforced throughout the trial. Following the Week 53 visit eligible patients may elect to enroll in an OLE study, pending study approval by the Independent Ethics Committee/Institutional Review Board (IEC/IRB) and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week

Post-Treatment Evaluation Period. All endpoints will be evaluated after the last patient has completed the Week 53/ET Visit.

Intervention

Olezarsen (ISIS 678354, an antisense oligonucleotide inhibitor of Apolipoprotein C-III production) or placebo will be administered as subcutaneous (SC) injections. Doses of 50 and 80 mg olezarsen administered once every 4 weeks were chosen based on the pre-clinical data and the pharmacodynamic and safety analysis of the Phase 1 study in healthy volunteers with hypertriglyceridemia and the Phase 2 study in patients with hypertriglyceridemia and established cardiovascular disease (CVD) or at high risk for CVD. Patients who will receive the placebo will be administered a matching volume of placebo (0.5 or 0.8 ml).

Study burden and risks

Burden:
The study will take about 70-78 weeks and will include 21 visits.
Procedures: Subjects will undergo physical exams (body weight and height), vital signs examination (blood pressure, body temperature, respiratory and pulse rate), several blood draws, urine assessments, MRI and electrocardiography. The medical and medication history will be reviewed. The subject has to fill in questionnaires. Patients are asked to be on a stable diet and should limit their alcohol consumption, for optimal control of triglycerides; diet counseling will be provided for this. Furthermore, male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent or practice effective contraception from the time of signing the informed consent form until at least 17weeks after their last dose of Study Drug. Before collecting fasting blood samples, the subject must fast for at least 10 hours
The study drug (side effects) and procedure (e.g. skin irritation from ecg, feeling faint due to fasting, bruise from collecting blood) are associated with some risks.
Benefits: If the subject participates in this research, it does not mean that the subject's disease will be cured or he/she will suffer less from his/her disease. But if the subject takes part he/she will help the investigators to get more insight into the treatment of Severe Hypertriglyceridemia.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Aged >= 18 years at the time of informed consent
3. Fasting Triglycerides (TG) >= 500 mg/dL (5.65 mmol/L) at both the Run-in period and the Qualification Period as follows:
a. Fasting TG >= 500 mg/dL (5.65 mmol/L) at Screening run-in visit. If the fasting TG is < 500 mg/dL and >= 350 mg/dL (3.95 mmol/L) up to 2 additional tests may be performed with the average of the tests used to be considered eligible
b. Fasting TG >= 500 mg/dL (5.65 mmol/L) at Screening Qualification visit. If the fasting TG is < 500 mg/dL and >= 350 mg/dL (3.95 mmol/L) up to 2 additional tests may be performed with the average of the tests used for qualification
4. Patients must be on lipid-lowering therapy that should adhere to standard of care (SOC) per local guidelines. Lipid-lowering medications should be optimized and stabilized for at least 4 weeks prior to Screening to minimize changes in these medications during the study. Patients taking over-the-counter (OTC)

omega-3 fatty acids should make every effort to remain on the same brand through the end of the study
5. Satisfy the following:
a. Females: must be non-pregnant and non-lactating and either:
a. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
b. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females <= 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved)
c. abstinent* or
d. if engaged in sexual relations of childbearing potential, agree to use a highly effective contraceptive method from the time of signing the informed consent form until at least 17 weeks after the last dose of Study Drug (olezarsen or placebo)
b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of childbearing potential, patient is utilizing a highly effective contraceptive method from the time of signing the informed consent form until at least 17weeks after the last dose of Study Drug (olezarsen or placebo)

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6. Patients must be willing to comply with diet and lifestyle recommendations as able.

Exclusion criteria

1. Diabetes mellitus with any of the following:
a. Newly diagnosed within 12 weeks prior to Screening or during the screening period
b. HbA1c >= 9.5% at Screening
c. Change in basal insulin regimen > 20% within 3 months prior to Screening or during the Screening period.
d. For patients with type 1 diabetes: episode of diabetic ketoacidosis, or >= 3 episodes of severe hypoglycemia within the 6 months prior to Screening or during the Screening period.
2. Acute coronary syndrome or stroke/TIA within 6 months prior to Screening or during the screening period. Major surgery, peripheral revascularization, or non-urgent percutaneous coronary intervention within 3 months prior to, or during Screening, or upcoming planned major surgery or major procedure (e.g.,

arterial revascularization) during the course of the study
3. Active pancreatitis within 4 weeks prior to Screening or during the screening period.
4. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion:
a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3.0 × ULN
b. Total bilirubin > 1.5 ULN unless due to Gilbert*s syndrome
c. Estimated GFR (eGFR) < 30 mL/min/1.73 m2 [as determined by the CKD EPI formula for creatinine clearance; (Levey et al. 2009)]
d. Urine protein/creatinine ratio (UPCR) >= 500 mg/g (56.5 mg/mmol)
5. Uncontrolled arterial hypertension (BP > 180/ /100 mmHg) despite antihypertensive therapy
6. Uncontrolled hypothyroidism such as those with thyroid-stimulating hormone (TSH) > 1.5 × ULN and free thyroxine (T4) < LLN, clinical evidence of hypothyroidism, or thyroid hormone therapy that has not been stable for >= 4 weeks prior to, or during Screening
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 or active Covid-19 infection with or without therapy that will not be resolved by Study Day 1
8. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing (HIV, Hepatitis C), or positive HBsAg (hepatitis B), respectively, or treatment for hepatitis C within 6 months prior to Screening. Patients at Screening who test positive by serology (for example, positive for Hepatitis C antibody), but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor or designee
9. Malignancy diagnosed or treated within 5 years prior to Screening or during the Screening period, except for non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor or designee
10. A diagnosis of FCS (type 1 Hyperlipoproteinemia) by documentation of confirmed homozygote, compound heterozygote or double heterozygote for loss-of-function mutations in type 1-causing genes (such as LPL, GPIHBP1, APOA5, APOC2, GPD1, or LMF1). Patients with suspected FCS and no prior such diagnosis should be genetically tested prior to randomization (Patients should be genetically tested if the score is >= 9).
11. Hypersensitivity to the active substance or to any of the excipients (olezarsen or placebo)
12. Treatment with another investigational drug (non-oligonucleotide), biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
13. Previous treatment with an oligonucleotide (including small interfering

ribonucleic acid [siRNA]) within 4 months, or 5 half-lives, whichever is longer, of Screening or during the Screening Period. This exclusion does not apply to vaccines
14. Concomitant medication/procedure restrictions:
a. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening or during the study unless approved by the Sponsor Medical Monitor or designee. This exclusion does not apply to local injections with no expected systemic effect.
b. Use of bile acid resins such as colestipol, cholestyramine, or colesevelam within 4 weeks prior to or during Screening or planned during the study
c. Plasma apheresis within 4 weeks prior to or during Screening or planned during the study
d. Change or expected need for significant change in titration of medications known to exacerbate hypertriglyceridemia such as non-selective beta blockers (e.g.,propranolol, nadolol, timolol, penbutolol, sotalol, pindolol), thiazides, isotretinoin, oral antidiabetic medications, tamoxifen, estrogens or progestins within 4 weeks prior to Screening or throughout the duration of the trial.
e. Change or expected need for significant change in titration of therapies known to significantly reduce triglycerides (such as GLP-1 agonists, other incretin mimetics, phentermine/topiramate, naltrexone/bupropion, xenical, or bariatric surgery) within 3 months prior to screening or throughout the duration of the trial.
f. Change or expected need for significant change in atypical antipsychotic medications (e.g., olanzapine and clozapine) within 3 months prior to Screening or throughout the duration of the trial.
15. Blood or plasma donation of 50 to 499 mL within 30 days prior to Screening or of > 499 mL within 60 days prior to Screening or planned during the study.
16. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
17. Have any other conditions, including current or recent (< 1 year) alcohol abuse or other substance abuse, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or complete the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-12-2022
Enrollment:	35
Type:	Actual

Ethics review

Approved WMO Date:	08-04-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-09-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-04-2023

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-510696-38-00
EudraCT	EUCTR2021-002192-19-NL
ClinicalTrials.gov	NCT05079919
CCMO	NL78070.000.22