A Phase 2 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of ARO-APOC3 in Adults with Dyslipidemia

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This study has been transitioned to CTIS with ID 2024-511331-96-00 check the CTIS register for the current data. Primary Objective• To evaluate the safety and efficacy of long-term treatment with ARO-APOC3 in adults with dyslipidemia.

Ethical review	Approved WMO
Status	Pending
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON53567

Source
ToetsingOnline

Brief title
AROAPOC3-2003

Condition

- Lipid metabolism disorders

Synonym
Dyslipidemia, severely high hypertriglyceridemia

Research involving
Human

Sponsors and support

Primary sponsor: Arrowhead Pharmaceuticals, Inc

Source(s) of monetary or material Support: Arrowhead Pharmaceuticals

Intervention

Keyword: ARO-APOC3, Dyslipidemia

Outcome measures

Primary outcome

Primary:

• Subject incidence of treatment-emergent adverse events (TEAEs)

Secondary outcome

Secondary:

• Change and percent change from baseline over time in fasting TG

• Change and percent change from baseline over time in apolipoprotein (Apo)C-III

• Change and percent change from baseline over time in fasting non-high-density lipoprotein cholesterol (non-HDL-C)

• Change and percent change from baseline over time in fasting HDL-C

• Change and percent change from baseline over time in fasting total apolipoprotein B (ApoB)

• Change and percent change from baseline over time in fasting LDL-C using ultracentrifugation

Exploratory:

• Change and percent change from baseline over time in other fasting lipid parameters (total cholesterol, LDL-C measured using Martin-Hopkins methodology, LDL/HDL ratio, VLDL-C, apolipoprotein B 48 [ApoB-48], lipoprotein[a] [Lp{a}], apolipoprotein B 100 [ApoB-100], apolipoprotein C-II [ApoC-II], apolipoprotein

A-I [ApoA-I], and apolipoprotein A-V [ApoA-V] [all values drawn after at least

a 10-hour fast])

• Change from baseline over time in fasting serum blood glucose, hemoglobin A1c

(HbA1c), homeostatic model assessment for insulin resistance, and C peptide

• Change and percent change from baseline over time in high sensitivity

C-reactive protein

• Emergence of and titers of anti-drug antibodies to ARO-APOC3 over time

• Incidence of positively adjudicated events of acute pancreatitis

• Incidence of hospitalizations for abdominal pain

• Subject incidence of emergent apheresis

Study description

Background summary

Dyslipidemia is defined as an imbalance in plasma lipids (eg, cholesterol, low-density lipoprotein cholesterol [LDL-C], triglycerides [TG], and/or high-density lipoprotein cholesterol [HDL-C]) that includes severely high hypertriglyceridemia (SHTG) and mixed dyslipidemia (MD), two conditions that are associated with clinical complications. SHTG is characterized by marked elevations in TG levels, which can lead to acute pancreatitis, as well as an increased risk of cardiovascular disease and atherosclerosis (Hegele 2014; Scherer 2014). MD is defined as the presence of high LDL-C combined with at least one other lipid abnormality (ie, high LDL-C with either low HDL-C and/or high TG) and is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) (Kersten 2017). The prevalence of SHTG in adults in the US is approximately 1.7%, based on the National Health and Nutrition Examination Survey (NHANEs) database (2001-2006) of individuals with TG levels between 500 and 2000 mg/dL (5.65 to 22.6 mmol/L) (Christian 2011; Laufs 2020), while the prevalence of MD in adults in the US is approximately 21% (42.0 M). Currently, the therapeutic options that can adequately treat SHTG and MD are limited, and additional treatments options are needed.
ApoC3 is an 8.8 kilodalton (kDa) protein component of triglyceride-rich lipoproteins (TRLs), such as very-low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol, chylomicrons, HDL-C, and remnant

particle lipoproteins. ApoC3 is synthesized predominantly in hepatocytes. It inhibits the hydrolysis of TG on TRLs at the muscle and adipose tissue capillary level through inhibition of lipoprotein lipase (LPL) and delays clearance of lipoprotein remnants by the liver by inhibiting hepatocyte receptor-mediated uptake. ApoC3 functions as a key regulator of fasting and postprandial plasma TG levels.
ARO-APOC3 is a synthetic, double-stranded, hepatocyte-targeted RNA interference (RNAi) trigger designed to specifically silence messenger RNA (mRNA) transcripts from the APOC3 gene using an RNAi mechanism. Given the important role of ApoC3 in serum TG level modulation and its primary source of synthesis in hepatocytes, reduction of ApoC3 through a hepatocyte-targeted RNAi strategy is likely to reduce circulating TG by preventing ApoC3-mediated inhibition of LPL, thus allowing enhanced peripheral LPL activity. Additionally, ApoC3 silencing is expected to remove the steric blockade of ApoC3 at the hepatocyte, leading to enhanced clearance of TRLs from circulation by the liver.

Study objective

This study has been transitioned to CTIS with ID 2024-511331-96-00 check the CTIS register for the current data.

Primary Objective
• To evaluate the safety and efficacy of long-term treatment with ARO-APOC3 in adults with dyslipidemia.

Study design

This is an open-label extension (OLE) Phase 2b clinical study. Subjects who have signed an Ethics Committee (EC)/Institutional Review Board (IRB) approved informed consent form (ICF) may be enrolled after completing either AROAPOC3-2001 or AROAPOC3-2002 (parent studies). Subjects must continue to maintain a stable diet and stable lipid-lowering therapy in accordance with local standard of care, as well as other background medications taken during the parent study (see Section 8.2), throughout the duration of the 24-month OLE period (refer to Table 3).
All eligible subjects from AROAPOC3-2001 and AROAPOC3-2002 studies will receive ARO-APOC3, administered open-label, consistent with the dose level and regimen (once every 3 months [Q3M] or once every 6 months [Q6M]) as assigned in the parent study. Subjects will remain blinded to their treatment assignment from the parent study and will initially receive ARO-APOC3 in this OLE study at the dose corresponding to their assigned study treatment dose in the parent study. Thus, subjects who had previously received ARO-APOC3 10 mg, 25 mg, or 50 mg Q3M (in Study AROAPOC3-2001); or ARO-APOC3 10 mg, 25 mg, or 50 mg Q3M, or ARO-APOC3 50 mg Q6M (in Study AROAPOC3-2002) will continue to receive the same dose in this OLE study until a final dose is selected from the parent studies. Subjects previously receiving placebo in the parent study will transition to active

treatment based on the initial dosing group to which they were assigned (ie, 10 mg Q3M, 25 mg Q3M, or 50 mg Q3M or Q6M). After the last subject in the parent study reaches the Month 12/end of study (EOS) visit of the parent study and a dose has been selected, all subjects in this OLE study will receive open-label treatment with the selected ARO-APOC3 dosing regimen.

Intervention

Investigational Product, Dosage, and Mode of Administration:
The test formulation is active ARO-APOC3 administered SC. The active pharmaceutical ingredient contained in ARO-APOC3 is a synthetic, double-stranded, small interfering RNA oligonucleotides (siRNA) duplex conjugated to an N-acetyl galactosamine (NAG) targeting ligand to facilitate hepatocyte delivery.

Dosage information: ARO-APOC3 on Day 1, then Q3M (or Q6M if assigned to the 50 mg dose group in study AROAPOC3-2002) through EOS: initial dosage, 10 mg, 25 mg, or 50 mg as assigned in the parent study (see Methodology).
Following the final data analysis in the parent studies, a single dose will be determined and all active subjects will be transitioned to the selected dose for the duration of the study.

Duration of Treatment:
The duration of the OLE study is approximately 2 years. All subjects in the placebo group of the parent study who opt to continue will switch to active drug during the OLE study.

Reference Therapy, Dosage and Mode of Administration:
Not applicable

Study burden and risks

ARO-APOC3 has been shown to have a favorable benefit-risk profile to date that warrants further clinical investigation and longer exposure periods. As of the October 08, 2020 (for non-safety) and October 15, 2020 (for safety) cutoff dates, interim PD data from the Phase 1 study AROAPOC31001 showed that administration of ARO-APOC3 at doses ranging from 10 to 100 mg resulted in significant and durable reduction of serum APOC3 when compared with placebo in healthy volunteers as well as in subjects with HTG and CM.
Silencing of APOC3 led to reductions in the levels of serum TG and other lipid parameters. Results using single doses of ARO-APOC3 in normal healthy volunteers (NHVs) demonstrated dose-dependent reductions in serum APOC3 of up to -94%when compared to baseline. As would be predicted, knockdown of APOC3 resulted in decreased fasting serum TG (up to -66%) and non-HDL-C (up to -31%) as well as increased serum HDL-C levels (up to +74%) with a dose response generally correlating with APOC3 serum level reductions in subjects receiving

the active drug. Results for repeat doses of ARO-APOC3 in NHVs demonstrated consistent reductions of APOC3 (up to -94%), TGs (up to -75%), and non-HDL-C (up to -34%) and increases in HDL-C levels (up to +75%). These responses were overall sustained through Week 16, which is 12 weeks after the last dose.
Results for repeat doses of ARO-APOC3 in subjects with HTG and/or CM demonstrated similar or even larger effects of ARO-APOC3 at similar doses studied in NHVs. Reductions of serum APOC3 (up to -98%), TGs (up to -88%), non-HDL-C (up to -58%), and increases in HDL-C levels (up to +122%) were observed. The effects of ARO-APOC3 treatment on these and other key lipid parameters were sustained over the 16 weeks of study duration.
ARO-APOC3 has been generally well tolerated and has demonstrated favorable safety and tolerability. There have been no deaths in the study or study discontinuation due to AEs. Three (3) SAEs involving 3 subjects have been reported, all of which were deemed not related to study drug, and the subjects completed the study. There is no clear pattern of an increased frequency or intensity of AEs with increasing dose level. The combined placebo TEAEs reported were comparable to those seen in the ARO-APOC3 treatment group. The majority of the reported TEAEs were not related to study treatment, and there were no subjects that discontinued from the study due to TEAEs. The most frequently reported AEs that were drug-related were the ISRs, which were all mild in intensity. The AEs at the injection site are anticipated based on similar findings reported in other clinical studies of SC-administered siRNA therapeutics. Overall, there were no clinically significant adverse laboratory trends observed. There were no clinically significant adverse ECG, vital sign, or physical examination findings during the mentioned study period.
The totality of the data described above represents robust evidence to support the continuation of the clinical development program for ARO-APOC3.

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. Adults >=18 years of age who are nonpregnant, nonlactating, and do not plan to become pregnant during the study

2. Able and willing to provide written informed consent prior to the performance of any study specific procedures

3. Completed the 48-week study treatment period in the parent study

Exclusion criteria

1. Subject was permanently discontinued from ARO-APOC3 in the parent study due to elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT)

2. Any new condition or worsening of existing condition (eg, renal, hematologic, gastrointestinal, endocrine, cardiovascular, pulmonary, immunologic, psychiatric) or any other situation that, in the Investigator*s judgment, would make the subject unsuitable for enrollment, could interfere with the subject participating in or completing the study, would make it difficult to comply with protocol requirements, or put the subject at additional safety risk

3. Unwilling to limit alcohol consumption to within moderate limits for the duration of the study, as follows: not more than 14 units per week (1 unit approximately corresponds to 80 mL of wine, 200 mL of beer, or 25 mL of 40% alcohol)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	12-05-2023
Enrollment:	7
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ARO-APOC3
Generic name:	ARO-APOC3

Ethics review

Approved WMO Date:	19-10-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	06-02-2023
Application type:	First submission
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:	10-05-2023
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)

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	CTIS2024-511331-96-00
EudraCT	EUCTR2022-001135-85-NL

Register	ID
CCMO	NL82028.000.22