# A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA*APOCIII*LRX Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Published: 21-12-2020
Last updated: 17-01-2025

Primary objectiveTo evaluate the efficacy of ISIS 678354 as compared to placebo on the percent change in fasting triglycerides (TG) from BaselineSecondary objectives• Proportion of patients who achieve >= 40% reduction in fasting TG from Baseline...

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| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Metabolic and nutritional disorders congenital |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON52139

**Source**
ToetsingOnline

**Brief title**
ISIS 678354-CS3

### Condition

- Metabolic and nutritional disorders congenital
- Lipid metabolism disorders

**Synonym**
Familial Chylomicronemia Syndrome

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** AKCEA-APOCIII-LRx, Familial Chylomicronemia Syndrome

## Outcome measures

### Primary outcome

The primary endpoint is the percent change in fasting TG from Baseline at 6 months (average of Weeks 23, 25 and 27) compared to placebo

### Secondary outcome

Secondary endpoints include the following:

• Percent change in fasting TG from Baseline at 12 months (average of Week 51 and Week 53) compared to placebo

• Proportion of patients who achieve >= 40% reduction in fasting TG from baseline at 6 months compared to placebo

• Percent change in fasting apoB-48 from Baseline at 6 months compared to placebo

• Proportion of patients who achieve fasting TG <= 750 mg/dL at 6 months compared to placebo

• Proportion of patients who achieve fasting TG <= 500 mg/dL at 6 months compared to placebo

• Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo, in patients with >= 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment

• Adjudicated acute pancreatitis event rate during the Treatment Period (Week 1 through Week 53) compared to placebo

• 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

• Adjudicated acute pancreatitis event rate from Week 13 to Week 53 compared to placebo

• Proportion of patients who achieve >= 70% reduction in fasting TG from Baseline at 6 months compared to placebo

• Proportion of patients who achieve fasting TG <= 500 mg/dL at 6 months compared to placebo

Additional/Exploratory Endpoints

Frequency and severity of patient-reported abdominal pain and other FCS-related symptoms, diet, and impacts, HRQoL, and ER visits, incidence of all-cause hospitalizations and total inpatient days, compared to placebo

Safety Endpoints

Safety and tolerability assessments include adverse events, clinical laboratory tests, ECGs, use of concomitant medications, and independently adjudicated events rates of Major Adverse Cardiovascular Events (MACE) for ISIS 678354 as compared to placebo

# Study description

### Background summary

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood. FCS is characterized by frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and in children, can result in a failure to thrive. Fasting plasma triglycerides (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake). The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective TG clearance. ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels. The study drug, ISIS 678354, is designed to reduce the amount of apoC-III in the blood. Reducing the amount of apoC-III in the blood may help lower the amount of TG and chylomicrons. These results hopefully alleviate some of the symptoms of FCS patients which are related to high TG levels.

### Study objective

Primary objective
To evaluate the efficacy of ISIS 678354 as compared to placebo on the percent change in fasting triglycerides (TG) from Baseline

Secondary objectives
• Proportion of patients who achieve >= 40% reduction in fasting TG from Baseline
• Percent change in fasting apoB-48 from Baseline
• Proportion of patients who achieve fasting TG <= 750 mg/dL (8.4 mmol/L)
• 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
• Proportion of patients who achieve >= 70% reduction in fasting TG from Baseline
• Proportion of patients who achieve fasting TG <= 500 mg/dL (5.7 mmol/L)

Additional / Exploratory Objectives
Patient reported abdominal pain, other FCS-related symptoms, diet, and impacts, health-related quality of life (HRQoL), cognitive function, and emergency room (ER) visits, incidence of all-cause hospitalizations and total inpatient days

Safety Objective
To evaluate the safety and tolerability of ISIS 678354

### Study design

This is a multi-center, randomized, double-blind, placebo-controlled study. Eligible patients will enter an approximately 4-week, but no more than 8-week, Screening Period that includes an at least 2-week diet stabilization/run-in period for patients not already on a stable diet, and an approximately 2-week qualification period. Following qualification, approximately 60 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 ISIS 678354 or placebo in a 53 week Treatment Period. Patients in Cohort A will receive 50 mg of ISIS 678354 once every 4 weeks or matching volume of placebo (0.5 mL) Weeks 1-49, of the Treatment Period. Patients in Cohort B will receive 80-mg ISIS 678354 once every 4 weeks or matching volume of placebo (0.8 mL) Weeks 1-49 of the Treatment Period. Randomization will be stratified by (1) prior history of pancreatitis (within 10 years prior to Screening) and (2) previous treatment with volanesorsen. Dietary counseling will commence at the start of the diet stabilization period and will be reinforced at intervals throughout the Treatment and Follow-up Period. Following the Week 53 visit, eligible patients may elect to enroll in an open-label extension (OLE) study pending study approval by the institutional review board/independent ethics committee (IRB/IEC) and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week Post-Treatment Evaluation Period. The primary endpoint for the study will be evaluated after the last patient has completed the Week 53/ET Visit and will be based on the percent change in fasting TG from Baseline at the primary analysis time point (Month 6).

**Intervention**

ISIS 678354 or placebo will be administered as subcutaneous (SC) injections. Doses of 50 mg or 80 mg 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.

**Study burden and risks**

Burden: During the study, the patients will be asked to come to the hospital for 22 visits.
Subjects will be treated with ISIS 678354 or placebo every 4 weeks during the treatment period, they will receive the treatment via subcutaneous injection in their abdomen, thigh, or upper arm 13 times in total. A physical examination and heart tracing (ECG) will be done and weight, height, and vital signs will be measured. Urine and blood tests will be done to check general health, pregnancy, post-menopausal status, for genetic testing, and to test for HIV and hepatitis B and C. Information about adverse events will be collected during the study visits. On a daily basis, subjects will complete the FCS Symptoms and Diet daily dairy to record FCS symptoms and changes in their diet. A

demographic questionnaire, health, and medication questionnaire, and quality of life questionnaire will be conducted. The patient will be asked not to consume alcohol and is encouraged to follow a low-fat diet of not more than 20 gram of fat per day during the study.
Risk: Possible side effects of the study drug and study procedures.

# Contacts

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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

## 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. A diagnosis of Familial Chylomicronemia Syndrome (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)

4. Fasting TG >= 880 mg/dL (10 mmol/L) at Screening. If the fasting TG is < 880 mg/dL up to 2 additional tests may be performed with any single test used to qualify
5. History of pancreatitis (defined as a recorded diagnosis of acute pancreatitis or hospitalization or emergency room (ER) visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made) within 10 years prior to Screening. Patients without a recorded history of pancreatitis, or no recorded history within 10 years prior to Screening, are also eligible but their enrollment will be capped at 35% (i.e., <= 21 of the 60 planned patients)
6. Willing to follow a diet comprising <= 20 g fat per day during the study
7. Willing to complete all Patient Reported Outcome assessments throughout the study as described in Section 6.2.5
8. Satisfy the following:
a. Females: must be non-pregnant and non-lactating and either:
i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
ii. 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 FSH levels in the postmenopausal range for the laboratory involved)
iii. abstinent* or
iv. if engaged in sexual relations of child-bearing 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 (ISIS 678354 or placebo)
b. Males: Surgically sterile, abstinent*, or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing 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 (ISIS 678354 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
9. Atypical antipsychotic medications (e.g., olanzapine and clozapine) will be allowed if on a stable dose for at least 3 months prior to Screening and dose and regimen expected to remain constant through the end of their participation in this study
10. The following concomitant medications will be allowed if on a stable dose for at least 4 weeks prior to Screening and dose and regimen expected to remain constant through the end of their participation in this study (occasional or intermittent use of over-the-counter (OTC) medications will be allowed at Investigator*s discretion):
a. Statins, omega-3 fatty acids (prescription and OTC), fibrates, or other lipid-lowering medications. Patients taking OTC omega-3 fatty acids should

make every effort to remain on the same brand through the end of the study
b. Antidiabetic medications
c. Antihypertensive medications
d. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) and regular clinical monitoring is performed
e. Tamoxifen, estrogens or progestins

## Exclusion criteria

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Active pancreatitis within 4 weeks prior to Screening
3. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion:
a. Platelet count < 100K/mm3 at Screening or Qualification. If the platelet count is < 100K/mm3 up to 2 additional tests may be performed to qualify at both Screening and Qualification
b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3.0 × upper limit of normal (ULN)
c. Total bilirubin > ULN unless due to Gilbert*s syndrome
d. Estimated GFR< 45 mL/min/1.73 m2 [as determined by the CKD-EPI formula for creatinine clearance; (Levey et al. 2009)]
e. Urine protein/creatinine ratio (UPCR) >= 500 mg/g or urine albumin/creatinine ratio (UACR) >= 300 mg/g
4. Uncontrolled arterial hypertension (blood pressure [BP] > 160/100 mmHg)
5. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at Screening
6. 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.
7. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor
8. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix 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
9. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening
10. 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
11. Previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening, or 5 half-lives, whichever is longer. This exclusion does not apply to vaccines.
12. Concomitant medication/procedure restrictions:
a. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening and during the study unless approved by the Sponsor Medical Monitor
b. Plasma apheresis within 4 weeks prior to Screening or planned during the study
13. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
14. Have any other conditions, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study

# Study design

## Design

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| 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

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|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 12-08-2021 |
| Enrollment: | 9 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 21-12-2020 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 19-04-2021 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 12-05-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 27-05-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 30-06-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 07-07-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 22-09-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |

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|---|---|
| Date: | 26-10-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 17-01-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 01-03-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 23-12-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 04-01-2023 |
| 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 |
|---|---|
| EudraCT | EUCTR2020-002536-67-NL |
| ClinicalTrials.gov | NCT04568434 |
| CCMO | NL75086.000.20 |

# Study results

Date completed: 12-10-2023

Results posted: 01-05-2024

**First publication**
15-03-2024