ISRCTN12904794 https://doi.org/10.1186/ISRCTN12904794

A phase 3 study to evaluate the efficacy and safety of ARO-APOC3 in adults with familial chylomicronemia syndrome

Submission date
15/02/2022

Recruitment status
No longer recruiting

Registration date
06/04/2022

Overall study status
Completed

Last Edited
13/05/2026

Condition category
Genetic Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Familial chylomicronemia syndrome (FCS) is a severe and ultrarare genetic disease, with a prevalence of approximately 1 in 1,000,000. FCS is caused by various gene mutations which leads to extremely high fasting triglyceride (TG) levels. Such severe elevations in TG lead to various serious signs and symptoms including acute pancreatitis, chronic daily abdominal pain, type 2 diabetes mellitus, hepatic steatosis, and cognitive issues. Currently, the only effective treatment is a diet extremely low in fat, the therapeutic options that can adequately treat FCS are very limited.

AROAPOC3-3001 is a phase 3, randomised, double blind, multicentre study evaluating subcutaneous injection of ARO-APOC3 compared to placebo in adults with FCS. The study drug, ARO-APOC3, has been developed by Arrowhead Pharmaceuticals Inc. as a treatment for dyslipidemias (including FCS and severe hypertriglyceridemia). It works as an RNA inhibitor and is thought to lower serum TG by preventing lipoprotein lipase inhibition. A previously completed Phase 1 study has shown ARO-APOC3 is well tolerated in healthy volunteers.

The primary objective of the study is to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS.

Who can participate?
Adults over 18 years with FCS.

What does the study involve?
Approximately 60 eligible patients globally will be randomised 1 of 4 treatment groups (ARO-APOC3 25mg, volume matched placebo, ARO-APOC3 50mg, volume matched placebo) in a 2:1:2:1 ratio. Participants will receive 4 total doses of ARO-APOC3 or placebo once every 3 months. The total duration for participation is approximately 56 weeks from screening to the Month 12 end of study visit.

What are the possible benefits and risks of participating?
Benefits:
Participants are not expected to receive any direct medical benefits from their participation in the study. The information developed in this study may be used to further develop ARO-APOC3, which may help people with hypertriglyceridemia in the future.
Risks:
Study Drug Risks:
There may be side effects that are not yet known. There will be laboratory studies and exams that will help identify adverse effects.
The most common (>10%) side effects reported include:
•Injection site reactions, including bruising and redness
•Upper respiratory tract infection
•Sore throat
•Headache
•Elevated liver enzymes
•Diarrhoea

Less common side effects (<10%) include muscle pain, dizziness, abdominal pain, rash and abnormal sensation of the skin (tingling, pricking, chilling).
Drugs similar to ARO-APOC3 have been previously studied. Possible side effects include, but are not limited to:
•Changes in liver function and damage to liver cells.
•Pain or a local immune reaction, such as redness, swelling, at the injection site which may vary in severity.
•Changes in liver related blood tests which may be short term or may require study discontinuation and possibly additional medical care.
•Allergic reaction, which is a potential risk with any new drug.
If not treated promptly, a serious allergic reaction can be life-threatening.

Study Procedures Risks:
Blood Samples: Possible adverse effects from taking blood samples include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. Slight possibility of infection.
ECG: The sticky pads used could cause some discomfort such as redness/itching. If hair under patches needs to be shaved, irritation from shaving could occur.

Pregnancy risks:
The effect of the study drug on an unborn baby, a breast-fed child, the female egg or on sperm is unknown.
Patients cannot participate in this study if they are pregnant, planning to become pregnant, are breastfeeding a child during the study and for 24 weeks after the last dose of the study drug. Females of childbearing potential or are not infertile must use 2 highly effective forms of contraception. Male subjects capable of fathering a child must agree not to donate sperm for same duration.

Where is the study run from?
Arrowhead Pharmaceuticals (USA)

When is the study starting and how long is it expected to run for?
February 2022 to April 2026

Who is funding the study?
Arrowhead Pharmaceuticals (USA)

Who is the main contact?
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Contact information

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Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05089084

Clinical Trials Information System (CTIS)
2021-003680-10

Clinical Trials Information System (CTIS)
2024-514336-24

Integrated Research Application System (IRAS)
1004639

Central Portfolio Management System (CPMS)
51500

Protocol serial number
AROAPOC3-3001

Study information

Scientific Title
A phase 3 study to evaluate the efficacy and safety of ARO-APOC3 in adults with familial chylomicronemia syndrome (FCS)

Study objectives
The primary objective of the study is to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 04/04/2022, East Midlands - Leicester Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8066; leicestercentral.rec@hra.nhs.uk), ref: 22/EM/0055

Primary study design
Interventional

Study design
Interventional double-blind randomized parallel-group placebo-controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Familial Chylomicronemia Syndrome

Interventions
Experimental Arm: ARO-APOC3 25mg
4 doses of ARO-APOC3 by subcutaneous (sc) injection (every 3 months for 1 year)

Placebo Comparator Arm: Placebo (sterile normal saline 0.9% NaCl)
calculated volume to match active treatment (25mg ARO-APOC3) by sc injection (4 doses in total - every 3 months for 1 year)

Experimental Arm: ARO-APOC3 50mg
4 doses of ARO-APOC3 by subcutaneous (sc) injection (every 3 months for 1 year)

Placebo Comparator Arm: Placebo (sterile normal saline 0.9% NaCl)
calculated volume to match active treatment (50mg ARO-APOC3) by sc injection (4 doses in total - every 3 months for 1 year)

Randomisation: Each participant will be randomly assigned 2:1:2:1 to the dose cohorts (ARO-APOC3 25 mg, volume-matched placebo, ARO-APOC3 50 mg, and volume-matched placebo, respectively). Treatments will be administered per the randomised sequence generated by an Interactive Web Response System (IWRS). The allocation of active treatment or placebo will be performed using a block randomisation algorithm.

Follow-Up: After Month 12, participants will be eligible and invited to consent and continue in an open-label extension study. All participants in the placebo group who opt to continue will switch to active drug during the extension study. Subjects who do not enter the open-label extension study will be monitored monthly for safety and pharmacodynamic endpoints for 9 months post last dose.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)

ARO-APOC3

Primary outcome(s)
1. Percent Change from Baseline in Fasting Triglycerides (TG) at Month 10 measured using blood test [Time Frame: Baseline, Month 10]

Key secondary outcome(s)
Measured using blood test or CRFs:
1. Percent Change from Baseline in Apolipoprotein C-III (APOC3) at Month 10 [Time Frame: Baseline, Month 10]
2. Percent Change from Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Month 10 [Time Frame: Baseline, Month 10]
3. Percent Change from Baseline in High Density Lipoprotein Cholesterol (HDL-C) at Month 10 [Time Frame: Baseline, Month 10]
4. Percent Change from Baseline in Fasting TG at Month 12 [Time Frame: Baseline, Month 12]
5. Percent Change from Baseline in Fasting APOC3 at Month 12 [Time Frame: Baseline, Month 12]
6. Percent Change from Baseline in Fasting Non-HDL-C at Month 12 [Time Frame: Baseline, Month 12]
7. Percent Change from Baseline in Fasting HDL-C at Month 12 [Time Frame: Baseline, Month 12]
8. Proportion of Patients Achieving TG of < 500 mg/dL at Month 10 [Time Frame: Month 10]
9. Proportion of Patients Achieving TG of < 500 mg/dL at Month 12 [Time Frame: Month 12]
10. Change from Baseline in Fasting TG Over Time [Time Frame: Baseline, up through Month 12]
11. Percent Change from Baseline in Fasting TG Over Time [Time Frame: Baseline, up through Month 12]
12. Number of Participants with Treatment-Emergent Adverse Events (AEs) and/or Serious Adverse Events (SAEs) [Time Frame: From first dose of study drug through Month 12]
13. Number of Participants with Positively Adjudicated Events of Acute Pancreatitis [Time Frame: From first dose of study drug through Month 12]

Completion date
21/04/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 22/07/2025:

1. Males or nonpregnant (who do not plan to become pregnant), nonlactating females ≥18 years of age (or ≥19 years of age, where applicable according to the local regulation)
2. Able and willing to provide written informed consent prior to the performance of any study specific procedures
3. Fasting TG ≥10 mmol/L (≥880 mg/dL) at screening, that is refractory to standard lipid lowering therapy (sample drawn after at least the minimum time on stable lipid lowering regimen described in the protocol). Two repeat tests are allowed to qualify.
4. A diagnosis of FCS based on a documented history of fasting TG levels in excess of 1000 mg /dL on repeated testing (for at least 3 prior occasions), and at least one of the following:
4.1. A supportive genetic test (from a source-verifiable medical record or based on screening genotype). Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss of function or otherwise inactivating mutations in

genes affecting lipoprotein lipase activity including LPL, APOC2, APOA5, GPIHBP1, GPD1, or LMF1; or evidence of low LPL activity (<20% of normal) based on source verifiable documentation; or
4.2. Documented history of recurrent episodes of acute pancreatitis, not caused by alcohol or cholelithiasis; or
4.3. Documented history of recurrent hospitalizations for severe abdominal pain without other explainable cause; or
4.4. Documented history of childhood pancreatitis; or
4.5. Family history of hypertriglyceridemia-induced pancreatitis
5. Willing to follow dietary counseling as per PI judgment based on local standard of care, consistent with an intake of ≤20 g of fat per day during the study
6. If on medications for management of type 2 diabetes, or other medications specified in the protocol, the dosing regimen must be stable before collection of qualifying lipid parameter at screening.
7. Participants with a medical history of clinical atherosclerotic cardiovascular disease (ASCVD) or those with elevated 10-year ASCVD risk (eg, ≥7.5% per American Heart Association / American College of Cardiology risk calculator) must be on appropriate lipid-lowering therapy as per local standard of care (ie, including moderate to high intensity statin, as indicated) prior to collection of qualifying TG levels.
8. Participants of childbearing potential must agree to use a highly effective form of contraception in addition to a male condom, during the study and for at least 24 weeks after the last dose of IMP. Women of childbearing potential on a hormonal contraceptive must be stable on the medication for ≥2 menstrual cycles prior to Day 1. Men must not donate sperm during the study and for at least 24 weeks after the last dose of IMP.

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Previous inclusion criteria:

1. Males or nonpregnant (who do not plan to become pregnant), nonlactating females ≥18 years of age
2. Able and willing to provide written informed consent prior to the performance of any study specific procedures
3. Fasting TG ≥10 mmol/L (~880 mg/dL) at screening, that are refractory to standard lipid lowering therapy (sample drawn after at least the minimum time on stable lipid lowering regimen described in the protocol). Two repeat tests are allowed to qualify.
4. A diagnosis of FCS based on a documented history of fasting TG levels in excess of 1000 mg /dL on repeated testing (for at least 3 occasions), and at least one of the following:
4.1. A supportive genetic test (from a source-verifiable medical record or based on screening genotype). Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss of function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including LPL, APOC2, APOA5, GPIHBP1, GPD1, or LMF1; or evidence of low LPL activity (<20% of normal) based on source verifiable documentation; or
4.2. Documented history of recurrent episodes of acute pancreatitis, not caused by alcohol or cholelithiasis; or
4.3. Documented history of recurrent hospitalizations for severe abdominal pain without other explainable cause; or
4.4. Documented history of childhood pancreatitis; or
4.5. Family history of hypertriglyceridemia-induced pancreatitis
5. Willing to follow dietary counseling as per PI judgment based on local standard of care, consistent with an intake of ≤ 20 g of fat per day during the study

6. If on medications for management of type 2 diabetes, or other medications specified in the protocol, the dosing regimen must be stable before collection of qualifying lipid parameter at screening.
7. Participants with a medical history of clinical atherosclerotic cardiovascular disease (ASCVD) or those with elevated 10-year ASCVD risk (eg, ≥7.5% per American Heart Association / American College of Cardiology risk calculator) must be on appropriate lipid-lowering therapy as per local standard of care (ie, including moderate to high intensity statin, as indicated) prior to collection of qualifying TG levels.
8. Participants of childbearing potential must agree to use 2 highly effective forms of contraception as defined in the protocol, during the study and for at least 24 weeks after the last dose of IP. Women of childbearing potential on hormonal contraceptives must be stable on the medication for >2 menstrual cycles prior to Day 1. Men must not donate sperm during the study and for at least 24 weeks after the last dose of IP.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
110 Years

Sex
All

Total final enrolment
76

Key exclusion criteria
Current exclusion criteria as of 22/07/2025:

1. Current use or use within the last 365 days from Day 1 of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule
2. Diabetes mellitus with any of the following:
a. Newly diagnosed within 12 weeks of screening
b. HbA1c ≥9.0% (or >75 mmol/mol International Federation of Clinical Chemistry [IFCC] units) at screening
3. Active pancreatitis within 12 weeks before Day 1
4. History of acute coronary syndrome events (myocardial infarction or unstable angina) or procedures (coronary revascularization, angioplasty, or stenting) within 24 weeks of Day 1
5. History of major surgery within 12 weeks of Day 1 (including cardiac and vascular surgeries, eg, coronary artery bypass graft)
6. Any of the following laboratory values at screening:
6.1. ALT or AST ≥3×ULN at screening

6.2. Total bilirubin ≥1.5 ULN (if the participant has a prior diagnosis and documentation of Gilbert's syndrome, then total bilirubin must be ≤3 mg/dL at screening)
6.3. Estimated glomerular filtration rate <30 mL/min/1.73 m2 at screening, using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (Levey 2009)
6.4. Spot urine protein/spot urine creatinine ratio greater than 3 grams per day
6.5. Clinically significant abnormality in prothrombin time, partial thromboplastin time, or INR
7. Uncontrolled hypertension (blood pressure >160/100 mmHg at screening); if untreated, participant may be rescreened once hypertension is treated and controlled
8. Use of any of the following:
8.1. Systemic use of corticosteroids or anabolic steroids within 4 weeks prior to Day 1 or planned use during the study
8.2. GLP-1 receptor agonists
8.3. Plasma apheresis within 4 weeks prior to Day 1 or planned during the study
8.4. Blood donation of 50 to 499 mL within 4 weeks of collection of qualifying lipid parameter collection or of >499 mL within 8 weeks of qualifying lipid parameter collection
9. On treatment with HIV antiretroviral therapy (Note: determination of HIV status is not a required study procedure)
10. Seropositive (hepatitis B surface antigen [HBsAg] +) for hepatitis B virus (HBV) or hepatitis C virus (HCV) (HCV seropositivity requires positive test for antibodies confirmed with positive test for HCV RNA)
11. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%
12. Clinical evidence of primary hypothyroidism (screening TSH > ULN and free T4<LLN), primary subclinical hypothyroidism (screening TSH > ULN and free T4 WNL), or secondary hypothyroidism (screening TSH < LLN and free T4< LLN)
13. History of stroke, transient ischemic attack, or peripheral artery disease within 24 weeks of first dose
14. History of bleeding diathesis or coagulopathy
15. Current diagnosis of nephrotic syndrome
16. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week for women and men (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)
17. History of malignancy within the last 2 years prior to the date of consent requiring systemic treatment except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Currently receiving systemic cancer treatment(s) or, in the PI's opinion, at risk of relapse for recent cancer.
18. Use of an investigational agent or device within 30 days or within 5 half-lives, based on plasma PK (whichever is longer) prior to Day 1 or current participation in an interventional investigational study. Participants previously exposed to ARO APOC3 or ARO-ANG3 will require a washout period of at least 1 year from last dose.
19. Any concomitant medical or psychiatric condition or social situation or any other situation that, in the PI's judgment, would make it difficult to comply with protocol requirements or put the participant at additional safety risk.
20. Clinical evidence of Cushing's syndrome.

Previous exclusion criteria:

1. Current use or use within the last 365 days from Day 1 of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule
2. Diabetes mellitus with any of the following:

a. Newly diagnosed within 12 weeks of screening
b. HbA1c ≥9.0% at screening
3. Active pancreatitis within 12 weeks before Day 1
4. History of acute coronary syndrome event within 24 weeks of Day 1
5. History of major surgery within 12 weeks of Day 1
6. Any of the following laboratory values at screening:
6.1. ALT or AST ≥3×ULN at screening
6.2. Total bilirubin ≥1.5 ULN (if the participant has a prior diagnosis and documentation of Gilbert's syndrome, then total bilirubin must be ≤3 mg/dL at screening)
6.3. Estimated glomerular filtration rate <30 mL/min/1.73 m2 at screening, using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (Levey 2009)
6.4. Spot urine protein/spot urine creatinine ratio greater than 3 grams per day
6.5. Clinically significant abnormality in prothrombin time, partial thromboplastin time, or INR
7. Uncontrolled hypertension (blood pressure >160/100 mmHg at screening); if untreated, participant may be rescreened once hypertension is treated and controlled
8. Use of any of the following:
8.1. Systemic use of corticosteroids or anabolic steroids within 4 weeks prior to Day 1 or planned use during the study
8.2. GLP-1 receptor agonists
8.3. Plasma apheresis within 4 weeks prior to Day 1 or planned during the study
8.4. Blood donation of 50 to 499 mL within 4 weeks of collection of qualifying lipid parameter collection or of >499 mL within 8 weeks of qualifying lipid parameter collection
9. Known history of HIV infection
10. Seropositive (hepatitis B surface antigen [HBsAg] +) for hepatitis B virus (HBV) or hepatitis C virus (HCV) (HCV seropositivity requires positive test for antibodies confirmed with positive test for HCV RNA)
11. New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%
12. Clinical evidence of primary hypothyroidism (screening TSH > ULN and free T4<LLN), primary subclinical hypothyroidism (screening TSH > ULN and free T4 WNL), or secondary hypothyroidism (screening TSH < LLN and free T4< LLN)
13. History of hemorrhagic stroke within 24 weeks of first dose
14. History of bleeding diathesis or coagulopathy
15. Current diagnosis of nephrotic syndrome
16. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week for women and men (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)
17. History of malignancy within the last 2 years prior to the date of consent requiring systemic treatment except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Currently receiving systemic cancer treatment(s) or, in the PI's opinion, at risk of relapse for recent cancer.
18. Use of an investigational agent or device within 30 days or within 5 half-lives, based on plasma PK (whichever is longer) prior to Day 1 or current participation in an interventional investigational study. Participants previously exposed to ARO APOC3 or ARO-ANG3 will require a washout period of at least 1 year from last dose.
19. Any concomitant medical or psychiatric condition or social situation or any other situation that, in the PI's judgment, would make it difficult to comply with protocol requirements or put the participant at additional safety risk.

Date of first enrolment
27/10/2021

Date of final enrolment
04/04/2023

Locations

Countries of recruitment
Argentina

Australia

Austria

Belarus

Belgium

Canada

Croatia

France

Germany

Ireland

Japan

Mexico

New Zealand

Poland

Russian Federation

Serbia

Türkiye

Ukraine

Sponsor information

Organisation
Arrowhead Pharmaceuticals, Inc.

Funder(s)

Funder type
Industry

Funder Name
Arrowhead Pharmaceuticals

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No