Amsterdam, 23 April 2026
EMA/145871/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Redemplo

International non-proprietary name: plozasiran

Procedure No. EMEA/H/C/006579/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA Anti-drug antibody
ADR Adverse drug reaction
ADME Absorption, distribution, metabolism, and excretion
AE Adverse event
AEX-LCFL Anion-exchange liquid chromatography with fluorescence detection
AKI Acute kidney injury
ALP Alkaline phosphatase
ALT Alanine aminotransferase
AMQ Arrowhead Standardised Medical Dictionary for Regulatory Activities Query
APGAR Appearance, pulse, grimace, activity, and respiration
apoB Apolipoprotein B
apoC3 Apolipoprotein C-III
APOC3 Apolipoprotein C-III gene
AUC Area under the plasma concentration-time curve
ASGPR Asialoglycoprotein receptors
AST Aspartate aminotransferase
BMI Body mass index
CHMP Committee for Medicinal Products for Human Use
COVID-19 Coronavirus disease 2019
CI confidence interval
CS Chylomicronaemia syndrome
CSR Clinical Study Report
CYP450 Cytochrome P450
DB Double-blind
DBPC Double-blind placebo-controlled
DDI Drug-drug interaction
DILI drug-induced liver injury
EAIR Exposure-adjusted incidence rate
EBD European birth date
ECG Electrocardiogram
EMA European Medicines Agency
EORTC QLQ European Organisation for the Research and Treatment of Cancer QoL
EQ-5D-5L EuroQol 5-dimension instrument
EU European Union
EURD list List of Union reference dates
FCS Familial chylomicronaemia syndrome
GCP Good Clinical Practice
GFR Glomerular filtration rate
GMR Geometric mean ratio
HbA1c Glycosylated hemoglobin
HDL-C High-density lipoprotein cholesterol
HTG Hypertriglyceridemia
IC50 Half-maximal inhibitory concentration
IBD International birth date
ISR Incurred sample reproducibility
LDL-C Low-density lipoprotein cholesterol
LPL Lipoprotein lipase
LoQ List of questions
LoOI List of outstanding issues
LLOQ Lower limit of quantification
MAA Marketing Authorisation Application
MCS Multifactorial chylomicronemia syndrome
MedDRA Medical Dictionary for Regulatory Activities
mRNA Messenger RNA
NAG N-acetylgalactosamine
NAS New Active Substance
non-HDL-C Non-high-density lipoprotein cholesterol
OLE Open-label extension
OR Odds ratio
PD Pharmacodynamic(s)
PFS Prefilled syringe
PIP Paediatric investigation plan
PNA Peptide nucleic acid
PK Pharmacokinetic(s)

PT Preferred term
PRAC Pharmacovigilance Risk Assessment Committee
Q12W Every 12 weeks
Q24W Every 24 weeks
Q3M Every 3 months
QoL Quality of life
RNAi Ribonucleic acid interference
ROW Rest of World
RMP Risk management plan
SAE Serious adverse event
SC Subcutaneous(ly)
SHTG Severe hypertriglyceridemia
siRNA Small interfering RNA oligonucleotide
SMQ Standardised Medical Dictionary for Regulatory Activities query
SmPC Summary of product characteristics
SOC System Organ Class
TEAE Treatment-emergent adverse event
TRL Triglyceride-rich lipoprotein
TK Toxicokinetic
Tmax Time to achieve maximum plasma concentration
ULN Upper limit of normal
ULOQ Upper limit of quantification
VLDL Very low-density lipoprotein

1.1. *Protocol assistance*

The applicant did not seek Protocol assistance from the CHMP.

1.2. *Eligibility to the centralised procedure*

The applicant Arrowhead Pharmaceuticals Ireland Limited submitted on 28 February 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Redemplo (plozasiran), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2024.

The applicant applied for the following indication: adjunct to diet to reduce triglyceride levels in patients with familial chylomicronaemia syndrome.

1.3. *Legal basis and dossier content*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies.

1.4. *Information on paediatrics*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision P/0071/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-003420-PIP0l-23 had not yet been completed as some measures had been deferred.

1.5. *Information on orphan market exclusivity*

Redemplo was designated as an orphan medicinal product (EU/3/21/2459) on 19 July 2021 in the following condition: treatment of familial chylomicronaemia syndrome.

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure (Waylivra (volanesorsen) and Tryngolza (olezarsen)).

1.6. *Applicant's request(s) for consideration*

1.6.1. Accelerated assessment request

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. However, during the assessment the CHMP concluded that the accelerated assessment timeline was no longer feasible, as requested by the applicant.

1.6.2. New active substance status

The applicant requested the active substance plozasiran contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6.2.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that plozasiran is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

1.7. *Patient experience data*

Table 1: Patient experience data relevant to the application

Patient experience data submitted with this application				***Section where discussed (if applicable)***
■	Patient experience data submitted by the applicant:			
	■	Clinical outcome assessments (COAs) such as		
		■	Patient-reported outcomes (PRO)	5.3.2.1.4
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☐	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	☐	CHMP early dialogue with patient organisations		

Patient experience data submitted with this application			Section where discussed (if applicable)
	☐	Third party interventions from patients and patient groups	
	☐	Other (e.g. medical literature, summaries/analysis from patient engagement activities - please specify)	

1.8. *Steps taken for the assessment of the product*

The rapporteur and co-rapporteur appointed by the CHMP were:

rapporteur:	Patrick Vrijlandt
Co-rapporteur:	Ewa Bałkowiec Iskra

The application was received by the EMA on	28 February 2025
An application for accelerated assessment was filed by the applicant. Accelerated assessment procedure was agreed-upon by CHMP on 31 January 2025 The procedure was reverted to standard timetable at list of questions at day 90.	20 December 2024
The procedure started on	20 March 2025
The CHMP rapporteur's first assessment report was received on	20 May 2025
The CHMP co-rapporteur's first assessment report was added to the rapporteur's report on	22 May 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	26 May 2025
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP rapporteur and co-rapporteur declared that they had completed their assessment report in less than 80 days	21 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 June 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	17 June 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 December 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs' joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	2 February 2026
The CHMP rapporteur circulated the updated CHMP and PRAC rapporteurs' joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	20 February 2026
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	26 February 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	24 March 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs' Joint assessment report on the applicant's responses to the list of outstanding issues	8 April 2026

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Redemplo on	23 April 2026
The CHMP adopted a report on similarity of Redemplo (plozasiran) with Waylivra (volanesorsen) and Tryngolza (olezarsen) on (see Appendix on similarity)	23 April 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	23 April 2026

1.9. *CHMP outcome*

1.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.9.2.1. Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Redemplo (plozasiran) is not similar to Waylivra (volanesorsen) and Tryngolza (olezarsen) within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.9.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Redemplo is favourable in the following indication(s):

Redemplo is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with familial chylomicronaemia syndrome (FCS) (see section 4.2 for patient selection criteria).

1.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.9.5. Other conditions and requirements of the marketing authorisation

1.9.5.1. Periodic safety update reports

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency web-portal.

The Marketing Authorisation Holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

1.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.9.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.9.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. *Therapeutic context*

FCS is a severe and ultrarare genetic disease that is present from childhood and is characterized by extremely high fasting triglyceride (TG) levels, typically over 10 mmol/L, representing the top 0.1% of TG levels. FCS has an estimated prevalence of 0.2 per 10.000 in Europe.

Patients with FCS have inherited recessive defects that limit or impair functionality of LPL, an essential enzyme in hydrolysis of plasma TGs, resulting in chylomicronemia and consequently leading to extremely high fasting TG levels (>10 mmol/L) (Hegele 2020).

The severe elevations in TG routinely seen in FCS patients lead to various serious complications and debilitating symptoms including acute pancreatitis (which can be fatal), chronic and even daily

abdominal pain, diabetes mellitus, and hepatic steatosis. Quality of life (QoL) and cognitive issues include difficulty concentrating, 'brain fog', anxiety, fear, and worry. Patients with FCS are also at risk of large (often >500 mg/dL) increases in postprandial TG, which can lead to severe abdominal pain and places patients at risk for postprandial pancreatitis and pancreatitis-related hospitalisation. Pancreatitis is a major life-threatening complication of FCS caused by digestion of large amounts of chylomicron-TGs by pancreatic lipases, which can be fatal and may also be complicated by other life-threatening conditions such as sepsis, acute respiratory distress syndrome, hypovolemic shock, and renal failure. Recurrent episodes of acute pancreatitis occur in ≥50% of patients with FCS and can lead to chronic pancreatitis, whereby patients develop pancreatic failure, insulin-dependent diabetes, and chronic abdominal pain. The overall associated mortality rate for recurrent acute pancreatitis is 5% to 6% and increases to 30% for patient subgroups with severe complications (infected pancreatic abscess or persistent multiple organ failure that can result in pancreatic necrosis) (Gaudet 2016; Stroes 2017).

The risk of acute pancreatitis increases relative to the elevation in serum TG levels, with the incidence of acute pancreatitis increasing 3% to 4% for every 100 mg/dL (1.13 mmol/L) increase in TG levels (Gelrud 2017; Scherer 2014). Thus, the current goal of treatment in FCS is to maintain TG values well below 10 mmol/L (885 mg/dL), the threshold above which the risk of acute pancreatitis significantly increases (Blom 2018).

The mainstay for management of FCS is a diet severely restricted in fat and simple carbohydrate, and avoidance of alcohol as well as drugs known to raise TG levels (Brahm 2015; Mach 2020; Stroes 2017). However, achieving triglyceride values <11.3 mmol/L (<1000 mg/dL) remains challenging even for dietician and medical team supported patients (Gaudet 2010). Long-term compliance with such a dietary fat restriction diet is extremely difficult to maintain, can negatively impact patients' quality of life, and does not mitigate the high risk of pancreatitis in all patients (Blom 2018; Buxbaum 2018).

Lipid-lowering medications to lower TG levels are for the most part ineffective in FCS as they work mainly by decreasing very low-density lipoprotein (VLDL) output from the liver and/or increasing LPL activity. Decreasing VLDL secretion is not likely to have a major effect on TGs in FCS because chylomicrons (CMs) arising in the gut account for the bulk of TGs in such patients. Drugs designed to increase LPL activity will also not benefit patients who have no or minimal residual inducible LPL activity (Blom 2018). Thus, conventional pharmacological therapies (fibrates, niacin, statins), other than omega-3 fatty acids, which lower plasma TG levels predominantly by the stimulation of LPL activity, are rendered less effective in the case of a severely dysfunctional LPL protein and/ or its major cofactors (Blom 2018; Brahm 2015; Stroes 2017; Surendran 2012).

The therapeutic options for treating FCS in the EU are limited. Two products are approved in the EU for the treatment of FCS in adult patients with genetically confirmed FCS. Waylivra (volanesorsen sodium) is an antisense oligonucleotide inhibitor of apolipoprotein C-III (apoC3) gene (APOC3) with a conditional marketing authorisation for use as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and TG lowering therapy has been inadequate. Tryngolza (olezarsen) is an antisense oligonucleotide-triantennary N-acetylgalactosamine conjugate approved as an adjunct to diet in adult patients for the treatment of genetically confirmed FCS.

At the time of marketing authorisation of Redemplo (plozasiran), there are no products authorised in the EU for the treatment of patients with FCS without the restriction of genetically confirmation of the diagnosis, which underpins the unmet medical need.

2.2. *Aspects of development*

Clinical studies supporting the use of plozasiran in patients with FCS are summarized in Table 2 below. The main body of evidence supporting the efficacy of plozasiran in patients with FCS is based on data from the pivotal phase 3 AROAPOC3-3001 in patients with FCS, which includes a completed double-blind, placebo-controlled period and an ongoing open-label extension period. Supportive evidence of efficacy is provided by data from the 2 randomised dose-finding phase 2b studies AROAPOC3-2001 and AROAPOC3-2002 and an open-label study AROAPOC3-2003 in related populations, including severe hypertriglyceridaemia (SHTG) and mixed hyperlipidaemia.

Table 2: Clinical Studies Supporting the Use of Plozasiran in Patients With FCS

Study No./Name/Title	Population	Study Design	Study Duration
Pivotal Study			
AROAPOC3-3001 (PALISADE) Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Familial Chylomicronemia Syndrome	Adult subjects with genetically confirmed or clinically diagnosed FCS	Randomized DB period, 12 months (completed) • Plozasiran 25 mg or PBO randomized 2:1 (n=26:13) • Plozasiran 50 mg or PBO randomized 2:1 (n=24:12) Total of 4 doses of plozasiran or matching placebo administered SC Q3M OLE Period A (ongoing) Subjects randomized to plozasiran continued to receive their assigned original treatment (blinded). Subjects who received placebo switched to active treatment in the OLE based on the initial dosing group to which they were assigned. OLE Period B (ongoing) All subjects switched to the selected clinical dose (plozasiran 25 mg Q3M).	52 weeks in randomized DB Period and 104 weeks in OLE Period

Study No./Name/Title	Population	Study Design	Study Duration
Supportive Efficacy and Safety Studies			
AROAPOC3-2001 (SHASTA-2) A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia	Adult subjects with SHTG (including 5 subjects with FCS)	<u>Randomized DB period (completed)</u> • Plozasiran 10 mg (n=54) or PBO (n=20) • Plozasiran 25 mg (n=55) or PBO (n=20) • Plozasiran 50 mg (n=57) or PBO (n=20) Total of 2 doses of plozasiran or matching placebo administered SC on Day 1 and Week 12 for each dose cohort.	48 weeks in randomized DB Period
AROAPOC3-2002 (MUIR) A Double-blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Hyperlipidemia	Adult subjects with mixed hyperlipidemia	<u>Randomized DB period (completed)</u> • Plozasiran 10 mg (n=67) or PBO (n=21) Day 1 and Week 12 • Plozasiran 25 mg (n=67) or PBO (n=22) Day 1 and Week 12 • Plozasiran 50 mg (n=66) or PBO (n=22) Day 1 and Week 12 • Plozasiran 50 mg (n=66) or PBO (n=22) Day 1 and Week 24 Total of 2 doses of plozasiran or matching placebo administered SC.	48 weeks in randomized DB Period

Study No./Name/Title	Population	Study Design	Study Duration
Other Supportive Studies			
AROAPOC31001 A Phase 1 Single and Multiple Dose-escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Effects of ARO-APOC3 in Adult Healthy Volunteers as well as in Severely Hypertriglyceridemic Patients and Patients with FCS	Adults: healthy volunteers, patients with SHTG, and patients with FCS	Open-label treatment (completed) Phase 1 study of 20 subjects with FCS or CM (including n=4 with genetically confirmed FCS). All subjects received open-label plozasiran 50 mg Q4W for 2 doses [Other cohorts not providing efficacy or safety results for FCS: healthy volunteers (n=52, plozasiran or PBO) and patients with SHTG (n=40, plozasiran or PBO)]	12 weeks
AROAPOC3-1002 A Phase 1, Randomized, Double-Blind, Placebo- and Positive-Controlled, Crossover Thorough QT/QTc Study to Evaluate the Effects of a Supratherapeutic Dose of ARO-APOC3 on Cardiac Repolarization in Healthy Subjects	Healthy adult subjects	Randomized DB, crossover (completed) Phase 1 study of 36 healthy subjects, randomized to ABC, ACB, BAC, BCA, CAB, or CBA with 1 week between single doses of the following: (A) plozasiran 100 mg SC; (B) placebo SC; and (C) moxifloxacin 400 mg tablet	4 weeks
AROAPOC3-1003AAn Open-Label, Randomized, Crossover Study to Compare the Relative Bioavailability of 2 Formulations and Presentations (Prefilled Syringe and Vial) of Plozasiran (Also Known as ARO-APOC3) Administered Subcutaneously in Healthy Adult Subjects	Healthy adult subjects	Open-label, randomized, crossover (completed) Phase 1 study of 20 healthy subjects, randomized to AB or BA with 6 weeks between single doses of plozasiran 25 mg, formulated as (A) 200 mg/mL vial and (B) 50 mg/mL PFS (a second cohort of 20 healthy subjects to compare 50 mg formulations was stopped after 15 subjects had received their first dose)	8 weeks
AROAPOC3-2003 A Phase 2 Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of ARO-APOC3 in Adults with Dyslipidemia	Adult subjects with hyperlipidemia from AROAPOC3-2001 and AROAPOC3-2002	Open-label extension (ongoing) Initially all subjects received plozasiran at the same dose or PBO-matched dose. Up until protocol Amendment 2 (dated 22 Nov 2022), subjects were on their assigned dosing per respective protocols. As of 04 Dec 2023, all subjects who were not on the 25 mg Q12W were switched to 25 mg Q12W.	24 months

2.3. *Description of the product*

Mode of action

Plozasiran is a small interfering RNA (siRNA, double-stranded oligonucleotide) conjugated with N acetylgalactosamine to facilitate delivery to and uptake by hepatocytes. In hepatocytes, plozasiran selectively degrades the mRNA for apolipoprotein C3 (APOC3) through the RNA interference

mechanism resulting in reduced levels of hepatic and serum APOC3 protein. This, in turn, enhances the activity of lipoprotein lipase and hepatocyte uptake of TG-rich lipoprotein remnants leading to decreases in serum TG.

Therapeutic indication (agreed):

Redemplo is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with familial chylomicronaemia syndrome (FCS) (see section 4.2 for patient selection criteria).

Posology:

The recommended dose of plozasiran is 25 mg administered as a single subcutaneous injection every 3 months.

2.4. *Inspection issues*

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

3. Quality aspects

3.1. *Introduction*

The finished product is presented as a solution for injection in pre-filled syringe containing 25 mg plozasiran (as plozasiran sodium) in 0.5 mL solution as active substance.

Other ingredients are sodium chloride and water for injections.

The product is available in type I glass pre-filled syringe with a bromobutyl stopper and needle with shield, as described in section 6.5 of the SmPC.

3.2. *Active substance*

3.2.1. General information

The active substance plozasiran is a small interfering ribonucleic acid (siRNA) duplex comprising of two complementary RNA strands conjugated to a tris-(N-acetylgalactosamine) moiety.

Both the sense strand and the antisense strand contain a mixture of 2'F modified and 2'-OMe modified ribonucleotides. Both strands contain twenty-one 2'-modified ribonucleotide residues, one of which (on the sense strand) is a 2'-O-methylinosine nucleotide. Additionally, the sense strand also contains two inverted abasic nucleotides, one at the 3'-end and one at the penultimate position of the 5'-end, and a tris-(N-acetylgalactosamine)-based targeting moiety at the 5'-end. Finally, the internucleotide linkages include a total of seven phosphorothioate linkages with the rest being phosphate linkages.

The chemical name of plozasiran sodium is ([1' -de(6-amino-9H-purin-9-yl)]dA-(5' →5')-sp-Am-Cm-Gm-Gm-Gm-Am-Cm-Am-(2' -deoxy-2' -fluoro)G-(2' -deoxy-2' -fluoro)U-(2' -deoxy-2' -fluoro)AUm-Um-Cm-Um-Cm-Am-Gm-Um-Im-Am-(3' →3')-sp-[1' -de(6-amino-9H-purin-9-yl)]dA),3' -[O-[cis-4-[(3S,8S)-17-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-3,8-bis[[[2-[2-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]ethoxy]ethyl]amino]carbonyl]-1,6,11-trioxo-15-oxa-2,7,12- triazaheptadec-1-yl]cyclohexyl] hydrogen phosphorothioate] sodium salt, complex with RNA(Um-sp-(2'-deoxy-2'-fluoro)C-sp-Am-sp-(2'-deoxy-2'-fluoro)C-Um-(2'-deoxy-2'-fluoro)G-Am-Gm-Am-Am-Um-(2'-deoxy-2'-fluoro)A-Cm-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)U-Cm-(2'-deoxy-2'-fluoro)C-Cm-(2'-deoxy-2'-fluoro)G-sp-Um) sodium salt (1:23:1:20) corresponding to the molecular formula $C_{493}H_{611}F_{11}N_{164}Na_{43}O_{311}P_{43}S_7$ (sodium form).

It has a relative molecular mass of 16563.9 Da (sodium salt) and the following structure:

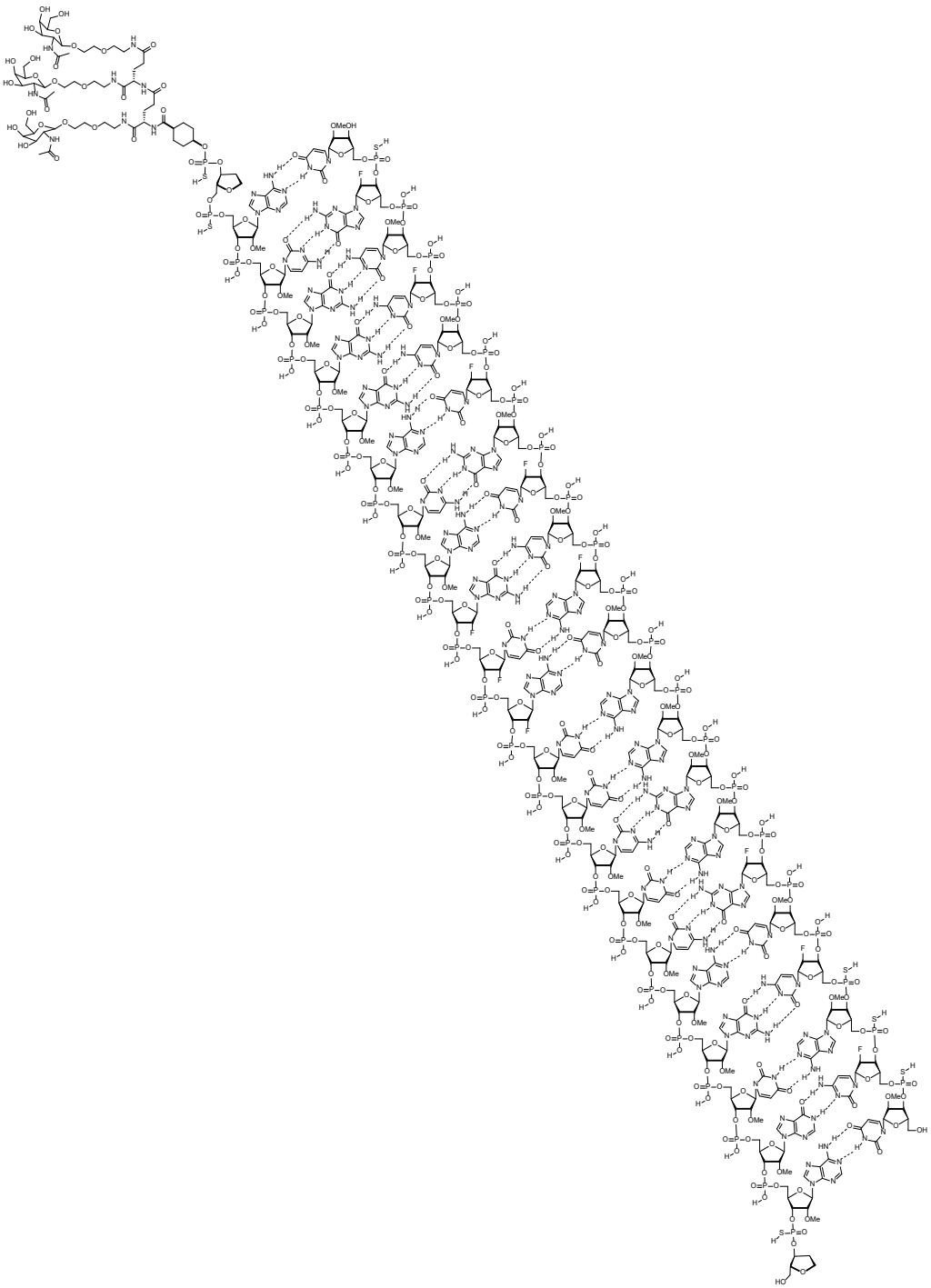


Figure 1: Active substance structure

The chemical structure of plozasiran was elucidated by a combination of spectroscopic techniques: Electrospray Ionization Mass Spectrometry (ESI-MS) and tandem Mass Spectrometry (MS/MS) for sequence confirmation and molecular weight determination for each of the single strands. Nuclear Magnetic Resonance (NMR) (^{1}H, ^{13}C, ^{19}F, ^{31}P), Infrared (IR), Ultraviolet (UV), and Circular Dichroism (CD) spectroscopy were used to confirm the structure of the active substance. The melting temperature (Tm) was also determined.

The active substance is a hygroscopic white to off-white solid, freely soluble in water. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD) and indicate that plozasiran is an amorphous powder. Thereby, polymorphism is not relevant.

Plozasiran exhibits stereoisomerism due to the presence of four phosphorothioate linkages in the antisense strand which lead to 16 possible diastereomers, and of three phosphorothioates in the sense strand which lead to 8 possible diastereomers. the provided data on the characterisation of diastereomeric ratios at phosphorothioate linkages demonstrate that synthesis is under inherent and consistent stereo control.

3.2.2. Manufacture, characterisation, and process controls

The active substance is manufactured at one site. Satisfactory GMP documentation has been provided.

The active substance is synthesised via solid-phase oligonucleotide synthesis (SPOS) using well defined starting materials with acceptable specifications. The manufacturing process consist of the following 8 main steps: synthesis of the individual single strands (step 1), cleavage and deprotection of the individual single strands (step 2), ultrafiltration of the individual crude single strand solutions (step 3), purification of the single strands individually by anion-exchange chromatography (step 4), concentration and desalting of the individual single strands via ultrafiltration (step 5), mixing of the two single strand solutions and annealing to form the duplex (step 6), concentration in vacuo of the duplex solution (step 7) and lyophilization, sampling, and packaging of the active substance (step 8).

The manufacturing process has been described in sufficient detail. Adequate in-process controls are applied during the synthesis. With respect to specification limits of the IPCs, the applicant proposed to re-evaluate and tighten them where possible, especially those of purity and impurities, when data from enough commercial batches (additional 30 batches) are available (see discussion below on REC1).

The starting materials used in the manufacture of plozasiranhave been described. During the procedure two Major Objections have been raised on the control strategy for critical impurities of two starting materials (MO1 & MO2).

In response to the MOs, the applicant updated its control strategy for critical impurities of both starting materials including appropriately validated analytical methods and well justified limits. The applicant presented adequate discussion on potential impurities.

Adequate specifications are also provided for the raw materials.

Process validation has been adequately performed on three consecutive commercial scale batches of the active substance at the proposed manufacturing facility.

Sufficient information on the manufacturing process history and changes made to the manufacturing process and/or manufacturing sites of the active substance used in producing non-clinical, clinical and production scale batches has been provided. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Related impurities have been analysed using two orthogonal

denaturing HPLC methods. Potential structures were assigned based on their molecular weight and comparison to synthesised reference compounds. Five impurities that were found present above 0.5% in the batch of plozasiran used for chronic toxicological and clinical studies were designated as specified impurities (A – E). As it is not possible to resolve all components of the specified impurities, a grouping strategy is applied and was considered acceptable. The identity, structure, and origin of all components of the specified impurities are provided.

The active substance is packaged in gamma irradiated high density polyethylene (HDPE) bottle with polypropylene (PP) screw closure placed in a secondary tri-layered bag (PE/Al/PE), which comply with Commission Regulation (EU) 10/2011, as amended.

3.2.3. Specification

The active substance specification includes tests for appearance (visual), identity (LC-MS, Denaturing IP-RP UHPLC, Non-denaturing IP-RP UHPLC, thermodynamic profile), purity and impurities (Denaturing IP-RP UHPLC, Non-denaturing IP-RP UHPLC, Denaturing AEX HPLC), water content (KF), assay (UV), sodium content (Flame Atomic absorption spectroscopy), heavy metals (ICP-MS), residual solvents (GC-FID, HPLC), sulfur content (^{31}P NMR), fluorine content (^{19}F NMR), pH of solution, bacterial endotoxins (Ph. Eur.) and bioburden (Ph. Eur.).

The active substance specification covers all relevant quality attributes.

Several orthogonal methods are used to determine identity and purity/impurities. Impurities as determined by UHPLC methods are grouped according to their retention times. The concept of grouping of impurities is considered adequate. The acceptance criteria are based on toxicological data, batch data, stability data, process understanding and manufacturing capability. Upon CHMP request, the acceptance limits for purity, total impurities and all specified impurities (groups and individual) controlled by the denaturing AEX HPLC and denaturing IP-RP UHPLC methods as well as for the duplex content, single strand regions and total impurities controlled by the non-denaturing IP-RP UHPLC method were tightened based on the available batch release and stability data. The revised impurity limits are considered acceptable. Although based on the currently available release and stability data, further tightening may be feasible as the currently available data is still limited. During the procedure the applicant proposed to re-evaluate the specification limits when data from a sufficient number of commercial batches (additional 30 batches) are available. This point is raised as Recommendation for future quality development (REC1).

The proposed acceptance limits for the specified impurities A-G all exceed the qualification threshold of 1.0%, but have been adequately qualified based on toxicological data.

Residual solvents are controlled according to ICH Q3C limits. There are no ICH class 1 solvents used in the manufacturing process, however, benzene can be present as a potential contaminant in solvents such as ethanol or toluene which are used during manufactureDuring the procedure a MO has been raised to request to tighten the limit for benzene in toluene specification and to introduce benzene control to the ethanol specification (MO3). To address the CHMP question, routine control of benzene has been introduced to the active substance specification in line with ICH limits. In addition, the limit for benzene in ethanol complies with Ph. Eur.

In relation to assay, CHMP requested to tighten the limits for assay by UV in line with batch data. The limits were revised accordingly.

Upon CHMP request, the acceptance criteria for melting temperature and sodium content were also tightened during the procedure based on method capability, process performance, and batch-to-batch variability.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for active substance and impurities has been presented.

Batch analysis data from commercial scale batches and from further supporting batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

3.2.4. Stability

Stability data from at least 3 commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions (-20ºC ± 5ºC) and under intermediate conditions (5ºC ± 3ºC) and for up to 6 months under accelerated conditions (25ºC ± 2ºC / 60 ± 5% RH) according to the ICH guidelines were provided. Supportive data from 3 additional batches used in clinical studies were provided.

The following parameters were tested: appearance, water content, assay, identity (by IP-RP UHPLC denaturing and non-denaturing), purity and impurities (by denaturing and non-denaturing IP-RP UHPLC and AEX HPLC), pH, bacterial endotoxins and bioburden. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long term conditions, with exception of results which were not considered representative. All batches were shown to be stable when stored under long term conditions.

Results on stress conditions (acid, base, heat, oxidation, UV exposure) were also provided on 1 batch. Photostability testing following the ICH guideline Q1B was performed on 1 batch. It was demonstrated that the active substance is not sensitive to light exposure.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months at -20ºC ± 5ºC in the proposed container.

3.3. *Finished medicinal product*

3.3.1. Description of the product and pharmaceutical development

Redemplo 25 mg solution for injection in pre-filled syringe (PFS) is a sterile and ready-to-use solution intended for a single subcutaneous (SC) administration. The solution is a clear, colourless to yellow solution, essentially free of visible particles. The formulation contains 50 mg/mL plozasiran free acid, sodium chloride and water for injection.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Pharmaceutical development has been presented in sufficient detail.

The final formulation intended for commercial use has not been used in the pivotal phase 3 clinical study or any of the phase 1-3 clinical studies. Comparability studies between the batches used in the clinical studies and final formulation have been presented.

The finished product is sterilised by using a combination of sterile filtration, pre-sterilised containers and aseptic processing. During the development of finished product, steam sterilisation at 121°C was evaluated, but resulted in a significant decrease in purity. It was concluded that steam sterilisation was not suitable. The choice of the sterilisation method is considered justified. Adequate filter validation studies have been performed confirming the suitability of the sterilising filters.

Sufficient information on the container closure development has been provided. The syringe barrels are made of clear Type I glass, which is preferred, especially as the finished product is not sensitive to light exposure. Compatibility of the finished product with the primary packaging components was sufficiently demonstrated in the formal stability studies. Container closure integrity and dose accuracy (extractable volume) are routinely tested at release and during storage. Extractable studies have been adequately performed, demonstrating that no extractables were found at relevant levels from the glass barrels, plunger stopper and needle shield under exaggerated conditions. No further leachable studies are needed.

The primary packaging is type I glass pre-filled syringe with a bromobutyl stopper and needle with shield. The material complies with Ph.Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

During the procedure, a MO has been raised by the CHMP to request submission of a positive Notified Body Opinion (NBOp) for the ready-to-use pre-sterilised prefilled syringes and stoppers (MO4). In response, the applicant submitted the requested NBOp on the conformity of the integral device part of the finished product with the relevant GSPRs according to Annex I of the Regulation (EU) 2017/745 (MDR).

3.3.2. Manufacture of the product and process controls

The finished product is manufactured at one site. For all sites involved in the manufacture, control and batch release of the finished product, sufficient evidence of GMP compliance has been provided.

The manufacture of the finished product includes the following main steps: the dissolution of plozasiran in saline solution, filtration through a 0.22 µm filter for bioburden reduction into a sterile bag, followed by sterile filtration through two 0.22 µm filters in series and aseptic filling at a target fill volume.

The manufacturing process has been described in sufficient detail, including process parameters, in-process controls and holding times.

The manufacturing process is considered non-standard. The manufacturing process has been adequately validated at the proposed commercial scale, including the assembly of the prefilled syringe. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

3.3.3. Product specification

The finished product release specification includes tests for appearance (visual), identity (HPLC-MS, Denaturing IP-RP UHPLC, Non-Denaturing IP-RP UHPLC), assay (UV), purity and impurities (Denaturing IP-RP UHPLC, Non-Denaturing IP-RP UHPLC, Denaturing AEX HPLC), container content (extractable volume), dose uniformity (Ph.Eur.), pH, container closure integrity, break loose and glide force (in-house), bacterial endotoxins (Ph. Eur.), osmolality, particulate matter and sterility (Ph. Eur.).

The finished product specification are in accordance with the requirements of the Ph. Eur. on parenteral preparations and ICH Q6A.

In line with the discussion under the section on the active substance specification, it was requested to the applicant to tighten the finished product impurity limits according to available batch release and stability data. In response to the question, the applicant provided acceptable revised impurity limits. In addition, the applicant committed to further re-evaluate the specification limits when data from a sufficient number of commercial batches (additional 30 batches) is available (REC1).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The analytical methods used for the finished product specification are the same as the ones used for the active substance specification. Reference standards are also the same as for the active substance specification. Satisfactory information has been presented.

Batch analysis results are provided for commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.3.4. Stability of the product

Stability data from at least 3 commercial scale batches of finished product stored for up to 24 months under long term conditions (5ºC ± 3ºC), up to 24 months at intermediate conditions (25ºC / 60% RH) and for up to 9 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, pH, identity, purity and impurities, endotoxins, osmolality, container content, content closure integrity, syringe functionality (break loose and glide force), particulate matter (sub-visible particles) and sterility.

The analytical procedures used are stability indicating.

Under accelerated conditions, considerable decrease in purity and increase in total impurities was observed with the denaturing IP-RP UHPLC and AEX HPLC methods. Under intermediate conditions a slight decrease in purity and increase in total impurities was observed up to 18 months storage.

No clear trends or changes were observed in any of the other tested parameters at all three storage conditions.

Studies were performed to demonstrate that after storage in a refrigerator the finished product can be safely stored for 30 days at room temperature. Samples pulled from 2-8°C at 12, 18, 24 and 36 months are stored at 25°C/60% RH for 30 days. Available results up to at 18 months for the primary stability batches have been provided, showing. Results show no clear negative impact on finished product quality.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and results demonstrate that the product is not sensitive to light exposure when stored in its primary container closure system.

Based on available stability data, the proposed shelf-life of 2 years at the proposed storage conditions "Store in a refrigerator (2°C – 8°C). Do not freeze" as stated in the SmPC (section 6.3) are acceptable. In addition, the proposal that the finished product may be stored in the original carton, within its overall shelf life of 2 years, for a single period of up to 30 days at room temperature (15°C – 25°C) is supported by the presented data and considered acceptable.

The need to store the finished product in a refrigerator at 2-8°C was questioned during the procedure based on the presented stability data. Finished product storage conditions should not be unnecessarily restrictive in accordance with the EMA Guideline on Declaration of storage conditions. Since it was demonstrated that the finished product is stable at 25°C/60% RH for up to 18 months, a storage condition of at least 'Store below 25°C' may be feasible. The applicant committed to re-evaluate the storage condition once additional stability data is obtained. This point is raised as recommendation for future quality development (REC2).

3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

3.4. *Discussion on chemical, pharmaceutical and biological aspects*

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure, four MOs have been raised pertaining to: 1) & 2) the control strategy for critical impurities of two starting materials (MO1 & MO2) 3) benzene limits in solvents (toluene and ethanol)

used in the active substance manufacture (MO3); 4) missing NBOp for the integral device part of the finished product (MO4).

The applicant adequately addressed the four MOs by updating the control strategy for critical impurities of the two starting materials (MO1 & MO2); introducing benzene control to the active substance specification (MO3) and by providing a valid NBOp for the integral device part of the finished product (MO4).

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to: 1) Re-evaluation and tightening of the active substance and finished product specification limits (including those of the active substance IPCs and intermediate specifications), especially those of purity and impurities, when data from a sufficient number of commercial batches will be available; 2) Re-evaluation and revision of the finished product temperature storage conditions to 'Store below 25°C' or 'Store below 30°C' if possible, once more stability data are available. These points are put forward and agreed as recommendations for future quality development.

3.5. *Conclusions on chemical, pharmaceutical and biological aspects*

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.6. *Recommendation(s) for future quality development*

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The active substance and finished product specification limits (and consequently those of the active substance IPCs and intermediate specifications), especially those of purity and impurities, are to be re-evaluated and tightened where possible when data from a sufficient number of commercial batches (additional 30 batches) are available (REC).

- Once more stability data are available (preferably also at 30°C/65% RH) the applicant should revise the finished product temperature storage conditions to 'Store below 25°C' or 'Store below 30°C' if possible based on the data by means of a variation post-approval (REC).

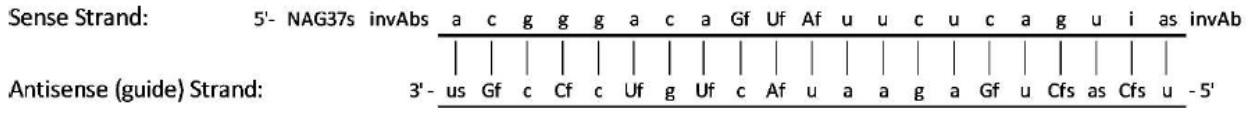
4. Non-clinical aspects

4.1. *Introduction*

Plozasiran is a siRNA (double-stranded oligonucleotide) conjugated with N-acetylgalactosamine to facilitate delivery to and uptake by hepatocytes. In hepatocytes, plozasiran selectively degrades the mRNA for apolipoprotein C3 (APOC3) through the RNA interference mechanism resulting in reduced levels of hepatic and serum APOC3 protein.

The plozasiran molecule is modified at the 2' positions of the ribose subunits with either fluorine (2'F) or methoxy (2'MeO) groups. This chemical modification of the ribose subunits protects the complex

from ribonuclease and decreases the likelihood of activation of the innate immune system. Both the antisense and sense strands of plozasiran contain 21 2' modified nucleotide subunits. In addition to containing the non-canonical nucleotide 2'O-Me inosine, the sense strand additionally contains two inverted abasic subunits, one at the 3' end and one at the penultimate position of the 5' end, and a N-acetyl galactosamine targeting moiety (NAG37) at the 5' end. The sense strand includes three phosphorothioates and the antisense strand includes four phosphorothioates, as shown below:



Abbreviations: n = 2'O-Me; Nf = 2'F; inv = inverted; Ab = abasic; i = inosine; s = phosphorothioate; underline represents the hybridization region; NAG37 = NAG targeting moiety.

The primary pharmacodynamics (PD) of plozasiran was studied in the transgenic TgAPOC3 mouse model and in monkey. Secondary PD was investigated *in silico* and *in vitro*. A standard battery of safety pharmacology studies was performed. Regarding pharmacokinetics (PK), single dose absorption studies were conducted in rat and monkey. Toxicokinetic (TK) assessments in mouse, rabbit, rat and monkey were performed as part of repeat-dose toxicity studies. *In vitro* PK studies evaluated the binding and (metabolic) stability of plozasiran. General toxicity was tested in repeat-dose studies in rat and monkey. A full battery of genotoxicity tests was performed. Carcinogenic potential of plozasiran was tested in a 6-month transgenic mouse study. For the evaluation of developmental and reproductive toxicity, FEED and PPND studies were conducted in rat, and EFD studies in both rat and rabbit. The safety pharmacology, pivotal toxicology and TK studies (except method validation) were conducted in compliance with GLP.

4.2. *Analytical methods*

The bioanalytical methods were developed to support PK/TK analysis of plozasiran in mouse, rat, monkey and rabbit (K2EDTA) plasma samples from both GLP and non-GLP toxicology studies. Plasma and tissue concentrations of the antisense strand of plozasiran were quantified by using a complementary fluorescence-labelled peptide nucleic acid (PNA) probe in combination with anion-exchange liquid chromatography with fluorescence detection (AEX-LCFL). This method was validated for all species to be used in the pivotal GLP studies with respect to intra- and inter-assay accuracy and precision, sensitivity, linearity, reproducibility, matrix effect and long-term stability. The analytical range (lower limit of quantification (LLOQ)-upper limit of quantification (ULOQ)) of measuring plozasiran in plasma was 1-500,000 ng/mL. Incurred sample reproducibility (ISR) for non-clinical sample analysis was conducted once per species.

AEX-LFCL was also used for the determination of plozasiran in tissue homogenates of rat and monkey. This method was not validated but considered fit for purpose. The lower limit of quantification (LLOQ) of measuring plozasiran was 10 ng/g and 40 ng/g in fetal and other tissues, respectively.

In vitro metabolic stability of plozasiran in serum and liver S9 extracts was evaluated using a high-performance liquid chromatography coupled high resolution mass spectrometry (LC-HRMS) or LC-MS/MS for quantitation. The amounts of protein bound plozasiran in rat, monkey, and human plasma were evaluated using native gel electrophoresis with SYBR gold staining for detection.

4.3. *Pharmacology*

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

To support the *in vitro* primary pharmacology of plozasiran, no dedicated studies were conducted. Limited information on the silencing of the on-target gene *APOC3* can be derived from the secondary PD study (SR-00676) in human hepatocellular carcinoma cell lines (see section 5.3.1.1). At all concentrations tested, plozasiran potently silenced *APOC3* (expression relative to negative control <4% in Huh7 cells at 0.5 nM and <20% in Hep3b cells at 0.1 nM). Since a low-concentration range was not included, a concentration-response relationship or an IC50 were not established.

Regarding homology of the target gene sequence in different species, the *APOC3* gene sequence in monkey is identical to that of humans, hence, plozasiran is expected to be pharmacologically active at clinically relevant doses in monkey. The rodent transcript has 6-7 mismatches to the human sequence, though a PD study in rats showed partial cross-reactivity of plozasiran at high doses. Plozasiran has 1 mismatch against the rabbit *Apoc3* reference sequence.

The *in vivo* primary pharmacology of plozasiran was studied using a transgenic dyslipidemic mouse model expressing human *APOC3* (TgAPOC3) and healthy or dyslipidemic monkeys. An exploratory study in rats was also performed.

In the transgenic dyslipidemic mouse model (SR-006740), plozasiran was administered by a single SC injection. After one week, doses of 0.25, 0.5, 1 or 3 mg/kg resulted in maximum mean serum APOC3 protein reductions of 66%, 81%, 84% and 91%, respectively. The high levels of human APOC3 transgene expression in this model caused high levels of serum TG, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), all of which were dose-dependently reduced after treatment. Maximum mean reductions of TG, TC, and LDL-C were 91%, 45%, and 64%, respectively. At the end of the study (day 37), dose-dependent reduction in liver *APOC3* mRNA levels was shown.

In rats (SR-01070), despite that pharmacological activity of plozasiran was not expected due to mismatches with the rodent transcript, *Apoc3* mRNA in the liver was reduced up to ~50% after weekly dosing at 60 or 120 mg/kg. Serum TG were reduced by 75% even at 60 mg/kg. Lower doses were not tested.

In regular chow-fed cynomolgus monkeys (SR-00675), two SC doses of plozasiran at 4 mg/kg, 3 weeks apart, reduced *APOC3* expression in the liver by more than 80%, which was maintained for at least 4 weeks after the end of treatment. Serum APOC3 protein levels were only reduced by 50-60%. The remaining serum APOC3 is likely primarily derived from the small intestine. In this study, there was no effect on serum lipids.

In rhesus monkeys maintained on high fructose corn syrup diet (SR-00822), two SC doses of plozasiran at 4 mg/kg, 4 weeks apart, reduced APOC3 protein levels in serum by 60-80%. Liver samples were not collected. Only the animals with a marked diet-induced increase in serum APOC3 and lipid levels at the start of treatment, had an improved lipid profile (reduced TG, cholesterol and LDL-C, and increased HDL-C) compared to the saline-treated control animals.

4.3.1.2. Secondary pharmacodynamics

The secondary pharmacology of plozasiran was assessed by an in-silico analysis which aimed at identifying any human expressed off-target gene candidates, including regulatory RNAs, with partial complementarity to the sense or antisense strands of plozasiran. There were no homologies with any known off-target RNAs with full complementarity.

One off-target gene candidate (TRAF3) has a single mismatch (position 10) to the sense strand of plozasiranTRAF3 is typically not expressed in healthy liver or kidney, though it could be expressed in certain disease states. Literature indicates that TRAF6 knockdown would rather have a protective effect.

20 genes and 315 genes were identified with 2 and 3 mismatches to plozasiran, respectively. None of the genes with 2 mismatches contained a neutralizing SNP, while 52 of the genes with 3 mismatches contained a neutralizing SNP. Detailed information on the off-target candidates with up to 2 mismatches was presented, including gene identity, target sequence and mismatch locations, tissue expression, known sequence variants found in the population, sequence similarity of the target sequence in animal models, and literature information regarding the effects of gene silencing.

Nine off-target human gene candidates were selected for in vitro screening in human hepatocellular carcinoma (HUH7, Hep3B) or in renal cell carcinoma (A498) cell lines: TRAF3, HNF1B, ITIH4, ITIH5, MAGI2, NAMPT, OSMR, PCCA, and RIT1. Plozasiran did not reduce the expression of the 9 tested genes up to a concentration of 500 nM.

4.3.1.3. Safety pharmacology

A standard GLP-compliant battery of safety pharmacology studies was performed.

At a concentration of 6.4 µM (100 µg/mL), plozasiran did not affect hERG tail current amplitude *in vitro*. This represents a large safety margin to the human unbound Cmax (15.6 ng/mL) at the proposed therapeutic dose.

No effects on cardiovascular parameters were observed in cynomolgus monkeys up to 300 mg/kg (SC) plozasiran.

Plozasiran treatment up to 300 mg/kg (SC) had no effect on the central nervous system or respiratory system of rats.

4.3.1.4. Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions were performed, and this was found to be acceptable.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

A dedicated IV and SC PK study was conducted in rat and cynomolgus monkey to determine the major PK parameters, including SC bioavailability, after a single dose of 3 mg/kg plozasiran.

In male Sprague Dawley rats (n=3 per timepoint), plozasiran was absorbed rapidly with a T_{max} of 0.25 h after a single SC dose of 3 mg/kg. Thereafter, elimination of plozasiran from the plasma was rapid, with mean plasma levels near the LLOQ (1.00 ng/mL) at 12 hours postdose and beyond, resulting in a terminal elimination half-life ($t_{1/2}$) of 0.6 and 1.4 h after single IV and SC dose, respectively. The volume of distribution after the IV dose was 41.8 mL/kg, which indicates a low distribution volume, but this may be influenced by plozasiran's fast tissue uptake in liver and kidney. Upon IV administration, the systemic clearance (CL) was approximately 5.8 mL/min/kg, meaning ~11% of hepatic blood flow, also suggesting high receptor-mediated uptake in the liver given the low free plasma fraction. The mean systemic bioavailability of plozasiran was approximately 19% after SC administration.

In male monkeys (n=3), plozasiran was also rapidly absorbed with a T_{max} of 1.5 h after a single SC dose. Elimination of plozasiran from the plasma was rapid, with mean plasma levels near the LLOQ (1.00 ng/mL) at 24 hours postdose and beyond, resulting in a $t_{1/2}$ of 1.1 and 2.5 h after single IV or SC dose, respectively. The volume of distribution after the IV dose was 259 mL/kg, which is consistent with distribution beyond the plasma volume, and the mean systemic clearance (CL=695 mL/h/kg) was approximately 27% of hepatic blood flow. Both values indicate efficient receptor-mediated uptake in the liver. The mean systemic bioavailability of plozasiran was approximately 40% after SC administration.

In addition, TK parameters (C_{max}, T_{max}, AUC_{0-t}, $t_{1/2}$) were evaluated as part of the toxicity studies (up to 37 weeks) conducted in rat, monkey, transgenic mice and rabbits with plozasiran given once every 2, 4 or 8 weeks. In general, no differences in exposure were observed between male and female animals, and C_{max} and AUC generally increased dose proportional in all non-clinical species. Determination of plasma $t_{1/2}$ values was hampered in multiple studies in mice and rats since no distinct elimination phase could be determined, however the plasma $t_{1/2}$ appeared to be much longer in mice (24.5-279 h) as compared to rat (2.23-3.96 h). Upon multiple dosing, no accumulation in plasma was observed in any non-clinical species.

Generally, these findings reflect the redistribution from the blood to the target tissue rather than elimination from the body, since plozasiran was measurable in the liver of rats and mice for more than 4 weeks after a single dose (see Section 3.3). These findings are in line with other GalNac-conjugated siRNAs.

4.3.2.2. Distribution

In vitro, the degree of plozasiran protein binding in plasma from rat, mouse, monkey, and human was evaluated using native gel electrophoresis and SYBR gold staining. Plozasiran is relatively highly bound in plasma with no significant differences between human and the toxicological species tested (mouse, rat, and cynomolgus monkey). The unbound fractions ranged between 6-15% (rodents) and 19-22% (monkey, human) at relevant test concentrations of 2-30 µg/mL, which is significantly higher than the clinical C_{max} (70.8 ng/mL), and were not concentration dependent. At lower testing concentrations, the unbound fractions reported were limited by the LLOQ of the analytical method.

The absence of a radiolabelled mass balance or a quantitative whole-body autoradiography (QWBA) study in preclinical species considered acceptable. Since oligonucleotide metabolism generally is relatively consistent across species, and the elimination profile from plozasiran was already characterized in humans, the added value of additional non-clinical studies was considered limited. Instead, select biodistribution and tissue PK data was obtained in two dedicated studies in rats and mice using unlabeled plozasiran.

Following a single SC administration of 3 mg/kg to rats, plozasiran tissue homogenate concentrations were determined in adrenal, brain, heart, kidney, liver, lung, and spleen tissue at different timepoints up to 28 days. As expected for GalNac-conjugated siRNAs, plozasiran mainly distributed to the liver and kidney, with the maximum observed concentration of 38 and 13 µg/g tissue, respectively, at 4 h postdose. Plozasiran was still quantifiable in these tissues at the final timepoint of 28 days (0.41 and 0.33 µg/g in liver and kidney, respectively). Other tissues demonstrated approximately 100-fold lower levels at T_{max}, and were below the LLOQ after ~ 9 days. The single observation of plozasiran levels in the brain (1 animal at 4 h just above LLOQ of 0.04 µg/g) is considered incidental and likely due to a contaminated sample. It can be concluded that plozasiran does not penetrate the blood-brain barrier.

Following a single SC administration of 3 mg/kg or 30 mg/kg to mice, plozasiran concentrations were determined in kidney and liver at different timepoints up to day 57 (3 mg/kg) or day 85 (30 mg/kg). Similar to the findings in rats, peak concentrations in the liver were observed 4 h postdose (20.7 and 87.2 µg/g at 3 and 30 mg/kg, respectively), but liver concentration increased less than proportionally to the dose. In contrast, the kidney concentration increased greater than proportionally to dose (1.86 and 55.5 µg/g at 3 and 30 mg/kg, respectively). These findings may be suggestive of saturation of transporter-mediated liver uptake at the highest tested dose. No plasma PK was determined in this distribution study, but TK data in mice (DRF carcinogenicity study) demonstrated a relatively long plasma terminal $t_{1/2}$ values (~45 h) at 30 mg/kg, which supports this assumption. Plozasiran concentrations were quantifiable in liver for 4 and 10 weeks following a single SC dose of 3 mg/kg and 30 mg/kg, respectively. This is similar to the finding in rats dosed with 3 mg/kg. The terminal elimination t½ values in mice were similar in kidney and liver (4.5 and 7.4 days at 3 and 30 mg/kg, respectively).

Plozasiran distribution into foetal tissue (on GD 17) was monitored in pregnant rats administered a single SC dose on GD 10 with plozasiran at 0, 12.5, 25, and 50 mg/kg. Concentrations were below the LLOQ (10 ng/g) in all foetal tissue samples, indicating that placental transfer was not observed in the female rats up to the limit of bioanalytical assay sensitivity.

Concentration in milk was not determined, but since oral bioavailability of siRNAs is very low, systemic exposure via milk is considered negligible in weaning pups.

4.3.2.3. Metabolism

Metabolic stability and metabolite identification were determined by LC-HRMS. Following *in vitro* incubation, both the antisense and sense strand were stable (>90%) in mouse, monkey, and human serum for at least 24 h at 37°C. In rat serum, a slight decrease (~14%) between 6h up to 24h was observed (> 76% stable). In addition, both strands were metabolically stable in rat, monkey and human liver S9 fractions after 2-hour incubation at 37°C, indicating a lack of CYP or UGT metabolism. This is expected, since plozasiran is assumed to undergo catabolism by ribonucleases inside the hepatocytes following ASGPR-mediated uptake.

No *in vivo* metabolism studies were conducted for plozasiran in non-clinical species, which is agreed given the knowledge of the metabolic parameters of similar compounds.

4.3.2.4. Excretion

No excretion studies were conducted for plozasiran in non-clinical species, which is agreed. The primary clearance pathway is liver uptake and subsequent metabolism in the liver. Plozasiran and

its chain-shortened metabolites are expected to be cleared by urinary excretion via the glomerular filtration in kidney, which is confirmed in humans.

4.3.2.5. Pharmacokinetic drug interactions

Please refer to Section 5.2.2.

4.3.2.6. Other pharmacokinetic studies

Not applicable.

4.4. *Toxicology*

4.4.1. Repeat-dose toxicity

Table 3: Repeated-dose toxicity results

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	No: Sex/ Group	**Dose** (mg/ kg)	Exposure		Major findings & NOAEL
			Cmax ng/ml	AUC ng/ml/h	
Repeat-dose toxicity studies (NOAELs highlighted)					
Rat (SD) 2w, 3 doses SC injection Non-GLP **SR-01393**	Main: 5 M/F Clinical candidate and rat surrogate	0	-	-	**≥15**: sinusoidal cell activation and damage in liver, hepatocyte proliferation (surrogate only) **≥30**: mononuclear cell retention in liver **=300**: ↑ ALP and GGT, injection site edema (surrogate only) and inflammatory cell infiltration, tubule epithelium vacuolation, hepatocyte proliferation (clinical candidate) **NOAEL: N.D.**
		15	N.D.	N.D.	
		30	N.D.	N.D.	
		300	N.D.	N.D.	
Rat (SD) 4w, 3 doses +2w	Main: 10 M/F TK: 6 M/F	0	-	-	**≥15**: ↓ retic and Hb(M), hepatocyte vacuolation, basophilic granules in kidney **≥30**: ↓ fibrinogen, ↑ ALT, ↑ hepatocyte mitosis, macrophage vacuolation in mandibular and mesenteric lymph nodes
		15	M: 7990 F: 4950	M: 19600 F: 11900	
		30	M: 15300 F: 13800	M: 51200 F: 34500	

SC injection GLP **SR-00657**	Recovery: 5 M/F (0, 60, 300)	60	M: 31400 F: 27500	M: 120000 F: 80700	**≥60:** ↑ chol (F), ↓ glob (M), hepatocyte necrosis, vacuolation Kupffer cells (F), tubule cell vacuolation **=300**: ↑ neutrophils, ↑ ALP <u>Recovery</u>: **≥60:** ↓ retic and Hb(M), ↓ fibrinogen ↑ ALT and ALP, ↓ glob (M), hepatocyte vacuolation, pigmentation Kupffer cells (F), basophilic granules in kidney, tubule cell vacuolation, macrophage vacuolation in mandibular and mesenteric lymph nodes **=300**: vacuolation Kupffer cells
		300	M: 94300 F: 102000	M: 733000 F: 550000	
Rat (SD) 24w, 7 monthly doses +4w SC injection GLP **SR-00803**	Main: 15M/F TK: 3-6 M/F Recovery: 5 M/F (all groups)	0	-	-	**≥15**:↑Hb, ↓liver weight (M), basophilic granules kidney, multinucleated and vacuolated hepatocytes and Kupffer cells **≥30**: ↓BW gain (M), ↓RBC (M), ↓glu (M), ↑chol (F), ↓trig (M), tubule cell vacuolation in kidney, ↑mitosis and necrosis hepatocytes, Kupffer cell pigmentation, capsule mineralization in spleen, macrophages at injection site **=120**: ↓BW gain (F) and food consumption, ↓APTT, ↑chol (M), ↓trig (F), ↑ALP, eosinophilic focus and oval cell hyperplasia in liver, macrophage vacuolation in mandibular and mesenteric lymph nodes <u>Recovery</u>: **≥15**: multinucleated and vacuolated hepatocytes **≥30**: basophilic granules and tubule cells vacuolation kidney, ↑mitosis hepatocytes, Kupffer cell pigmentation and vacuolation **=120**: eosinophilic focus and oval cell hyperplasia in liver, necrosis hepatocytes (M), capsule mineralization in spleen
		15	M: 2190 F: 1570	M: 9370 F: 5350	
		30	M: 7080 F: 5460	M: 35400 F: 19200	
		120	M: 21300 F: 26000	M: 184000 F: 118000	
Monkey (cyno) 4w, 3 doses +2w SC injection	Main: 3 M/F Recovery: 2 M/F (0, 60, 300)	0	-	-	**≥15**: macrophage vacuolation in mesenteric lymph nodes (F) **≥60**: basophilic granules in Kupffer cells, macrophage vacuolation in mandibular lymph nodes
		15	M: 6880 F: 9720	M: 38500 F: 35000	
		30	M: 17000 F: 15400	M: 87400 F: 87600	
		60	M: 26900 F: 26300	M: 208000 F: 217000	

GLP **SR-00656**		300	M: 95700 F: 96700	M: 1150000 F: 1170000	**=300**: ↑ ALP, ↑ total protein (F), macrophage vacuolation in mesenteric lymph nodes (M) Recovery: **≥60**: basophilic granules in Kupffer cells, macrophage vacuolation in mandibular and mesenteric lymph nodes
Monkey (cyno) 37w, 10 monthly doses +4w SC injection GLP **SR-00804**	Main: 7 M/F Recovery: 2 M/F (control and high dose)	0	-	-	**≥30**: ↓ prostate weight, hepatocyte pigmentation, vacuolated macrophages in mesenteric lymph nodes **≥90**: ↑ ALP, ↓ epididymis, seminal vesicle, testes weight, basophilic granules in Kupffer cells, vacuolated macrophages in mandibular lymph nodes, dermal fibrosis injection site **=180**: ↑ spleen weight (F) Recovery: ↓ epididymis, prostate, seminal vesicle, testes weight, basophilic granules in kupffer cells, hepatocyte pigmentation, vacuolated macrophages in mandibular and mesenteric lymph nodes, dermal fibrosis injection site
		30	10700	108000	
		90	29300	326000	
		180	41000	693000	

4.4.2. Genotoxicity

Table 4: Genotoxicity tests results

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results positive/negative/equivocal
Gene mutations in bacteria **SR-00667** GLP	Salmonella strains TA98, TA100, TA1535, TA1537, and Escherichia coli, WP2 uvrA	33.3, 100, 333, 1000, 3333, 5000 µg/plate +/- S9	Negative
In vitro micronucleus assay **SR-00668** GLP	Human TK6 lymphocytic cells	31.3, 62.5, 125, 250, 500 µg/mL +/- S9	Negative
Chromosomal aberrations in-vivo **SR-00669** GLP	Mouse, micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg	Negative

4.4.3. Carcinogenicity

Table 5:Carcinogenicity tests results

Study details Species Duration (weeks) Route GLP status (Study ID)	No.Sex / Group	**Dose** (mg/kg/ day)	Exposure AUC_{0-48h} ng/ml/h	Major (alt. Salient) findings
Carcinogenicity studies (NOAELs highlighted)				
Mouse (CByB6F1-Tg(HRAS)2Jic) 26 weeks (4 doses) SC GLP (**SR-01328**)	Main: 25 M/F TK: 18 M/F	0	-	<u>Non-neoplastic findings:</u> **≥30**: ↑ liver weight (M), hepatocyte vacuolation, **≥60**: vacuolated macrophages in mesenteric lymph nodes (F) **=120**: vacuolated macrophages in mesenteric lymph nodes (M) <u>Neoplastic findings:</u> None
		30	M: 6640 F: 12800	
		60	M: 16100 F: 20500	
		120	M: 53500 F: 51500	
Rat (SD) 105 weeks (13 doses) SC GLP (SR-01332)	Main: 60 M/F TK: 7 M/F	0	-	<u>Non-neoplastic findings:</u> **≥12.5/20**: ↓ chol (M), Karyocytomegaly **≥25/40**: ↓ TG (M) **=50/100**: Cholangiofibrosis, oval cell hyperplasia, epidermal hyperplasia and hyperkeratosis, neuroaxonal degeneration <u>Neoplastic findings:</u> **=50/100**: hepatocellular adenoma (incidence 1, 1, 0, 10 for M, 1, 2, 3, 12 for F), hepatocellular carcinoma (incidence 0, 0, 0, 1 for M, 0, 0, 0, 2 for F)
		12.5 (M) 20 (F)	M: 14400 F: 13900	
		25 (M) 40 (F)	M: 45400 F: 40100	
		50 (M) 100 (M)	M: 99900 F: 152000	
DRF studies (NOAELs highlighted)				
Mouse (CByB6F1-Tg(HRAS)2Jic) 4 weeks (2 doses)	Main: 10M/F TK: 18 M/F	0	-	**≥100**: ↓ WBC (F), ↓ chol (M) **=300**: ↓ platelets (F) (minimal)
		30	16100	
		100	82100	
		300	359000	

SC GLP (**SR-01151**)				
Surrogate (AD06313) study				
Rat (SD) 13 weeks (4 monthly doses) SC GLP (**SR-01150**)	Main: 10M/F TK: 6M/F	0	-	≥3: ↓ triglycerides, mononuclear infiltrate at injection site ≥10: ↓ chol (M), hepatocyte vacuolation =30: ↓ chol (F)
		3	1410	
		10	5720	
		30	38400	

4.4.4. Developmental and reproductive toxicity

Table 6: Developmental and reproductive toxicity

Study details Species treatment period Route GLP status (Study ID)	No:Sex/ Group	**Dose** (mg/ kg)	exposure		Major (alt salient) findings & NOAEL
			Cmax ng/ml	AUC ng/ml/h	
Fertility and early embryonic development studies (NOAELs highlighted)					
Example: Rat (Crl:CD[SD]) F: SC (Q3d) 16 d prior to mating until GD 6 M: SC (Q1w) from 29 d prior to mating GLP	20/sex/group	0	-	-	<u>plozasiran:</u> **≥25 mg/kg:** dose-dependent ↓body weight, body weight gain, and food consumption. <u>AD06313:</u> **=25 mg/kg**: ↓ body weight gain and food consumption
		12.5	5.250 (M) 5.680 (F)	21.900 (M) 17.800 (F)	
		25			
		50	15.500 (M) 23.800 (F)	108.000 (M) 77.000 (F)	
		25			

(SR-00880)					Paternal and maternal NOAEL: 12.5 mg/kg Male and female reproductive NOAEL: 50 mg/kg

Study details Species treatment period Route GLP status (Study ID)	No:Sex/ Group	**Dose** (mg/ kg)	exposure		Major (alt salient) findings & NOAEL
			Cmax ng/ml	AUC ng/ml/h	
Embryo-fetal toxicity studies (NOAELs highlighted)					
Rat(Crl:CD®(SD)) SC, once daily on GD 6-17 Non-GLP (SR-00781)	6F	0	-	-	**≥30 mg/kg**: mortality, beginning on GD16, ↓activity, tan discoloured faeces, red material in bedding, red discharge from the vulva, hunched posture, thin body condition, entire body cold to touch and discoloured pale, and difficult and rapid breathing. ↓ gestation body weight, body weight change, and food consumption. Tan discolored liver and edema of the pancreas. ↑ post-implantation loss and number of resorptions (not at 300 mg/kg). ↓ gravid uterine weight, adjusted GD 21 body weight, adjusted body weight gain (GD 6 to 21) and foetal body weights. **≥120 mg/kg:** ↑ absolute reticulocyte counts
		30	-	-	
		120	-	-	
		300	-	-	
Rat(Crl:CD®(SD))	22F	0	x	x	<u>Plozasiran:</u>

SC, once daily on GD 6-17 GLP (SR-00879)		5	**566**	**1940**	**≥5 mg/kg:** minimally to moderately ↑ ALT and AST, mildly to moderately ↓ platelet, mildly to moderately ↓fibrinogen , mildly to markedly ↓total protein, alb and glob **≥15 mg/kg:** mortality (n=1 at 15 mg/kg; n=9 at 60 mg/kg). Hunched posture and piloerection. ↓ body weight, body weight gain and food consumption. Minimally to moderately↑ gamma glutamyltransferase, minimally to mildly ↑ bilirubin. Minimally ↑ creat kinase and ↓ creat . Minimally ↓ sodium. Moderately ↓ glu and minimally to mildly ↑triglyceride. ↓ gravid uterine weight, ↓ fetal body weight, sternebrae not ossified **=60 mg/kg:** thin body condition, entire body cold to touch, pale skin, and red discharge from the vulva, early deliveries, ↑ in post-implantation loss (18.68%) and late resorptions (0.8). Hyoid not ossified. <u>AD06313</u> **=60 mg/kg:** minimally ↓ sodium. ↓ creat, moderately ↓glu and minimally ↓urea nitrogen. Bent humerus and bent scapula, bent ribs, gastroschisis Maternal NOAEL: <5 mg/kg Developmental NOAEL: 5 mg/kg
		15	3570	16700	
		60	13800	69100	
		60	-	-	
Rat (Crl:CD®(SD)) SC, once on GD 10 GLP (SR-00881)	22F	12.5	2630	6910	<u>Plozasiran:</u> **≥12.5 mg/kg:** minimal to mild ↓ in fibrinogen and/or total protein, alb, and glob **=50 mg/kg:** ↑ gestation food consumption. Minimal ↑ red cell mass (erythrocytes, hemoglobin, hematocrit) and ↓ glomerular filtration rate characterized by minimal ↑ in urea nitrogen which may be indicative of minimal subclinical dehydration; minimal inflammatory stimulus as indicated by minimal ↑ in neutrophils and monocytes; minimal ↓ platelets; a potential minimal hepatobiliary effect as suggested by minimal ↑ ALP, total bilirubin, AST and
		25	8190	18700	
		50	**27500**	**66300**	
		50	-	-	

					ALT; and minimal lipid effect as indicated by minimal ↑ cholesterol AD06313 No relevant effects observed. Maternal NOAEL: 50 mg/kg Developmental NOAEL: 50 mg/kg
Rabbit (Hra:(NZW)SPF) SC, once daily on GD 7-18 Non-GLP (SR-00825)	6F	30	-	-	**≥30 mg/kg:** ↓ gestation body weight change and food consumption throughout the post-treatment period, mild to moderate ↓ in fibrinogen **=300 mg/kg:** scabbing at one or more injection sites, ↓ adjusted body weight gain
		120	-	-	
		300	-	-	
Rabbit (Hra:(NZW)SPF) SC, once daily on GD 7-19 GLP (SR-00847)	22F	30	12.400	51.100	**180 mg/kg:** ↓ gestation body weight gain, and a minimal ↓ maternal fibrinogen Maternal NOAEL: 180 mg/kg Developmental NOAEL: 180 mg/kg
		60	18.500	146.000	
		180	**60.100**	**523.000**	

Study details Species treatment period Route GLP status (Study ID)	No:Sex/ Group	**Dose** (mg/ kg)	exposure		Major (alt salient) findings & NOAEL
			Cmax ng/ml	AUC ng/ml/h	
Prenatal and postnatal development studies (NOAELs highlighted)					
Rat (Crl:CD[SD])	22F	0	-	-	**≥24 mg/kg:** ↓ preweaning pup body weight, recovered at PND 29. **80 mg/kg:** ↑number of females with stillborn pups, percent of stillborn pups per litter and number of stillborn pups. ↓in the live birth index
		8	1.100	3.550	
		24	**6.080**	**25.000**	
		80	**21.300**	**161.000**	

SC once weekly on GD 6, 13, and 20 and LD 3, 10, and 17 GLP (SR-01539)					Maternal NOAEL: 80 mg/kg Preweaning NOAEL: 24 mg/kg Postweaning NOAEL: 80 mg/kg

Study details Species treatment period Route GLP status (Study ID)	No:Sex/ Group	**Dose** (mg/ kg)	exposure		Major (alt salient) findings & NOAEL
			Cmax ng/ml	AUC ng/ml/h	
Juvenile animal toxicity studies (NOAELs highlighted)					
Rat (Crl:CD(SD)) PND 4-25, once weekly SC Non-GLP (SR-01152)	6	0	-	-	<u>Plozasiran:</u> **≥20 mg/kg:** minimal basophilic granules in kidney **≥60 mg/kg:** ↓ white blood cells, neutrophils, lymphocytes, eosinophils, basophil, alanine aminotransferase, and alkaline phosphatase <u>AD06313:</u> **120 mg/kg**: microscopic findings of minimal to mild basophilic granules in kidney, increased incidence of minimal to mild cortical cysts. Macroscopic finding in the kidney (clear cysts) and ↓ in white blood cells, neutrophils, lymphocytes, eosinophils, basophil, alanine aminotransferase, alkaline phosphatase, and triglycerides
		20	7210	19900	
		60	26500	61400	
		120	54600	176000	
		120	-	-	

4.4.5. Toxicokinetics and exposure margins

With respect to the determination of the safety exposure margins, animal exposures are compared with human exposure values from the healthy volunteer study AROAPOC3-1001, which were dosed monthly with 25 mg plozasiran (AUC_{0-24}: 746 h*ng/mL, AUC_{0-inf} 754 h*ng/mL and C_{max} 70.8 ng/mL). Total plozasiran plasma fraction was used for the calculation of the exposure multiples, since only minor differences in plasma protein binding between non-clinical species and humans were observed, and since a potential effect on the fast target tissue uptake (plasma $t_{1/2}$ <3h) is expected to be limited in relation to the extended tissue effect (Liver $t_{1/2}$ 4-7 d). To more adequately reflect the expected accumulation in the liver upon dosing, the exposure margins are based on plasma AUC_{0-24} levels and are corrected for the total amount of doses given to non-clinical species in 1 month (dosing schedule used in healthy volunteers' population).

Table 7: Safety exposure margins in pivotal studies (NOAELs in bold if applicable)

Study ID/ species (D of measurement)	Dose (mg/kg)	Animal AUC_{0-24} (ng.h/ml)		C_{max} (ng/ml)		Animal:Human Exposure Multiple	
		Male	Female	Male	Female	AUC (M/F)	C_{max} (M/F)
SR-00803/ 24-wk, Q4W in rat, 7 doses in total (D169)	**15**	**7360**		**1800**		**10**	**25**
	30	27300		6110		37	86
	120	151000		22800		202	322
SR-00804/ 37-wk, Q4W in monkey, (D253)	30	108000		10700		145	151
	90	326000		29300		437	414
	180	693000		41000		929	579
SR-01328/ 26-wk, Q8W in mouse, 4 doses in total (D169)	30	9710		5300		6.5	75
	60	18300		8180		12	116
	120	**52500**		**26800**		**35**	**379**
SR-01332/ 105-wk, Q8W in rat, 13/12 doses in total (D393)	12.5/20	14400	13900	1620	3960	19	39
	25/40	45400	40100	4110	4160	57	58
	50/100	99900	152000	9260	17900	169	192
SR-00880/ F-EED, Q1W in male rat, 8 doses in total (D50)	12.5	21900	-	5250	-	117	74
	25	46400	-	9080	-	249	128
	50	**108000**	**-**	**15500**	**-**	**579**	**219**
SR-00880/ F-EED, Q3D in female rat, 8-13 doses in total (GD6)	**12.5**	**-**	**17800**	**-**	**5680**	**191**	**80**
	25	-	39200	-	14700	420	208
	50	**-**	**77000**	**-**	**23800**	**826**	**336**
SR-00879/EFD, QD in rat, 12 doses in total (GD17)	**5**	**-**	**1940**	**-**	**566**	**31**	**8**
	15	-	16700	-	3570	269	50
	60	-	69100	-	13800	1112	195

SR-00881/EFD, single dose in rat (GD10)	12.5	-	6910	-	2630	9.3	37
	25	-	18700	-	8190	25	116
	50	**-**	**66300**	**-**	**27500**	**89**	**388**
SR-00847/EFD, QD in rabbit, 13 doses in total (GD19)	30	-	51100	-	12400	890	175
	60	-	146000	-	18500	2544	261
	180	**-**	**523000**	**-**	**60100**	**9114**	**849**
SR-01539/ PPND, Q1W in rat, 6 doses in total (GD20)	8	-	3550	-	1100	19	16
	24	**-**	**25000**	**-**	**6080**	**134**	**86**
	80	**-**	**161000**	**-**	**21300**	**863**	**301**
SR-01152/3-wk, Q1W in juvenile rat, 4 doses in total (PND25)	**20**	**19900**		**8710**		**106**	**123**
	60	61400		26500		329	374
	120	176000		54600		943	771

4.4.6. Local tolerance

Not applicable

4.4.7. Other toxicity studies

Not applicable

4.4.8. Ecotoxicity/environmental risk assessment

Table 8: Summary of main study results: Phase I

Substance (INN/Invented Name):	plozasiran		
CAS-number (if available):	2379776-40-4		
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD 107	<-3.9 at pH 5 <-3.8 at pH 7 <-3.8 at pH 9	Potential PBT: N

Phase I			
Calculation	Value	Unit	Conclusion
PEC_{sw}, refined	0.0000027	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

The PEC_{SW} is below the action trigger for a phase II assessment. Plozasian is considered to be not PBT nor vPvB.

4.5. *Overall discussion and conclusions on non-clinical aspects*

4.5.1. Discussion

Pharmacology:

Limited information on the silencing of the on-target gene *APOC3* can be derived from the secondary PD study (SR-00676) in human hepatocellular carcinoma cell lines. At all concentrations tested, plozasiran potently silenced *APOC3* (expression relative to negative control <4% in Huh7 cells at 0.5 nM and <20% in Hep3b cells at 0.1 nM). Since a low-concentration range was not included, a concentration-response relationship or an IC50 were not established. For the *in vitro* primary pharmacology of plozasiran, no dedicated studies were conducted, which is acceptable.

An *in silico* analysis in which the target sequence of plozasiran was compared between major ethnic groups was performed. Two SNPs, based on the antisense strand of plozasiran, were found at position 15 (rs577085953) and position 12 (rs539003433). Given the low frequency of these SNPs (NMT 0.1 or 0.2%, respectively, in specific ethnic groups) and their positioning outside of the seed-binding region, an impact on clinical efficacy in the already rare patient population is not expected. Further testing to evaluate whether plozasiran will also bind to the mRNA of patients with polymorphic alleles is therefore not required.

Regarding homology of the target gene sequence in different species, the plozasiran sequence is only fully cross-reactive (based on having no mismatches) with human and monkey transcripts. Hence, plozasiran is expected to be pharmacologically active in monkey at clinically relevant doses. The rodent transcripts have 6-7 mismatches to the human sequence, though a PD study in rats showed cross-reactivity of plozasiran at high doses. Effects on *Apoc3* mRNA expression in rabbit were not evaluated, though pharmacological activity may be expected at clinically relevant doses in the conducted EFD studies (see toxicology), given that the only mismatch occurs outside of the seed-binding region of the rabbit *Apoc3* transcript. No PD or toxicological studies were done with wild-type mice, which is agreed.

The *in vivo* primary pharmacology of plozasiran was studied using a transgenic dyslipidemic mouse model expressing human *APOC3* (TgAPOC3) and healthy or dyslipidemic monkeys. An exploratory study in rats was also performed.

In the transgenic dyslipidemic mouse model (SR-006740), plozasiran was administered by a single SC injection. After one week, doses of 0.25, 0.5, 1 or 3 mg/kg resulted in maximum mean serum APOC3 protein reductions of 66%, 81%, 84% and 91%, respectively. The high levels of human APOC3 transgene expression in this model caused high levels of serum triglycerides (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), all of which were dose-dependently reduced after treatment. Maximum mean reductions of TG, TC, and LDL-C were 91%, 45%, and 64%, respectively. At the end of the study (day 37), dose-dependent reduction in liver *APOC3* mRNA levels was shown.

In rats (SR-01070), despite that pharmacological activity of plozasiran was not expected due to mismatches with the rodent transcript, *Apoc3* mRNA in the liver was reduced up to ~50% after weekly dosing at 60 or 120 mg/kg. Serum TG were reduced by 75% even at 60 mg/kg. Lower doses were not tested.

In regular chow-fed cynomolgus monkeys (SR-00675), two SC doses of plozasiran at 4 mg/kg, 3 weeks apart, reduced *APOC3* expression in the liver by more than 80%, which was maintained for at least 4 weeks after the end of treatment. Serum APOC3 protein levels were only reduced by 50-60%.

The remaining serum APOC3 is likely primarily derived from the small intestine. In this study, there was no effect on serum lipids.

In rhesus monkeys maintained on high fructose corn syrup diet (SR-00822), two SC doses of plozasiran at 4 mg/kg, 4 weeks apart, reduced APOC3 protein levels in serum by 60-80%. Liver samples were not collected. Only the animals with a marked diet-induced increase in serum APOC3 and lipid levels at the start of treatment, had an improved lipid profile (reduced TG, cholesterol and LDL-C, and increased HDL-C) compared to the saline-treated control animals.

Regarding the primary pharmacology of plozasiran, it can be concluded that the *in vivo* PD response of plozasiran was shown by the suppression of liver *APOC3* expression, reduction in serum APOC3 protein concentrations and lipid-lowering effects in serum. The extent of the decrease in TG induced by plozasiran in transgenic mice and monkeys appears dependent on the level of increased plasma TG before treatment. Since siRNA levels in the liver were not measured, the local concentration required to achieve effective knockdown of *APOC3* remains unknown.

The secondary pharmacology of plozasiran was assessed by an in-silico analysis which aimed at identifying any human expressed off-target gene candidates, including regulatory RNAs, with partial complementarity to the sense or antisense strands of plozasiran. There were no homologies with any known off-target RNAs with full complementarity.

One off-target gene candidate (TRAF3) has a single mismatch (position 10) to the sense strand of plozasiran. TRAF3 is typically not expressed in healthy liver or kidney, though it could be expressed in certain disease states. Literature indicates that TRAF6 knockdown would rather have a protective effect.

20 genes and 315 genes were identified with 2 and 3 mismatches to plozasiran, respectively. None of the genes with 2 mismatches contained a neutralizing SNP, while 52 of the genes with 3 mismatches contained a neutralizing SNP. Detailed information on the off-target candidates with up to 2 mismatches was presented, including gene identity, target sequence and mismatch locations, tissue expression, known sequence variants found in the population, sequence similarity of the target sequence in animal models, and literature information regarding the effects of gene silencing.

Nine off-target human gene candidates were selected for *in vitro* screening in human hepatocellular carcinoma (HUH7, Hep3B) or in renal cell carcinoma (A498) cell lines: TRAF3, HNF1B, ITIH4, ITIH5, MAGI2, NAMPT, OSMR, PCCA, and RIT1. Plozasiran did not reduce the expression of the 9 tested genes up to a concentration of 500 nM.

A PD study in rats showed partial cross-reactivity of plozasiran with the rat Apoc3 transcript despite 7 mismatches, which raises doubt about potential off-target activity of plozasiran against human gene candidates with more than 3 mismatches. However, this inhibitory effect in the rat was observed at high dose levels. Given that the 9 tested off-target candidates (with up to 3 mismatches) were not inhibited *in vitro*, it is unlikely that plozasiran will have any activity on other, less prominent off-target candidates (e.g. with more mismatches) at clinically relevant doses.

A standard GLP-compliant battery of safety pharmacology studies was performed.

At a concentration of 6.4 µM (100 µg/mL), plozasiran did not affect hERG tail current amplitude *in vitro*. This represents a large safety margin to the human unbound Cmax (15.6 ng/mL) at the proposed therapeutic dose. Since plozasiran was added to the media without a delivery system, cellular uptake and any meaningful change in hERG function is unknown, but since only a very small proportion of plozasiran is distributed to the heart, the risk can be considered low.

No effects on cardiovascular parameters were observed in cynomolgus monkeys up to 300 mg/kg (SC) plozasiran.

Plozasiran treatment up to 300 mg/kg (SC) had no effect on the central nervous system or respiratory system of rats.

No studies on pharmacodynamic drug interactions were performed, which is acceptable.

Pharmacokinetics:

Plozasiran was quickly absorbed after SC administration in all species, indicated by a T_{max} of ~1 h, 0.25-1 h, 1.5-4 h and 3-6 h in mice, rats, monkeys and humans, respectively. Systemic absorption after SC administration was 19% and 40% in rats and monkeys, respectively.

The plasma concentrations of plozasiran generally increased dose-proportionally in rat, mouse and monkey, and no significant or consistent differences in exposure was observed between male and female animals. Elimination of plozasiran from the plasma was rapid, resulting in a plasma $t_{1/2}$ of 0.6-1.4 h and 1.1-2.5 h after single IV/SC dose in rats and monkeys, respectively.

Volume of distribution was 41.8 mL/kg in rats and 259 mL/kg in monkeys, indicating fast tissue uptake in liver and kidney. As expected from GalNac-conjugated siRNAs, plozasiran was distributed predominantly to the liver in rodents, with substantial amounts also in kidney but ~100-fold lower levels in other tissues. The terminal elimination t½ values in rodents were similar in kidney and liver (4.5-7.4 days). Plozasiran was not measurable in fetuses of rats.

Plozasiran is highly bound in plasma with no significant differences between human and the toxicological species tested (mouse, rat, and cynomolgus monkey). The unbound fractions ranged between 6%-15% (rodents) and 19%-22% (monkey, human) at relevant test concentrations of 2-30 µg/mL and were not concentration-dependent.

Following *in vitro* incubation, both the antisense (AS) and sense strand (SS) were stable (>90%) in mouse, monkey, and human serum for at least 24 h (37ºC). In rat serum, a slight (~14%) decrease between 6h up to 24h (>76% stable) was observed.

The primary clearance pathway is liver uptake and subsequent metabolism in the liver. No *in vivo* metabolism and excretion studies were done but plozasiran and its chain-shortened metabolites are expected to be cleared by urinary excretion via the glomerular filtration in kidney in the nonclinical species as in human.

Toxicology:

With respect to the determination of the safety exposure margins, animal exposures are compared with human exposure values from the healthy volunteer study AROAPOC3-1001, which were dosed monthly with 25 mg plozasiran (AUC_{0-24}: 746 h*ng/mL, AUC_{0-inf} 754 h*ng/mL and C_{max} 70.8 ng/mL).

No single dose toxicity studies have been performed, which is acceptable. Plozasiran was tested in repeated dose studies in rats and monkeys, up to 24 and 37 weeks respectively. In subchronic studies animals were dosed weekly, while in the chronic studies dosing was monthly. This is considered acceptable, considering the long tissue half-life and extended pharmacological effect. In studies up to 4 weeks in duration, no PD effect (reduced triglycerides) was seen, but this might be due to a delayed PD effect, taking longer than 4 weeks to manifest itself. Indeed, in the chronic rat study, reduction in triglycerides levels was evident. In monkey however, no effect on cholesterol or triglyceride levels were seen, while the applicant reports full homology between human and monkey target gene. From PD studies using healthy monkeys on lipid increasing diet, it is clear that high baseline lipids are required

in the monkey before a lowering effect can be seen. It can therefore be assumed that plozasiran is pharmacologically active in monkeys.

As described previously with other oligonucleotide-based therapies (ONT), the target organs in the rats and monkey were liver, kidney, lymph nodes and injection site. In the monkey, the effects were not severe, but evident in liver and lymph nodes from the lowest dose onward in the chronic study. The exposure margin at the low dose as compared to the human dose is 145-fold (based on AUC). More prominent effects in liver and kidney were only seen at even higher doses. A similar toxicity profile was seen in the rat, with effects on kidney and liver evident from the low dose with exposure margins (based on AUC) of 12.5 and 7 in males and females, respectively. Effects on liver, kidney, lymph nodes and injection site can be seen as class effects of ONTs and are part of the known safety profile of ONTs. They are mainly due to accumulation of product in these organs.

In the chronic monkey study, a decrease of male reproductive organ weights was seen. This was seen in epididymis, prostate, seminal vesicle and testes. There was no clear dose-dependent response for the reduction in weight, and it did not coincide with any histopathological findings. Further, the effects were seen at large exposure margins. Taken together with the lack of effects on fertility in the dedicated rat fertility study, it is agreed that it is unlikely that plozasiran will have an effect on human fertility.

After 4 weeks of recovery in both species, some effects were less severe, indicating start of recovery. However, the period of recovery was not sufficient to conclude that recovery is evident for all effects, especially the reduced male reproductive organ weights.

A full battery of genotoxicity tests was performed with plozasiran. Plozasiran was negative in the gene mutation test in bacteria, the Ames test, at the tested concentrations up to 5000 µg/plate. In the in vitro micronucleus test in human lymphocytic cells, there was a small increase in micronucleated cells just outside the 95% upper historical control limit at 125 µg/ml. Due to the lack of dose response and the fact that the frequency was still within the complete historical control range, the test can be considered negative. The *in vivo* micronucleus test in mice was also negative up to a dose of 2000 - mg/kg. Overall, plozasiran can be considered negative for genotoxic potential.

Carcinogenic potential of plozasiran was tested in a 6-month transgenic mouse and a 2-year rat carcinogenicity study, the latter of which was submitted in the second round of the procedure. In the mouse study, no increase in tumour incidence was seen, while the positive control was carcinogenic. In the rat study at the high dose, there was an increase in hepatocellular adenomas and carcinomas. No other neoplastic effects were identified. Of note, the non-neoplastic findings observed in the 26-week repeated dose rat study were less severe (liver effects) or absent (kidney, spleen, lymph nodes) in the 105-week carcinogenicity study. This could be due to the less frequent dosing scheme of once every 8 weeks in both mouse and rat carcinogenicity studies, versus once every 4 weeks in the repeated dose study. Although it can be questioned if the dosing was sufficiently frequent to be able to observe chemistry-related effects, the exposure margins were sufficiently high to be able to draw conclusions. Further, the dosing frequency is more similar to the clinical dosing frequency, and therefore more relevant. At the NOAEL for neoplastic effects in the rat, the safety margin is around 60-fold for males and 53-fold for females, based on AUC. It is therefore unlikely that the hepatocellular tumours seen in rats are relevant for humans.

With regard to the role of the target biology in carcinogenicity, the WoE suggests that it is unlikely that reduction of APOC3 will lead to an increased risk.

For the evaluation of reproductive toxicity, FEED, EFD and PPND studies were conducted. FEED and PPND were conducted in rats, EFD in rats and rabbits. In the FEED study, females were dosed every 3 days, and males once weekly. While some maternal and paternal toxicity was seen (reduced body weight gain), there was no effect on fertility in any dose group. The maternal and paternal NOAELs for plozasiran was 12.5 mg/kg, representing safety margins of around 117-fold and 191-fold in males and females, respectively (based on AUCs). The male and female reproductive NOAEL was 50 mg/kg. These NOAELs represent safety margins of around 579-fold and 826-fold, respectively (based on AUCs). In the initial rat EFD study, rats were dosed daily, which resulted in severe maternal toxicity leading to embryotoxicity. These effects are not likely to be relevant due to severe overdosing. The NOAEL for developmental toxicity was 5 mg/kg, the NOAEL for maternal toxicity was < 5 mg/kg, resulting in exposure margins of 31-fold (based on AUC). Because it is unlikely that more than 1 dose of plozasiran will be administered during the developmental period in the human situation, an additional GLP compliant embryo-foetal development study in rats with a single SC dose of plozasiran or the rat specific analogue AD06313 on GD10 was conducted. With this study set up, only minor maternal toxicity was observed, with no effects on fetal mortality or skeletal malformations. The exposure margin compared to the human dose at the high dose was nearly 90-fold (based on AUC). In a rabbit EFD study with daily dosing, there were no effects on embryofetal development at any dose, resulting in an exposure margin of over 9000-fold (based on AUC). In a rat PPND study with weekly dosing, the only adverse effect was an increase in stillborn pups at the high dose. There is a safety margin of 134-fold at the NOAEL (based on AUC), and therefore, this effect is not likely to be relevant. Overall, it can be concluded there is no safety concern relating to reproductive and developmental toxicity for plozasiran at clinically relevant doses.

In a non-GLP juvenile toxicity study, no new toxicities were observed that could be of special concerns in the paediatric population.

ERA:

The PEC_{SW} is below the action trigger for a phase II assessment. Plozasian is considered to be not PBT nor vPvB.

4.5.2. Conclusions

The pharmacodynamics and pharmacokinetics of plozasiran have been adequately described. The toxicological profile of plozasiran was adequately characterized in several studies, which comply with the current guidelines. The profile is consistent with that of other siRNAs targeting the liver.

5. Clinical aspects

5.1. *Introduction*

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

5.1.2. Tabular overview of clinical trials

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
AROAPOC3-3001 (PALISADE)	Ongoing First patient screened: 21-12-2021 123 patients	A randomized, double-blind, placebo-controlled to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS	Randomized DB period, 12 months (completed) • Plozasiran 25 mg or PBO randomized 2:1 (n=26:13) • Plozasiran 50 mg or PBO randomized 2:1 (n=24:12) Total of 4 doses of plozasiran or matching placebo administered SC Q3M OLE Period A (ongoing) Subjects randomized to plozasiran continued to receive their assigned original treatment (blinded). Subjects who received placebo switched to the active treatment in the OLE based on the initial dosing group to which they were assigned. OLE Period B (ongoing) All subjects switched to the selected clinical dose (plozasiran 25 mg Q3M).	Adult subjects with genetically confirmed or clinically diagnosed FCS
AROAPOC3-2001 (SHASTA-2)	Completed First patient enrolled: 31-05-2021 Last patient completed: 31-07-2023 226 participants	A double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of ARO-APOC3 in adults with severe hypertriglyceridemia	Randomized DB period (completed) • Plozasiran 10 mg (n=54) or PBO (n=20) • Plozasiran 25 mg (n=55) or PBO (n=20) • Plozasiran 50 mg (n=57) or PBO (n=20) Total of 2 doses of plozasiran or matching placebo administered SC on Day 1 and Week 12 for each dose cohort.	Adult subjects with SHTG (including 5 subjects with FCS)

AROAPOC3-2002 (MUIR)	Completed First patient enrolled: 28-09-2021 Last patient completed: 14-07-2023 226 participants	A double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of ARO APOC3 in adults with mixed hyperlipidemia	<u>Randomized DB period (completed)</u> • Plozasiran 10 mg (n=67) or PBO (n=21) Day 1 and Week 12 • Plozasiran 25 mg (n=67) or PBO (n=22) Day 1 and Week 12 • Plozasiran 50 mg (n=66) or PBO (n=22) Day 1 and Week 12 • Plozasiran 50 mg (n=66) or PBO (n=22) Day 1 and Week 24 Total of 2 doses of plozasiran or matching placebo administered SC.	Adult subjects with mixed hyperlipidemia
AROAPOC3-2003	Ongoing 169 patients	A Phase 2 open-label extension study to evaluate the long-term safety and efficacy of ARO-APOC3 in adults with dyslipidemia	<u>Open-label extension (ongoing)</u> Initially all subjects received plozasiran at the same dose or PBO-matched dose. Up until protocol Amendment 2 (dated 22 Nov 2022), subjects were on their assigned dosing per respective protocols. As of 04 Dec 2023, all subjects who were not on the 25 mg Q12W were switched to 25 mg Q12W.	Adult subjects with hyperlipidemia from AROAPOC3 2001 and AROAPOC3-2002

5.2. *Clinical pharmacology*

5.2.1. Methods

The plasma and urine concentrations of plozasiran were determined by validated Good Laboratory Practice (GLP) bioanalytical methods using peptide nucleic acid (PNA) hybridization followed by anion-exchange high performance liquid chromatography with fluorescence detection. The method validation of plozasiran detection in plasma and urine was conducted in line with ICHM10 on bioanalytical method validation and study sample analysis.

In addition, a method was designed to detect the presence of anti-plozasiran IgG/IgM antibodies in human serum in a tiered approach. The method contains three components: (1) a screening assay, which identifies potentially positive or negative samples; (2) a confirmatory assay, which assesses specificity of the screened positive samples; and (3) a titration assay, which estimates the titer of anti-drug antibody (ADA) for the confirmed positive samples. Method validation has sufficiently been performed.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The clinical pharmacology of plozasiran was evaluated in the following studies: one phase 1/2a

study (AROAPOC31001) conducted in healthy volunteers and subjects with HTG or SHTG, and FCS; two phase 1 studies (AROAPOC3-1002 and AROAPOC3-1003) conducted in healthy volunteers; two Phase 2b studies conducted in subjects with SHTG (AROAPOC3-2001) and HTG/mixed hyperlipidemia (AROAPOC3-2002); one pivotal phase 3 study (AROAPOC3-3001) conducted in subjects with FCS.

Plozasiran has been administered to more than 80 healthy volunteers, 200 subjects with SHTG, 300 subjects with HTG/mixed hyperlipidemia, and 50 patients with FCS within a period of 12 months. Including single or multiple dose administrations, the range of plozasiran doses explored was from 10 mg to 100 mg by subcutaneous (SC) injection.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

Objective

The final PK model was developed to investigate whether plozasiran PK is similar or significantly different with respect to subject populations (FCS, SHTG, MD and HV) and other extrinsic and intrinsic factors including demographic characteristics.

Clinical studies

The population PK model included the pooled PK data collected in healthy volunteers from studies AROAPOC31001 and AROAPOC3-1002, patients with SHTG from Study AROAPOC3-2001, patients with mixed hyperlipidemia from Study AROAPOC3-2002, and patients with FCS from Study AROAPOC3-3001.

Out of a total of 147 subjects (70 HV, 27 subjects with SHTG, 38 subjects with MD and 12 subjects with FCS) with intensively collected PK samples, 146 (99.3%) subjects were retained for the model development. Amongst the 1832 plasma samples of plozasiran available in subjects with intensive PK samples, 1661 (90.7%) samples were retained for the model development.

Methods

Population PK modelling and model validation were performed using NONMEM Version VII (version 7.4). First order conditional estimation (FOCE) method of NONMEM with IIV and IOV, and residual variability interaction were used for population PK model development.

Plasma concentration-time data were analysed using standard nonlinear mixed effects (NLME) modelling approach to characterize plozasiran PK. The population PK model consisted of a description of the relationships between plasma concentration and time, a variance component characterizing inter-individual variability (IIV), inter-occasion variability (IOV) by dose administration, and residual unexplained variability.

Model discrimination was performed to identify an optimized structural model as demonstrated by diagnostic plots with acceptable goodness-of-fit (GOF). The quality-of-fit for development of the models was evaluated using a model discrimination process including statistical criteria (e.g., objective function value [OFV], condition number) as well as pertinent graphical representations of goodness of-fit (e.g., fitted and observed concentrations versus time, conditional weighted residuals). Estimation shrinkage of ETAs of the model parameters was evaluated for diagnostic purpose.

Covariates presenting relationships to PK parameters were formally tested in a stepwise process adjudicated by pre-specified statistical criteria for each step. The covariate selection was performed using a forward addition process followed by backward elimination. Visual predictive checks (VPC) were performed to allow visual comparison between distributions of simulated concentrations derived with the final models. The likelihood ratio test was used to evaluate the significance of incorporating or removing fixed effects into the population model based on significance levels that are set a priori. For forward addition and backward elimination, significance levels of $p<0.01$ and $p<0.001$ were employed, respectively. Covariates tested were: body weight, BMI, age, baseline APOC3 and TG, liver function tests, eGFR, sex, race, hepatic impairment, renal impairment, subject population (FCS, SHTG, MD or HV).

Evaluation

The model was parameterized in terms of dual first-order rate constants in absorption compartments #1 and #2 (Ka1 and Ka2) with a lag time on the 2nd absorption, distribution within one-compartment with a body weight effect on V/F and CL/F. In addition, BMI on V/F and the dose factor of 100 mg on CL/F were included in the model due to their capability of decreasing OFV. IIV for CL/F, V/F, and Ka1 were retained in the model and an IOV term was included on subcutaneous relative bioavailability (Frel).

Figure 2: Graphical representation of the popPK model structure for plozasiran

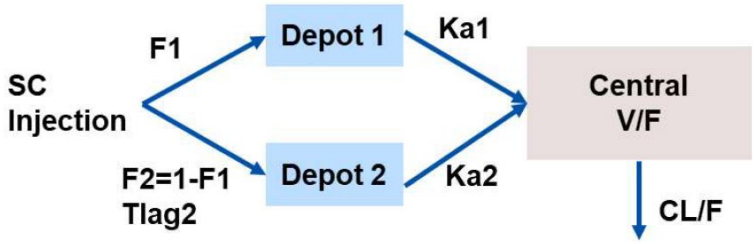


Table 9: Parameter estimates of the final popPK model

Parameter	Estimate	RSE%	95% CI	Shrinkage (%)
Typical Values				
CL/F (L/h)	40.7	5.10	36.6 – 44.7	
V/F (L)	204	10.1	164 – 245	
Ka1 (h^{-1})	1.03	5.79	0.916 – 1.15	
Ka2 (h^{-1})	0.421	15.6	0.292 – 0.550	
F1	0.587	3.61	0.545 – 0.628	
Lag time of depot compartment #2 (h)	5.01	3.95	4.62 – 5.39	
Covariate Effects				
WT on CL/F ×(WT [kg] /83.5)$^{\theta}$	0.881	23.2	0.481 – 1.28	
WT on V/F ×(WT [kg] /83.5)$^{\theta}$	1.00 Fixed			
BMI on V/F (BMI [kg/m^2]/28.2)$^{\theta}$	1.42	22.8	0.784 – 2.05	
Dose 100 mg on CL/F ×exp(θ)	-0.212	40.6	-0.381 – -0.0435	
Residual Error				
Additive error on logscale	0.362	1.01	0.355 – 0.370	
Between Subject Variability (Standard Deviation, CV%)				
On CL/F	0.338 (34.8%)	10.3	0.270 – 0.407	32.6
On V/F	0.551 (59.6%)	8.82	0.456 – 0.646	15.0
On Ka1	0.413 (43.2%)	12.0	0.316 – 0.511	27.1
Inter-Occasion Variability				
Frel at 1st dose	0.414 (43.2%)	3.03	0.389 – 0.438	37.9
Frel at 2nd dose	Same			24.6

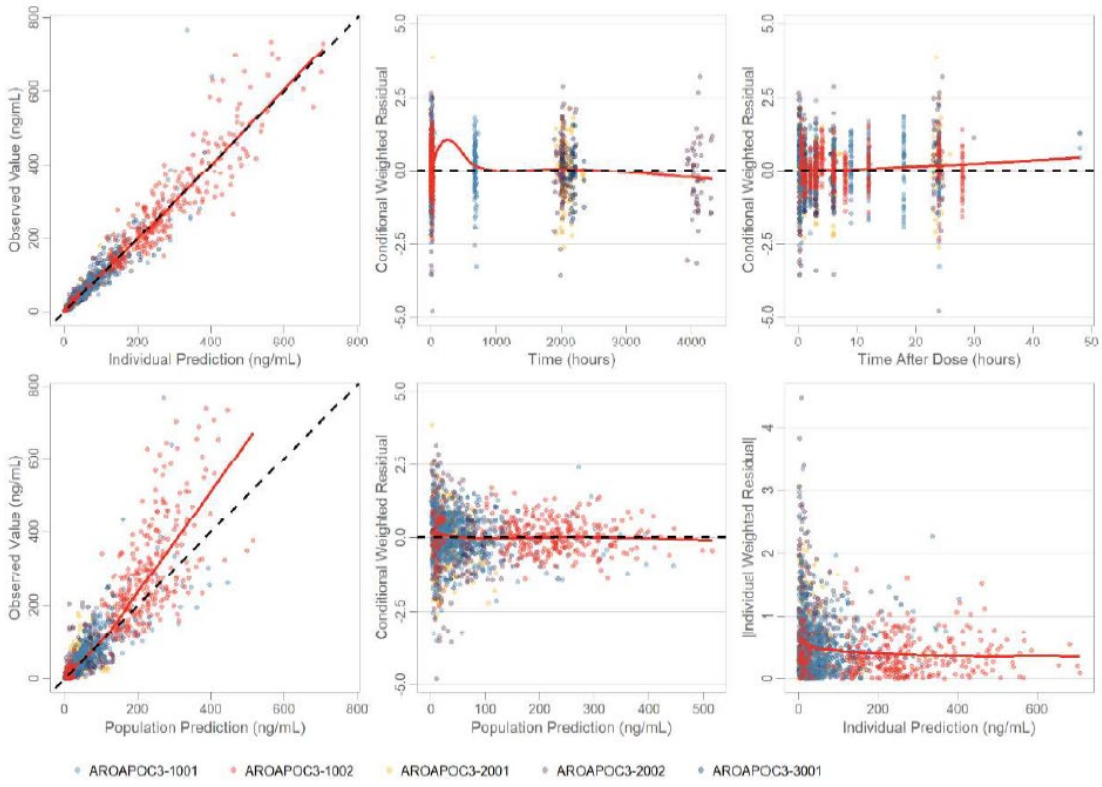
BMI= body mass index; CI= confidence interval; CL/F= apparent clearance; F1= fraction of absorbed dose in absorption compartment #1; Frel= relative fraction of absorption; Ka1= first-order rate constant in absorption compartment #1; Ka2= first-order rate constant in absorption compartment #2; nCL= individual variation of apparent clearance; nKA1= individual variation of first-order rate constant in absorption compartment #1; nOCC1= individual inter-occasion of relative fraction of absorption of first dose; nOCC2= individual inter-occasion of relative fraction of absorption of second dose; nV1= individual variation of apparent volume of distribution; RSE= relative standard error; V/F= apparent volume of distribution; WT= body weight

The final model indicated that 58.7% of the absorbed dose was absorbed with a fast rate of absorption (i.e., Ka1=1.03 h-1, absorption half-life of 40 min) without a lag-time. With the lag-time of 5.01 h for the absorption compartment number 2, the absorption process of 1st compartment is expected to be almost completed at the beginning of the 2nd phase of absorption. The remaining absorbed dose (41.3%) was absorbed with a slower rate (Ka2= 0.421 h-1, absorption half-life of 1.6 h).

For a subject with FCS and the mean body weight of 67.9 kg, CL/F and V/F of ARO-APOC3 are predicted to be 33.9 L/h and 166 L, respectively, corresponding to an elimination half-life (t1/2) of 3.4 h. CL/F is expected to be 39.7% lower for a subject weighing 47 kg, and 59.6% higher for a subject weighing 142 kg, compared to a reference subject with WT of 83.5 kg (the median value for the pooled population in this analysis).

The performance of the final population PK model of ARO-APOC3 was evaluated using goodness-of-fit graphs as presented in Figure 5.

Figure 3: Goodness of fit graphs for the final plozasiran popPK model



The appropriateness of the model to perform simulations was also evaluated using VPCs on plasma concentration-time profiles of plozasiran (Figure 6 and 7). A total of 1000 replicates of the original observed concentration of plozasiran were simulated with the final population PK model.

Figure 4: Visual predictive check for plozasiran PK profile after one or two SC injections (study AROAPOC3-3001)

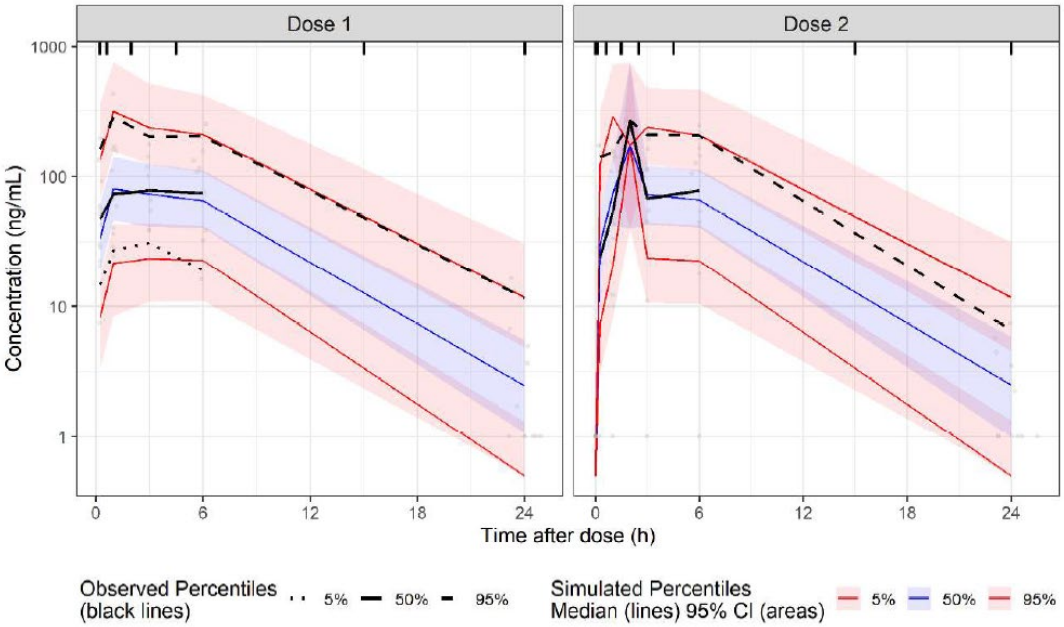
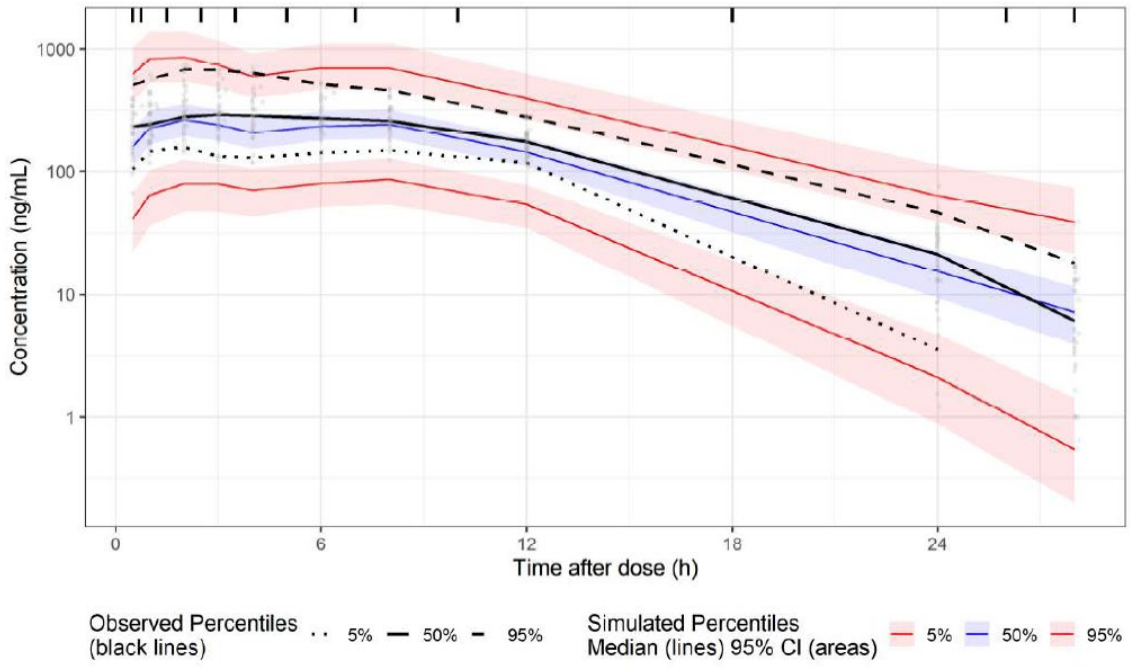


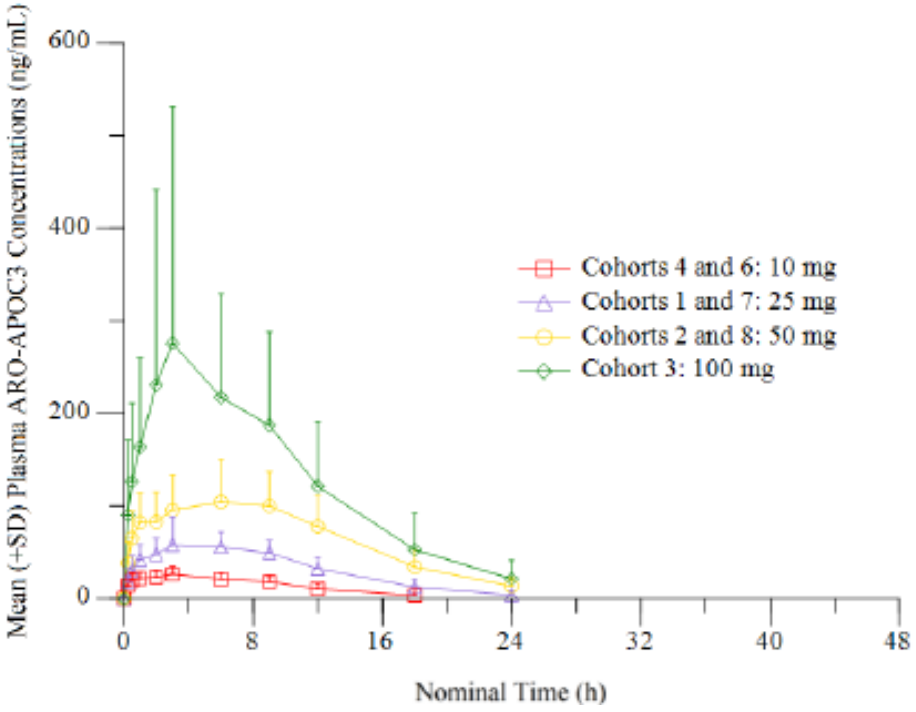
Figure 5: Visual predictive check for plozasiran PK profile after SC injection (study AROAPOC3-1002)



5.2.2.3. Absorption

After SC injection of a 25 mg dose, based on NCA, plozasiran exhibits systemic absorption with a median Tmax value around 6 hours. The peak plasma concentration (Cmax) after the 25 mg dose is 68.5 ng/mL. No absolute bioavailability is studied in human. Assuming the SC dose bioavailability is the same as in cynomolgus monkey, it is expected to be 40%.

Figure 6: Plozasiran PK profiles in SAD study (study AROAPOC3-1001)



5.2.2.4. Bioequivalence

Study AROAPOC3-1003 was conducted to assess the relative bioavailability/ bioequivalence of 25 mg plozasiran formulated as 50 mg/mL solution in PFS (test formulation = intended commercial formulation), compared to 25 mg plozasiran formulated as 200 mg/mL solution in vials (reference formulation = used in clinical studies). The study was conducted as an open-label, randomized, 2-cohort, 2-sequence, 2-period crossover study in healthy adult subjects. A washout period of 6 weeks was used. Results are depicted below (Table 13).

Table 10: Statistical summary of treatment comparison 25 mg test (PFS) v.s. 25 mg (vial) (study AROAPOC3-1003)

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means (%)	90% CI for Ratio
	Test (PFS)	Reference (Vial)		
Cohort 1: 25 mg Dose Level Plozasiran Formulation B (Test) vs. Plozasiran Formulation A (Reference)				
$AUC_{0\text{-}inf}$ (ng*h/mL)	1025 (n=18)	893.6 (n=15)	114.68	[106.28, 123.73]
$AUC_{0\text{-}t}$ (ng*h/mL)	987.7 (n=19)	812.7 (n=19)	121.53	[111.82, 132.09]
C_{max} (ng/mL)	100.9 (n=19)	88.35 (n=19)	114.18	[99.57, 130.94]

Cohort 1 Reference=25 mg (Vial, 200 mg/mL); Cohort 1 Test=25 mg (PFS, 50 mg/mL)

5.2.2.5. Distribution

The plozasiran unbound fraction for human plasma was 22% at a test concentration of 5 µg/mL.

The final popPK model showed an V/F of 204L indicating that plozasiran distributed outside of the systemic blood compartment. Subsequent to distribution in plasma and extracellular body water, plozasiran is primarily delivered to the liver mediated by the action of ASGPR expressed in

hepatocytes after delivery into the liver, and that plozasiran is minimally redistributed back to plasma circulation.

To assess the potential of plozasiran as a substrate of human BCRP and P-gp (MDR1) efflux transporters, a bidirectional permeability assessment was performed in MDCKII-BCRP and Abcb1KO-MDCKII-MDR1 monolayer assays, at several concentrations up to 156 µg/mL over 2 hours. Plozasiran showed very low permeability across the monolayer cell membranes.

Plozasiran was also evaluated as a potential substrate of the human uptake drug transporters, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2 SLC *in vitro*. Up to the highest test concentrations of 156 µg/mL, plozasiran was not a substrate for any of the above uptake transporters (SR-01236).

5.2.2.6. Metabolism

The metabolic stability of plozasiran was evaluated *in vitro* in the human liver subcellular S9 fractions to investigate the function of cytochrome P450s (CYPs) and uridine diphosphate (UDP)-glucuronosyltransferases (UGTs). Plozasiran was found to be metabolically stable during the 2 hours of incubation. Furthermore, no metabolites of plozasiran were identified after 2 hours of incubation related to the enzymatic activity of CYPs or UGTs.

Plozasiran is expected to be primarily metabolized by ribonucleases (RNases) in the liver to shorter oligonucleotides of varying lengths.

5.2.2.7. Elimination

The terminal elimination half-life of plozasiran in plasma is approximately 3-4 hours. The mean apparent systemic clearance is 33.8 L/hour. Plozasiran is active inside hepatocytes with prolonged pharmacodynamic (PD) activity that is disconnected from its PK profile in the plasma compartment.

Approximately 14% to 19% of the dose administered was recovered in urine as unchanged plozasiran. The mean (±SD) value of renal clearance for all subjects was 5.14±0.94 L/h, which is below the typical glomerular filtration rate (GFR) in healthy adults (~7.5 L/h).

5.2.2.8. Dose proportionality and time dependency

Plozasiran apparent SC dose clearance (CL/F) was dose-independent across the dose cohorts with an overall mean (±SD) value of 33.6±7.7 L/h, in the phase I study. Dose and/or time dependency was reported after single- and multiple-dosing.

Table 11: Plozasiran SD PK parameters (study AROAPOC3-1001)

Dose (mg) (No. of Subject)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h)
Single Dose Cohorts						
10 (n=6)	27.4 ± 5.45	4.5 (1.2-9.0)	290 ± 52.4	304 ± 53.4	3.7 ± 0.84	33.8 ± 5.77
25 (n=6)	67.0 ± 37.0	6.0 (3.0-9.0)	686 ± 100	686 ± 109	2.8 ± 0.62	37.2 ± 6.01
50 (n=6)	122 ± 47.5	6.0 (6.0-9.0)	1470 ± 398	1550 ± 420	4.5 ± 1.7	34.6 ± 10.9
100 (n=6)	318 ± 243	9.0 (3.0-9.1)	3100 ± 1100	3270 ± 1230	3.6 ± 1.4	34.8 ± 14.8
Multiple Dose Cohorts (the 1st dose)						
10 (n=4)	29.1 ± 10.9	3.0 (3.0-6.0)	263 ± 90.0	294 ± 93.7	2.9 ± 0.84	36.1 ± 9.75
25 (n=4)	68.6 ± 6.71	7.6 (6.0-9.0)	810 ± 80.8	838 ± 83.9	3.8 ± 0.97	30.1 ± 3.24
50 (n=4)	119 ± 39.6	7.5 (1.0-9.0)	1750 ± 299	1790 ± 337	5.0 ± 2.2	28.7 ± 5.84

Abbreviations: AUC_{0-inf}=Area under the time-concentration curve from time 0 to infinity; AUC_{0-t}=Area under the time-concentration curve from time 0 to the last measurable concentration; CL/F; apparent dose clearance; No.=number; $t_{½}$=half-life.
Parameter values are presented as arithmetic mean ± SD. T_{max} is presented as median (range).

Table 12: Plozasiran MD (2nd dose) PK parameters (study AROAPOC3-1001)

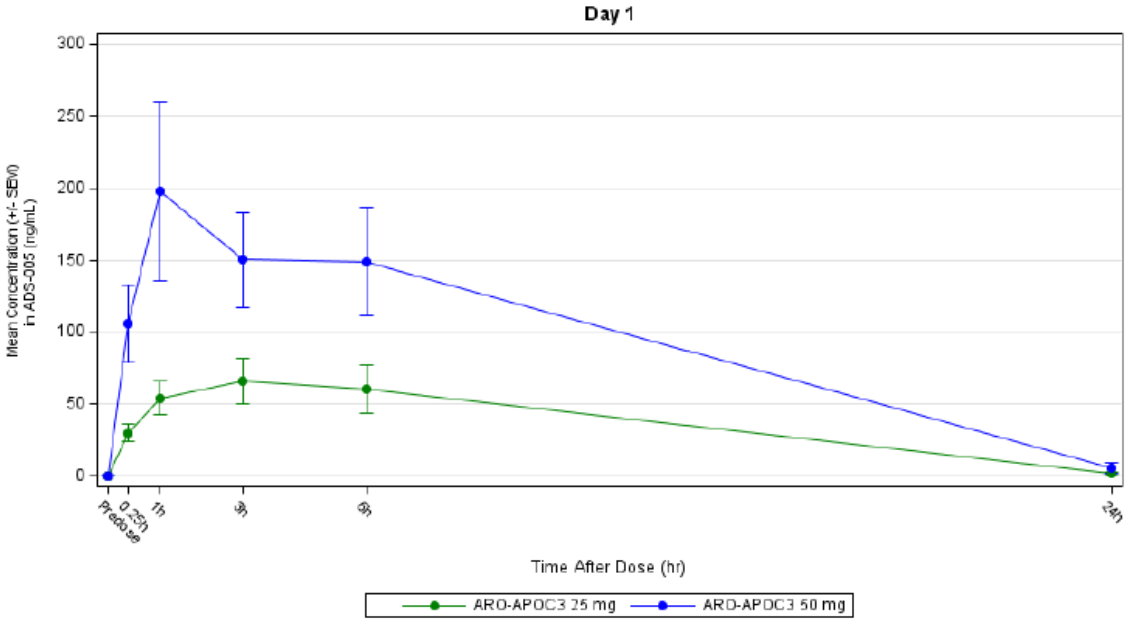
Dose (mg) (No. of Subjects)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h)
10 (n=3)	25.5 ± 7.21	3.0 (2.0-6.0)	277 ± 52.0	294 ± 69.0	3.9 ± 1.1	35.1 ± 7.26
25 (n=4)	70.8 ± 11.4	4.5 (3.0-6.0)	746 ± 57.4	754 ± 58.8	3.1 ± 0.48	33.3 ± 2.68
50 (n=4)	124 ± 52.7	6.0 (3.0-12)	1540 ± 261	1600 ± 248	5.0 ± 2.1	31.8 ± 5.10

Abbreviations: AUC_{0-inf}=Area under the time-concentration curve from time 0 to infinity; AUC_{0-t}=Area under the time-concentration curve from time 0 to the last measurable concentration; CL/F; apparent dose clearance; No.=number; $t_{½}$=half-life.
Parameter values are presented as arithmetic mean ± SD. T_{max} is presented as median (range).

5.2.2.9. Pharmacokinetics in the target population

The population PK modelling results indicated that disease state was not a covariate (i.e. FCS compared to other patient populations or healthy volunteers) and did not alter plozasiran PK. PK data from the FCS subjects in the phase 3 study with relatively dense PK sampling at pre-dose and, 0.25, 1, 3, 6, and 24 hours post-dose (n=12) is provided in Figure 9 below.

Figure 7: Plot of mean (± SEM) plasma PK profiles for plozasiran (study AROAPOC3-3001)



The variability in AUC and C_{max} is summarized in table 16. After the first dose, the arithmetic CV% was 30.6% and 50.2% for AUC_{inf} and C_{max} respectively, for the FCS population. After the second dose, the arithmetic CV% was 31.9% and 52.1% for AUC_{inf} and C_{max} respectively, for the FCS population. These values obtained in the FCS population are generally comparable to the PK variability observed in healthy subjects in the Phase 1 study AROAPOC31001.

Table 13. Model-Simulated Plozasiran Plasma Exposure Parameters in FCS Population

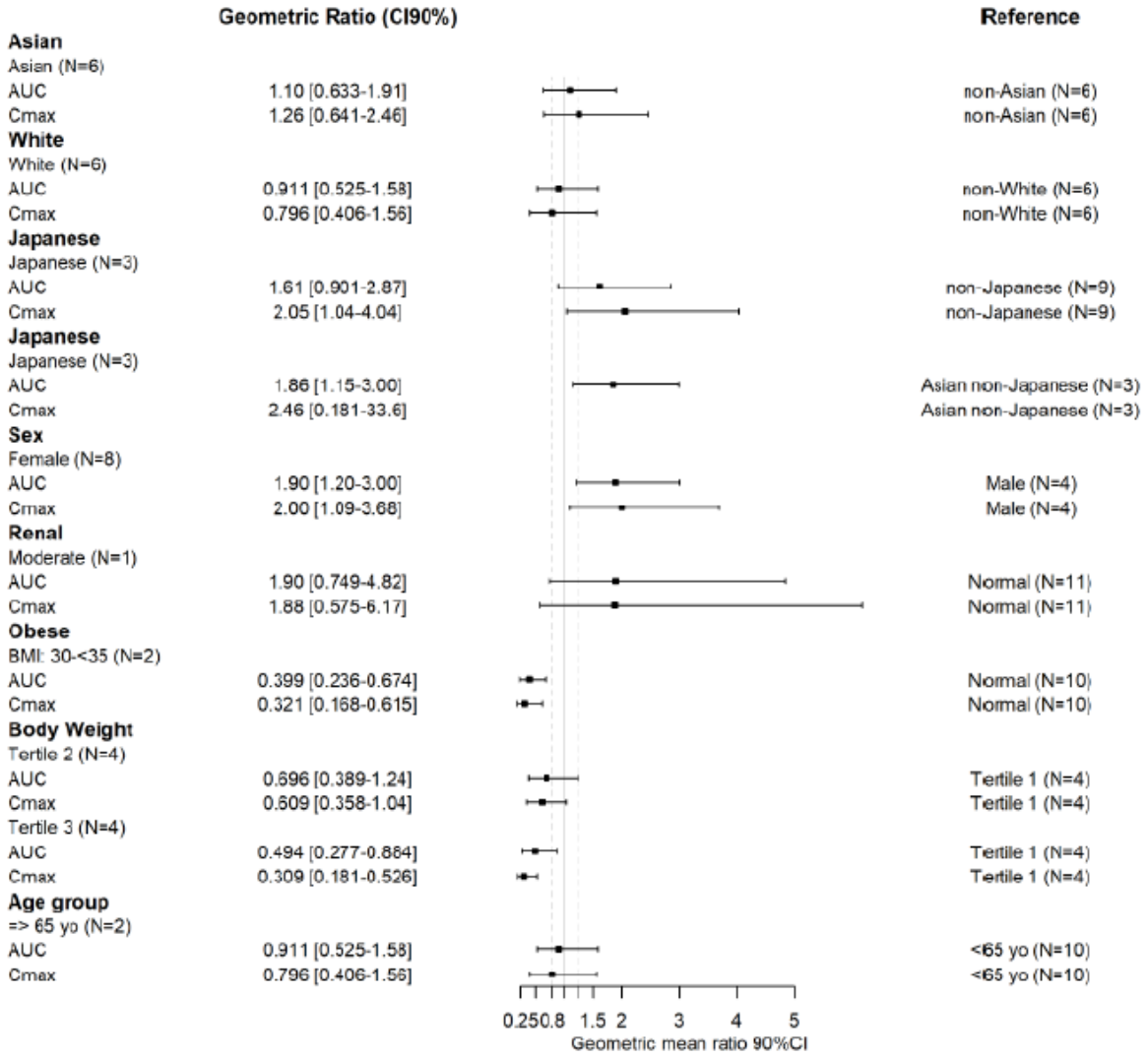
Exposure Parameters	**First Dose (N=1000)**	**Second Dose (N=1000)**
AUC (ng*h/mL)		
Mean (CV%)	751(30.6%)	760(31.9%)
Median [Min, Max]	713 [255, 1980]	721 [290,2060]
GeoMean [GeoCV%]	718 (31.0%)	724 (31.7%)
C_{max} (ng/mL)		
Mean (CV%)	73.7(50.2%)	74.7(52.1%)
Median [Min, Max]	65.1 [15.2, 329]	64.2[17.1, 343]
GeoMean [GeoCV%]	65.7(50.8%)	66.3(51.7%)

5.2.2.10. Special populations

No dedicated studies in special populations were performed. A popPK analysis was conducted to investigate effects of different factors on exposure. The final population PK model of plozasiran was utilized to obtain individual exposure levels (Cmax and AUC0-48 postdose) after single SC administration of 25 mg Plozasiran for each subject with intensively collected PK samples included in

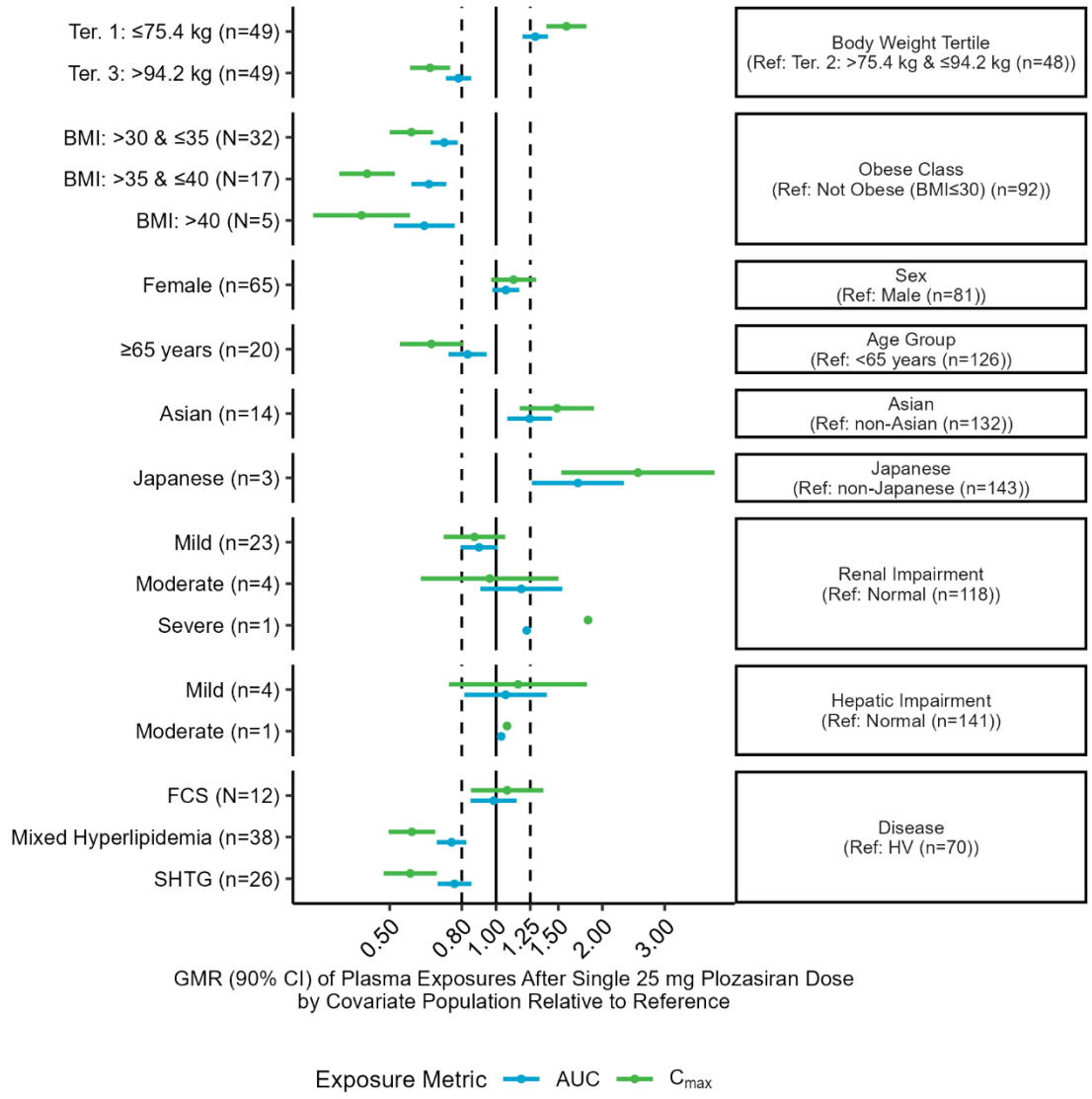
the PK population of phase 3 Study AROAPOC3-3001. This population includes 12 subjects (figure 10 below).

Figure 8: Post hoc subgroup analysis of plozasiran Cmax and AUC after one 25 mg SC injection in FCS subjects



A forest plot has also been generated based on the complete dataset of 146 subjects using the final popPK model, as shown in Figure 11 below.

Figure 9. Forest Plot of Covariate-Stratified Plasma Exposures (Cmax and AUC) After a Single Dose of 25 mg Subcutaneous Plozasiran Derived from Posterior Parameter Simulations



Abbreviations: AUC=area under the plasma concentration versus time curve from 0 to 48 hours after dosing; BMI=body mass index; CI=confidence interval; Cmax=maximum plasma concentration; FCS=familial chylomicronemia syndrome; GMR=geometric mean ratio; HV=healthy volunteer; Ref.=reference population; SHTG=severe hypertriglyceridemia; Ter.=tertile
Note: Black points and error bars reflect the geometric mean ratio and 90% CI of exposure metrics of the covariate population with reference to the reference population. The solid and dashed gray lines represent unity and the interval [0.80, 1.25], the traditional criteria for bioequivalence. CIs are omitted for comparisons where n=1.

No dedicated clinical studies have been conducted to investigate the effect of renal/hepatic impairment on plozasiran PK, PD and safety.

5.2.2.11. Pharmacokinetic interaction studies

In vitro studies were conducted to assess the potential of plozasiran to cause clinical drug-drug interactions (DDIs) via a set of cytochrome P450s (CYPs) enzymes or drug transporters that are

commonly involved in drug metabolism or transports.

Plozasiran was preincubated at 6 concentrations (16, 32, 64, 96, 128, 160 µg/mL, i.e. 1.0. 2.0, 4.1, 6.1, 8.2, 10.2 uM), above EMA cutoffs (50xCmax(u) = 0.05 uM), for 30 minutes with human liver microsomes (HML). The rates of metabolism for a set of specific and prototypical substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 were not affected by the presence of plozasiran.

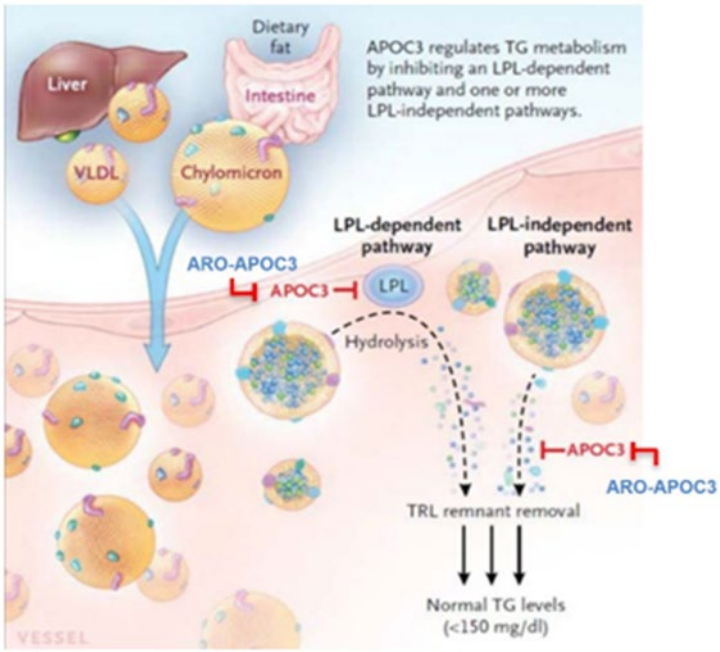
5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Plozasiran is a small interfering RNA (siRNA, double-stranded oligonucleotide) conjugated with N acetylgalactosamine to facilitate delivery to and uptake by hepatocytes. In hepatocytes, plozasiran selectively degrades the mRNA for apolipoprotein C3 (APOC3) through the RNA interference mechanism resulting in reduced levels of hepatic and serum APOC3 protein. This, in turn, enhances the activity of lipoprotein lipase and hepatocyte uptake of TG-rich lipoprotein remnants leading to decreases in serum TG.

The NAG moiety of the plozasiran molecule targets the RNAi trigger to hepatocytes by acting as a ligand for the highly expressed, hepatocyte-specific asialoglycoprotein receptor. Non-clinical distribution studies have confirmed that plozasiran is primarily distributed to the liver, where the trigger molecule is taken up by hepatocytes via receptor-mediated endocytosis.

Figure 10: Regulation of triglyceride metabolism and role of apoC3



Abbreviations: APOC3=apolipoprotein C-III; ARO-APOC3=plozasiran; LPL=lipoprotein lipase; TG=triglyceride(s); TRL=triglyceride-rich lipoprotein; VLDL=very low-density lipoprotein.

5.2.3.2. Primary and secondary pharmacology

Primary pharmacology

The pharmacodynamic effects of plozasiran on ApoC3 and TG were evaluated after single and multiple dose administrations in healthy subjects and in subjects with severe hypertriglyceridemia (SHTG), mixed hyperlipidemia (MH), FCS or non-FCS chylomicronemia (CM) in studies AROAPOC3-1001, AROAPOC3-1003, AROAPOC3-2001, AROAPOC3-2002, and AROAPOC3-3001 (Table 1). The studies AROAPOC3-1001 and AROAPOC3-1003 are presented below, the studies AROAPOC3-2001 and AROAPOC3-2002 are presented in section 6.3.1 "Dose response studies" and the study AROAPOC3-3001 is presented in section 6.3.2 "main study".

Single and multiple dose escalation study (study AROAPOC3-1001)

Study AROAPOC3-1001 was a first-in-human, multicenter, placebo-controlled or open-label, dose escalating study to evaluate the safety, tolerability, PK and PD profiles of plozasiran in healthy volunteers, as well as in patients with SHTG, genetically confirmed and clinically diagnosed FCS. A total of 112 subjects were enrolled in the study, and the duration of the primary study was 16 weeks excluding the screening period. Single and repeat doses (every 4 weeks [Q4W]) of 10 mg, 25 mg, 50 mg and 100 mg were evaluated in this study. The single ascending dose (SAD) part of the study was double-blinded, with participants receiving either ARO-APOC3 or placebo (ie, matching volume of normal saline [0.9%]). The multiple ascending dose (MAD) part of the study was open-label with all participants receiving 2 doses of ARO-APOC3. Intensive blood samples were collected in the healthy subjects for determination of plozasiran plasma PK. Plozasiran PD responses were assessed primarily by the changes from baseline in the 2 circulating biomarkers, serum APOC3 protein and TG in all subjects.

Results

All patients completed the study, and no participants were lost to follow-up or withdrew from the study.

Mean APOC3 levels at baseline ranged from 7.9 to 10.4 mg/dL in the healthy volunteers, and from 24.5 to 34.8 mg/dL in the patients with SHTG. Mean baseline APOC3 value was 48.1 mg/dL in the patients with genetically confirmed FCS and was 42.3 mg/dL in patients with clinically diagnosed FCS.

Following plozasiran administrations in the healthy subjects, the mean maximum reductions from baseline in serum APOC3 demonstrated a dose response with increasing doses, ranging from 82% to 94% after single dose administrations of 10 to 100 mg, and from 83% to 94% after repeat doses of 10 to 50 mg administered 4 weeks apart. In the subjects with SHTG, the mean maximal reductions in APOC3 were from 83% to 98% following 2 repeat doses of 10 mg, 25 mg, 50 mg and 100 mg administered 4 weeks apart. The lower responses of 82% to 83% were all associated with the 10 mg dose. The patients with clinically diagnosed FCS and genetically confirmed FCS who were dosed 50 mg on Day 1 and Day 29 had mean maximum reductions of 97% and 99% in APOC3, respectively. In all subject populations, the responses in mean serum APOC3 reduction were deep and durable especially for doses higher than 10 mg, lasting at least 16 weeks following 1 or 2 doses of plozasiran.

Mean TG levels at baseline ranged from 1.34 to 1.66 mmol/L (119 to 147 mg/dL) (median 1.31 to 1.66 mmol/L [116.0 to 147.0 mg/dL]) in the healthy volunteers, and from 6.90 to 14.92 mmol/L (611 to 1320 mg/dL) (median 5.41 to 19.38 mmol/L [478.5 to 1715.0 mg/dL]) in patients with SHTG. Mean baseline TG value was 26.78 mmol/L (2370 mg/dL) (median 19.38 mmol/L [1715.0

mg/dL]) in patient with genetically confirmed FCS and was 22.04 mmol/L (1950 mg/dL) (median 5.41 to 5.77 mmol/L [478.5 to 511.0 mg/dL]) in patients with clinically diagnosed FCS.

Following plozasiran administrations, there was no discernible hysteresis between TG and serum APOC3 responses, and the mean TG levels decreased by more than 62% at maximal percent reduction in all populations. Mean maximum TG reductions were generally dose dependent, ranged 62% to 69% and 67% to 76% following single and repeat dose administrations in HV volunteers, respectively, and 79% to 89% following 2 doses in subjects with SHTG. The patients with clinically diagnosed FCS and those with genetically confirmed FCS showed mean maximum reductions in TG of 92% and 89%, respectively, after receiving two 50 mg plozasiran doses on Day 1 and Day 29. The TG-lowering treatment benefit was durable and lasted at least through 16 weeks following either a single or double doses (4 weeks apart) of 25 mg or higher in all subjects.

Table 14: Summary of Plozasiran PD Parameters

	HV-SAD				**HV-MAD**			**Clinically diagnosed FCS****	**Genetically confirmed FCS*****	**SHTG**			
	10 mg x1	**25 mg x1**	**50 mg x1**	**100 mg x1**	**10 mg x2 Q4W**	**25 mg x2 Q4W**	**50 mg x2 Q4W**	**50 mg x2 Q4W**	**50 mg x2 Q4W**	**10 mg x2 Q4W**	**25 mg x2 Q4W**	**50 mg x2 Q4W**	**100 mg x2 Q4W**
Triglycerides													
Max change (%)	-62.0 ±7.96	-67.5 ±9.84	-68.1 ±5.48	-69.4 ±16.1	-67.3 ±6.04	-71.3 ± 8.11	-75.7 ± 7.36	-92.2 ±4.64	-89.3 ±7.88	-78.9 ±8.90	-88.6 ±6.40	-86.3 ±6.23	-87.2 ±6.69
*T_{onset} (day)	6.4 (2.0-17)	9.6 (1.9-20)	5.5 (1.8-11)	4.3 (1.6-6.6)	6.7 (1.8-11)	5.3 (2.0-19)	2.4 (1.8-3.4)	5.0 (4.3-14)	9.1 (5.4-13)	7.7 (4.1-20)	5.1 (4.6-10)	4.9 (3.9-20)	4.5 (3.8-5.6)
T_{max} (day, from D1)	28 (14-98)	49 (14-98)	28 (14-70)	63 (28-110)	28 (14-28)	56 (42-84)	56 (21-110)	65 (15-210)	70 (56-110)	42 (28-98)	56 (28-110)	43 (13-84)	42 (28-240)
APOC3													
Max change (%)	-82.3 ±15.7	-90.1 ±7.61	-88.9 ±7.14	-93.8 ±1.48	-83.0 ± 10.0	-93.8 ±2.86	-94.2 ± 0.950	-97.2 ± 2.80	-98.6 ± 0.528	-82.6 ±7.90	-94.8 ±5.01	-96.6 ±3.28	-98.2 ± 0.609
*T_{onset} (day)	6.3 (3.0-18)	4.6 (3.5-7.4)	4.3 (1.6-11)	3.2 (1.6-5.0)	7.3 (4.4-12)	6.5 (4.7-7.9)	3.0 (2.5-3.6)	4.5 (3.5-13)	5.1 (4.0-9.7)	6.6 (4.3-11)	5.1 (4.1-6.2)	3.9 (3.6-6.5)	4.0 (3.5-4.3)
T_{max} (day, from D1)	25 (7.0-70)	21 (7.0-56)	17 (7.0-70)	10 (7.0-15)	56 (42-98)	49 (42-110)	8.0 (7.0-14)	42 (6.9-57)	35 (14-110)	42 (28-98)	42 (28-56)	14 (6.9-56)	14 (7.0-49)

Abbreviations: CS=chylomicronemia syndrome; D=Day; FCS=familial chylomicronemia syndrome; HV=healthy volunteers; MAD=multiple ascending dose; Q4W=every 4 weeks; SHTG=severe hypertriglyceridemia; SAD=single ascending dose.
Max change is the percent maximum change of serum level from baseline.
*The PD onset time (Tonset) is defined as the first time to observe a 50% reduction from baseline for the biomarker. Max change is the percent maximum change of serum level from baseline. Max change values are presented as arithmetic mean ±SD. Tonset and Tmax values are presented as median (min-max).
** Clinically diagnosed FCS previously known as non-FCS CS
*** Genetically confirmed FCS previously known as FCS

Figure 11: Mean (+/-SD) Serum Concentrations of Triglycerides versus Time by Dose (US) in healthy volunteers – SAD at Day 1

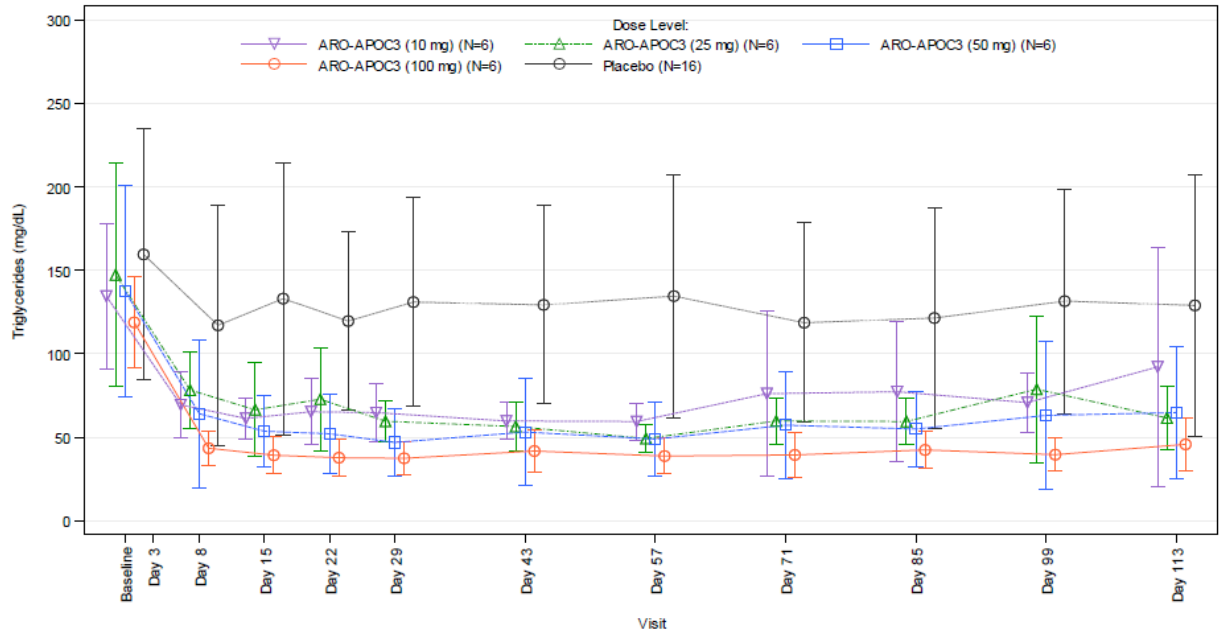


Figure 12: Mean (+/-SD) Serum Concentrations of Triglycerides versus Time by Dose (US) in healthy volunteers – MAD at Day 1 and 29

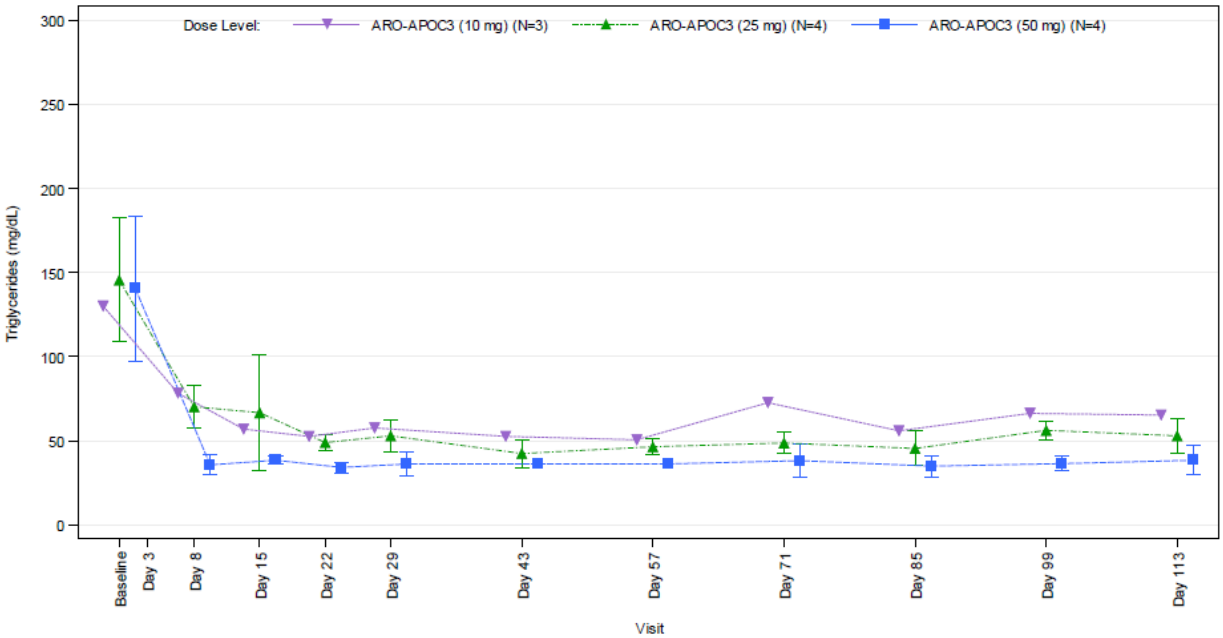


Figure 13: Mean (+/-SD) Serum Concentrations of Triglycerides versus Time by Dose (US) in patients with high triglycerides ≥ 300 mg/dL- MAD at Day 1 and 29

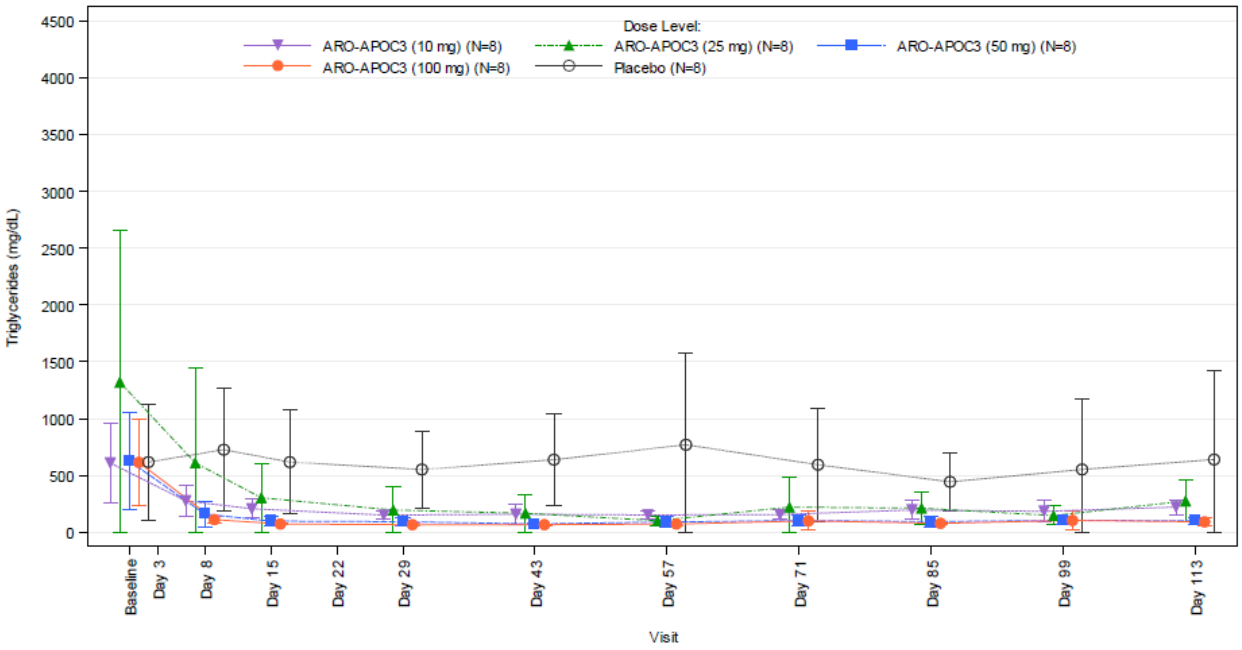
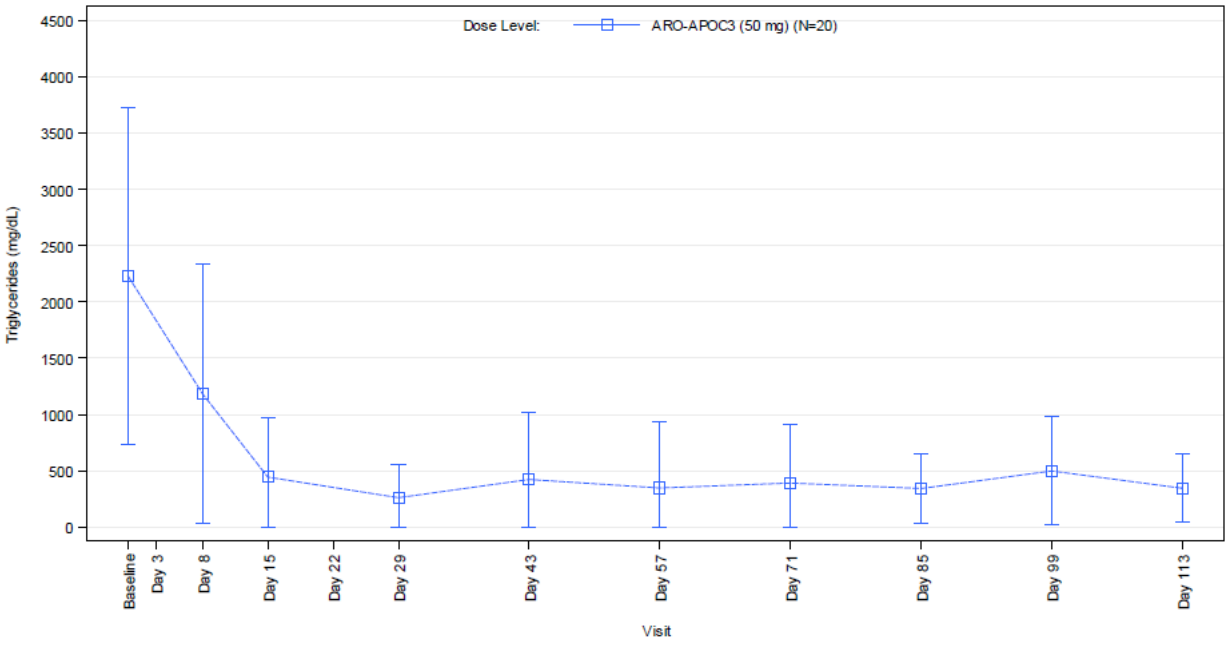


Figure 14: Mean (+/-SD) Serum Concentrations of Triglycerides versus Time by Dose (US) in patients with FCS – MAD at Day 1 and 29



Secondary pharmacology

QTc prolongation

Study AROAPOC3-1002 was a placebo and positive-controlled, double-blind (except for moxifloxacin), 3-way crossover thorough QT/QTc (TQT) study to evaluate the effects of a supratherapeutic dose (100 mg) of plozasiran on cardiac repolarization in healthy subjects. Thirty-six (36) healthy subjects were enrolled at a single center in the U.S. and randomized into 6 sequences to receive 3 treatments in 3 sequential treatment periods prespecified in a 6x3 crossover design. The 3 study treatments were (A) a single SC dose of 100 mg plozasiran, (B) a placebo SC injection with matching volume and appearance, and (C) moxifloxacin 400 mg tablet plus the placebo SC injection. The 100 mg supratherapeutic dose of plozasiran is 4-fold of the proposed therapeutic dose of 25 mg and was selected to provide adequate coverage of the highest possible plasma exposure in humans under the worst of circumstances. Moxifloxacin was used as a positive control to establish assay sensitivity. Due to the short elimination t1/2 of plozasiran and moxifloxacin in plasma, a PK washout period of 7 days was instituted between the 3 treatment periods. As is typical for TQT studies, the study was conducted in healthy subjects due to two reasons: 1) this helped eliminate any variables from comorbidity that may potentially influence electrocardiogram (ECG) parameters, and 2) there was no significant PK difference between healthy volunteers and patient populations

In all subjects, intensive blood samples were collected up to 28 hours postdose following each study drug administrations. For evaluation of cardiac electrophysiology, continuous 12-lead ECG signals were collected using Holter monitors. Assessment of QT intervals and ECG waveforms was conducted by a central ECG laboratory. The primary endpoint of analysis was the baseline and placebo adjusted QTcF (ΔΔQTcF). The sample size was prospectively powered to support the primary statistical analysis of the effect of plozasiran on QT prolongation based on concentration-QTcF modeling of the relationship between plozasiran plasma concentration and ΔQTcF using a linear mixed effect (LME) model. The by-time point analysis was performed as a secondary analysis to evaluate the effect of plozasiran on placebo-corrected change from baseline in HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS, respectively) at each post-dosing time point using the Intersection Union Test. In addition, a categorical analysis was also performed for changes in HR, QTcF, PR, QRS, and ECG morphology.

In the concentration-QTc analysis, a linear regression model with acceptable fitting was developed to assess the relationship between the observed ΔQTcF values and time-matched plasma concentrations for both plozasiran and moxifloxacin. The effect on ΔΔQTcF is predicted to be 0.27 ms (90% CI: -1.14 to 1.67) at the geometric mean Cmax value of plozasiran (344 ng/mL) after a supratherapeutic dose of 100 mg SC plozasiran (Table 14). This result excluded the possibility that at the proposed therapeutic dose level of 25 mg, plozasiran can cause an increase in QTcF greater than 5 ms, which is the threshold of regulatory concern on the pharmacologic effect on cardiac repolarization.

In the by-time point analysis, the LS mean placebo-corrected ΔQTcF (ΔΔQTcF) after administration of plozasiran varied from 1.4 ms (at 24 hours post-dose) to 1.0 ms (at 3 and 6 hours post-dose) across post-dose time points. The upper bound of the 2-sided 90% confidence interval (CI) of ΔΔQTcF was less than 5 ms at all time points post-dose, providing reasonable assurance that the mean effect of a supratherapeutic dose of plozasiran on the QT/QTc interval is not greater than approximately 5 ms.

At the 100 mg dose level, plozasiran did not have clinically relevant effects on heart rate (HR), cardiac conduction or electrocardiogram (ECG) morphology, including PR and QRS. In the categorical analysis, none of the subjects dosed with 100 mg plozasiran had QTcF >450 ms post dose, or change-from-baseline QTcF (ΔQTcF) greater than 60 ms.

On the other hand, the positive control (moxifloxacin 400 mg) used in this TQT study has demonstrated the expected QT prolongation effect. In the concentration-QTc analysis conducted for

moxifloxacin using the same linear regression model for plozasiran, the positive slope (0.0043 ms per ng/mL) estimated was statistically greater than the value of 0 (90% CI: 0.00330 to 0.00530; $P < 0.0001$). In the by-time point analysis, moxifloxacin showed significant max increase in LS mean ΔΔQTcF of 11.3 ms (90% CI: 9.45 to 13.10) that was observed at 1 hour post dose. The lower bound of the 90% CI of ΔΔQTcF was above 5 ms at all time points between 1 and 8 hours post-dose, and the lower bound of the 2-sided 90% CI of the predicted effect on ΔΔQTcF (11.88 ms [90% CI: 10.31 to 13.45]) at the geometric mean peak moxifloxacin concentration (2356 ng/mL) was above 10 ms.

Table 15: Parameter Estimates from LME model and Model-Derived Prediction Results for ΔΔQTcF at Plozasiran Cmax of the Supratherapeutic Dose

Treatment	**Final model: Plozasiran Slope Estimate ΔQTcF (ms) per ng/mL of Plozasiran concentration Increase (90%CI)**			**Geometric mean C_{max} of 100 mg Plozasiran (ng/mL)**	**Model-Derived ΔΔQTcF Estimate (ms) (90% CI) at 100 mg Plozasiran C_{max}**	
	Estimate	P value	90% CI		Estimate	90% CI
Plozasiran 100 mg SC	0.0048	0.1754	-0.00106 - 0.01072	344	0.27	-1.14, 1.67

Abbreviation: CI= confidence interval; Cmax=maximum concentration; LME= linear mix effects; ΔQTcF=baseline-adjusted QTcF; ΔΔQTcF=baseline-adjusted placebo-corrected; QTcF; SC= subcutaneous

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Plozasiran is designed to selectively degrade the mRNA coded for APOC3 protein inside hepatocytes. In preclinical development, extensive algorithm-based in silico searches were incorporated into the chemistry design to ensure plozasiran has minimal potential to hit unintended off-target gene sequences. Also, a down regulation of APOC3 gene expression is not known to have any effect to modulate the expression of enzymes or transporters commonly involved in clinical drug-drug interactions, such as the CYPs or major efflux drug transporters. In vitro experimental data indicates plozasiran is neither a substrate nor inhibitor of major CYPs or drug transporters. Therefore, plozasiran has a low potential to be a precipitant or an object drug of DDIs caused by other concomitant medications capable of modulating CYP or transporter activity or expression.

5.2.3.4. Genetic differences in PD response

In a pre-specified subgroup analysis, the reductions in APOC3, the target of plozasiran, and TGs, the primary endpoint of the study, were consistent between subjects with genetically confirmed versus clinically diagnosed FCS.

5.2.3.5. Immunological events

In the phase 3 study AROAPOC3-3001 (PALISADE), none of the 50 subjects with FCS treated with plozasiran over the placebo-controlled period of 12 months developed treatment-induced or treatment-boosted anti-drug antibodies (ADAs) against plozasiran. There was no evidence to indicate that plozasiran PK or efficacy change over time with multiple administrations of plozasiran 25 mg Q3M.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Population kinetic PD modelling

Objective

A population kinetic-pharmacodynamic (K-PD) model of plozasiran specifically for the FCS patient population was developed. The PD biomarkers in this analysis were the changes from baseline in serum APOC3 and TG following plozasiran treatment. Potential covariate effects on these PD biomarkers were investigated for statistical significance and clinical relevance. In addition, model-based projection of plozasiran PD effects were conducted to assist selecting a therapeutic dose regimen.

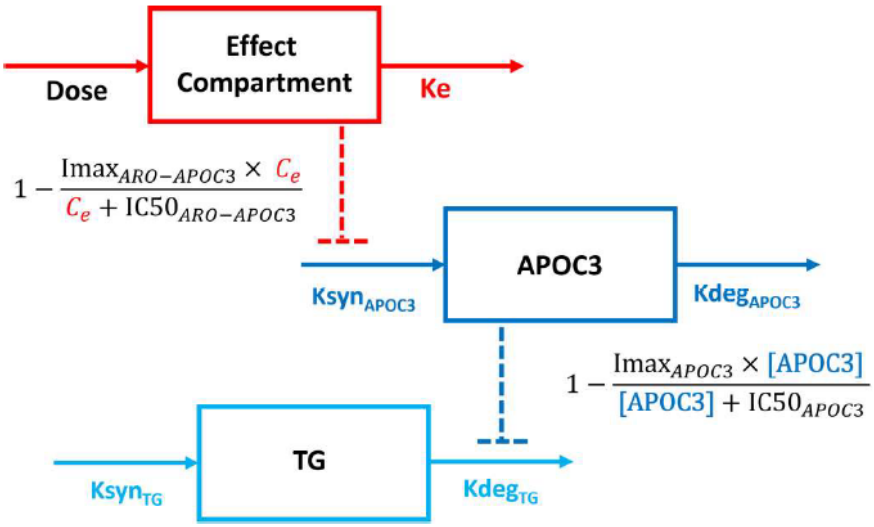
Clinical study data

Participants in the phase 3 study were randomized to receive 4 total SC doses of plozasiran of 25 mg once every 3 months (Q3M) or 50 mg Q3M, or matching placebo, with an allocation ratio of 2:1 (plozasiran vs placebo, n=75). Serum samples for fasting lipid/pharmacodynamic (PD) biomarkers, including APOC3 and TG, were collected at screening, at predose on Day 1, and at Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (lipids collected twice, 2 to 7 days apart), 11 and 12 post the initial treatment.

Methods

Population K-PD modeling and model validation were performed using NONMEM Version VII (version 7.4). The model incorporated a hypothetical effect compartment of plozasiran coupled with a serum APOC3 and TG turnover model. The plozasiran concentration in this compartment is unitless and is assumed to be proportional to the SC dose initially and decay over the time in a mono-exponential fashion with a first-order elimination rate constant from the effect compartment (Ke). Figure 13 is a schematic representation of this K-PD model. In this model, plozasiran in the effect compartment inhibits APOC3 biosynthesis in the liver, which in turn increases the rate of clearance of TG and thereby lowers its serum concentration.

Figure 15: Schematic representation of the population K-PD model for serum APOC3 and triglyceride levels after SC plozasiran



PD data was analysed using nonlinear mixed effects (NLME) modelling approach. The PD model consisted of a variance component characterizing inter-individual variability (IIV) and residual

unexplained variability. Estimates on shrinkage of ETAs of the model parameters was also evaluated for diagnostic purpose.

The following baseline covariates were considered in the covariate analysis for the population K-PD model of plozasiran: age, body weight, body mass index (BMI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), baseline alkaline phosphatase (ALP), albumin (ALB), bilirubin, eGFR, APOC3, TG, non-HDL-C, ApoB, FCS mutation, sex, race, ethnicity, Asian vs Non-Asian, Japanese vs non-Japanese, renal impairment, existing diabetic status based on hemoglobin A1c 6.5%), background TG-lowering therapies including Vascepa, omega-3 fatty acid or fish oil, statin or fibrate treatments. Hepatic impairment (HI) was not evaluated for potential covariate effect because all the FCS patients enrolled in Study AROAPOC3-3001 had normal HI at the baseline. Covariates selected from visual inspection were tested for statistical significance to influence plozasiran PD in a stepwise process that consisted of a stepwise forward-addition followed by a backward-elimination process. The likelihood ratio test was used to evaluate the significance of incorporating or removing fixed effects into the population model based on significance levels that are set a priori. For forward addition and backward elimination, significance levels of $p<0.05$ and $p<0.01$ were employed, respectively.

The quality-of-fit for development of the base and final models were evaluated using a model discrimination process including statistical criteria (OFV, condition number and Akaike information criterion [AIC]) as well as graphical representations of goodness of-fit (fitted and observed concentrations versus time, conditional weighted residuals). Visual predictive checks (VPC) were performed to allow visual comparison between distributions of simulated concentrations derived with the final models and those derived from the observed data.

Results

The value of KdegTG (i.e., the degradation rate constant of TG without any inhibitory effect from APOC3) was fixed to a same estimate in a previous model (i.e. phase II study model). The Imax values for APOC3 and TG were expected to approach 100% by the applicant and therefore were fixed at 100%. The IIV terms were incorporated for the baseline levels of APOC3 and TG, IC50ARO-APOC3, IC50APOC3, and Ke. A correlation between the random effects associated with the baseline levels of APOC3 and TG was included. Proportional residual errors on APOC3 and TG were used. The population K-PD model covariates retained after the covariate analysis were baseline levels of BMI on Ke and IC50APOC3, and TG-lowering therapy on IC50APOC3.

Table 16: Parameter estimates of the final plozasiran population K-PD model

Parameters	Estimate	RSE%	95% CI
Typical Values			
Ke (1/day)	0.0144	8.82	0.0119 – 0.0169
Baseline APOC3 (mg/dL)	30.9	5.34	27.7 – 34.2
$Ksyn_{APOC3}$ (mg/dL/h)	1.13 Fixed		
$Imax_{ARO\text{-}APOC3}$ (%)	100 Fixed		
$IC50_{ARO\text{-}APOC3}$ (mg)	2.185	18.3	1.401 – 2.969
ARO-APOC3 Hill coefficient (HILL)	1.00 Fixed		
Baseline TG (mg/dL)	1940	7.39	1659 – 2221
$Kdeg_{TG}$ (1/h)	0.724 Fixed		
$Imax_{APOC3}$ (%)	100 Fixed		
$IC50_{APOC3}$ (mg/dL)	17.4	59.9	-3.02 – 37.8
APOC3 Hill coefficient (HILL2)	1.00 Fixed		
Covariate Effects			
Observed Baseline APOC3 on Estimated Baseline APOC3 (baseline APOC3/34)$^{\theta}$	0.888	7.25	0.762 – 1.01
Observed Baseline TG on Estimated Baseline TG (baseline TG/2048)$^{\theta}$	1.05	9.15	0.864 – 1.24
Observed Baseline BMI on Ke (baseline BMI/25)$^{\theta}$	1.39	29.8	0.579 – 2.20
Observed Baseline BMI on $IC50_{APOC3}$ (baseline BMI/25)$^{\theta}$	-7.17	33.8	-11.9 – -2.42
Presence of TG lowering therapy on $IC50_{APOC3}$ exp(θ)	-1.79	35.6	-3.05 – -0.542
Between Subject Variability (Standard Deviation, CV%)			
On Ke	0.316 (32.4%)	17.9	0.205 – 0.427
On BASE1	0.176 (17.7%)	28.4	0.0780 – 0.274
On IC501	0.984 (128%)	17.1	0.654 – 1.31
On BASE2	0.337 (34.6%)	20.1	0.204 – 0.469
On IC502	0.765 (89.2%)	23.3	0.416 – 1.11
Correlation BASE1, BASE2	0.150 (15.1%)	129	-0.229 – 0.530
Residual Error			
APOC3 Proportional Error	36.2	2.04	34.8 – 37.7
TG Proportional Error	52.7	2.66	49.9 – 55.4

APOC3= apolipoprotein C3; BASE1= APOC3 baseline; BASE2= TG baseline; BMI= body mass index; CI= confidence interval; CV= coefficient of variation; IC501= $IC50_{APOC3}$; IC502= $IC50_{ARO\text{-}APOC3}$; HILL= APOC3 Hill coefficient; $IC50_{APOC3}$= effective concentration of APOC3 to provide 50% of the Imax on TG; $IC50_{ARO\text{-}APOC3}$= effective dose of ARO-APOC3 to provide 50% of the Imax on APOC3; K-PD= kinetic/pharmacodynamic; $Imax_{APOC3}$= maximum inhibition effect of APOC3 on TG; $Imax_{ARO\text{-}APOC3}$= maximum inhibition effect of ARO-APOC3 on APOC3; $Kdeg_{TG}$= first-order degradation rate constant of TG; Ke= elimination rate constant from the effect compartment; $Ksyn_{APOC3}$= baseline zero-order formation rate of APOC3; RSE = relative standard error; TG= triglyceride

Note 1: RSE values were based on NONMEM covariance step with MATRIX=S.

Note 2: Typical value of $Ksyn_{APOC3}$ was fixed to the previous value obtained in the previous model to achieve covariance step.

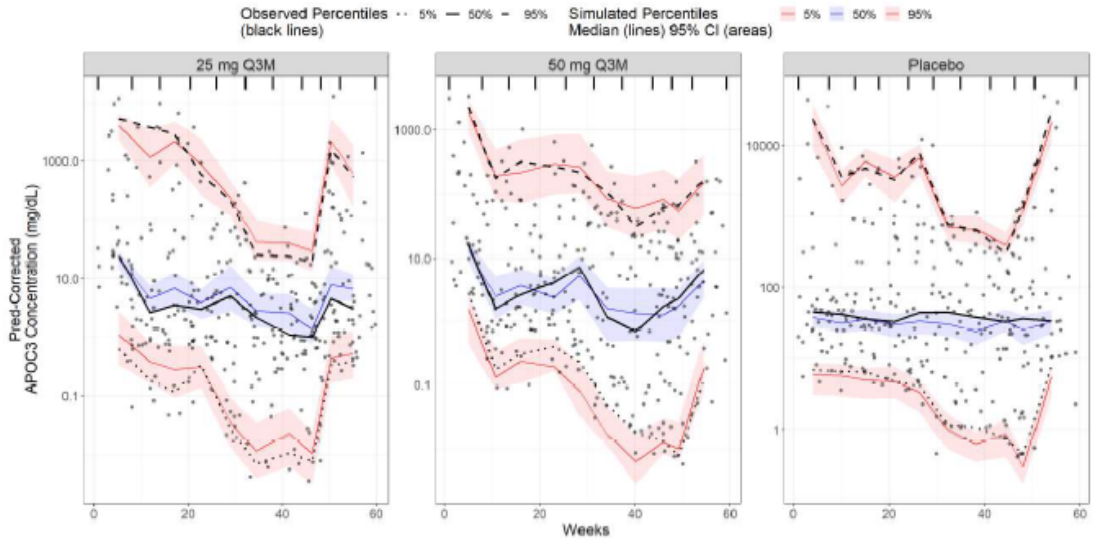
The estimated plozasiran elimination half-life (t1/2) in the effect compartment (liver), calculated as (0.693/Ke), was ~73 days, 48 days and 29 days in FCS patients with BMI of 18.5 kg/m2, 25 kg/m2 and 35.9 kg/m2, respectively. The population typical plozasiran dose to inhibit 50% of APOC3 (IC50ARO-APOC3) was estimated to be ~2.2 mg for subjects with FCS.

An inverse relationship was present between IC50APOC3 (the APOC3 concentration to inhibit 50% of TG degradation rate) and BMI; i.e., a higher degree of APOC3 normalization is required to achieve TG lowering in subjects with lower BMI. Due to the fact that BMI has an effect on Ke/half-life and IC50APOC3, for the same dose regimen of plozasiran, the time-averaged plozasiran effect compartment concentrations may be higher in subjects with FCS and lower BMI, driving deeper APOC3 reductions. However, the resulting response in TG reductions is less pronounced in subjects with lower BMI in comparison to subjects with higher BMI, due to the BMI effect on IC50APOC3.

Subjects on background TG lowering therapy are estimated to have 83% lower IC50APOC3 (i.e. 2.90 mg/dL for subjects with TG lowering therapy, compared to 17.4 mg/dL for subjects without the background therapy, assuming a median BMI of 25 kg/m2).

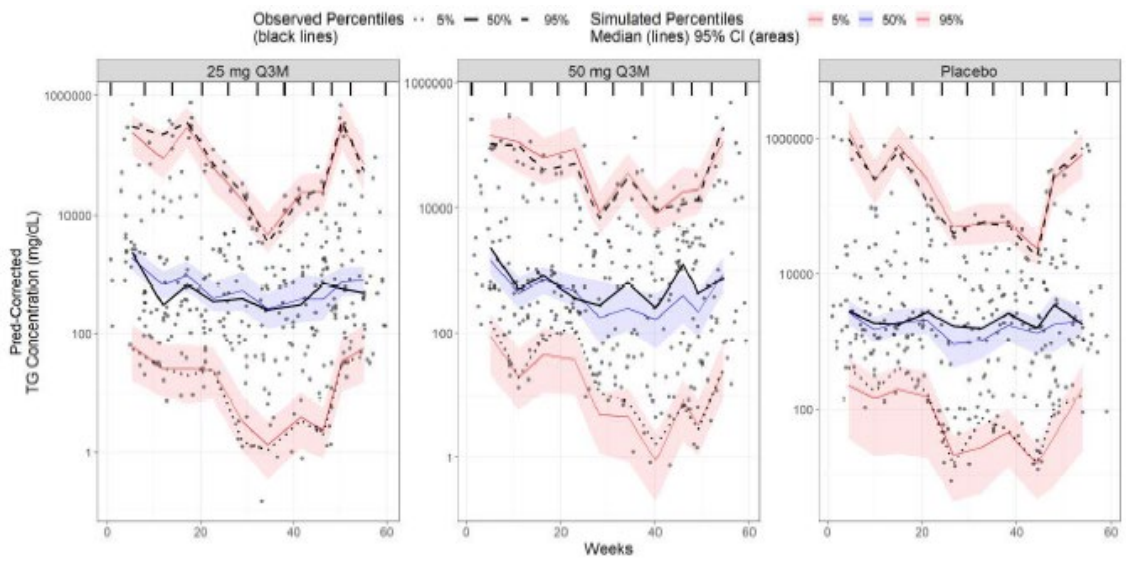
The appropriateness of the current K-PD model to perform simulations was evaluated using serum APOC3 and TG pcVPCs with 500 replicates. These are presented in Figure 18 for APOC3 and in Figure Figure 19 for TG.

Figure 16: pcVPC for serum APOC3 after administration of plozasiran in FCS subjects



APOC3= apolipoprotein C3; CI= confidence interval; FCS= familial chylomicronemia syndrome; LLOQ= lower limit of quantitation; Q3M= every 3 months
Note: APOC3 levels below 0.94 mg/dL were set to half of the LLOQ (i.e., ½ × 0.94 mg/dL)

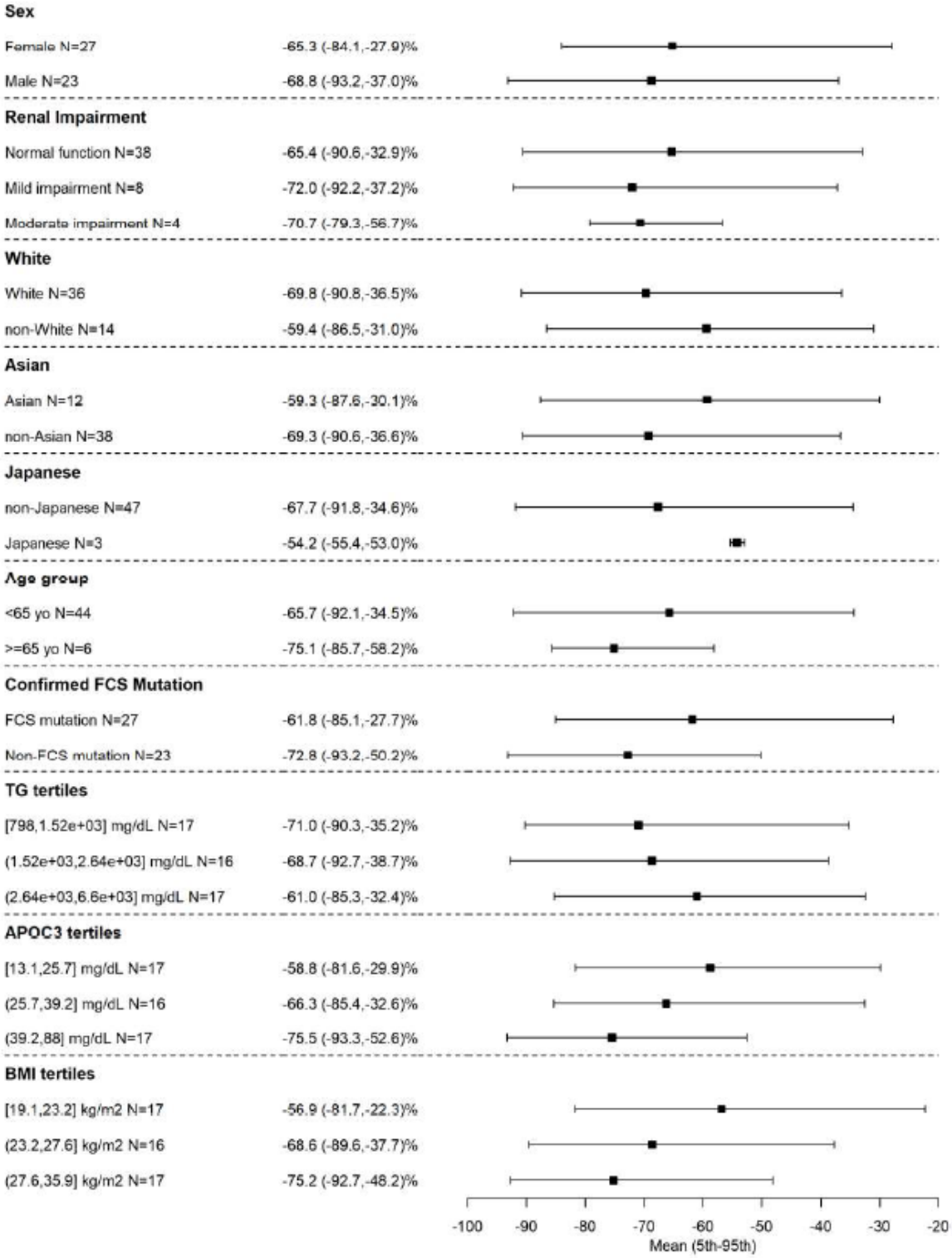
Figure 17: pcVPC for serum triglycerides after administration of plozasiran in FCS subjects

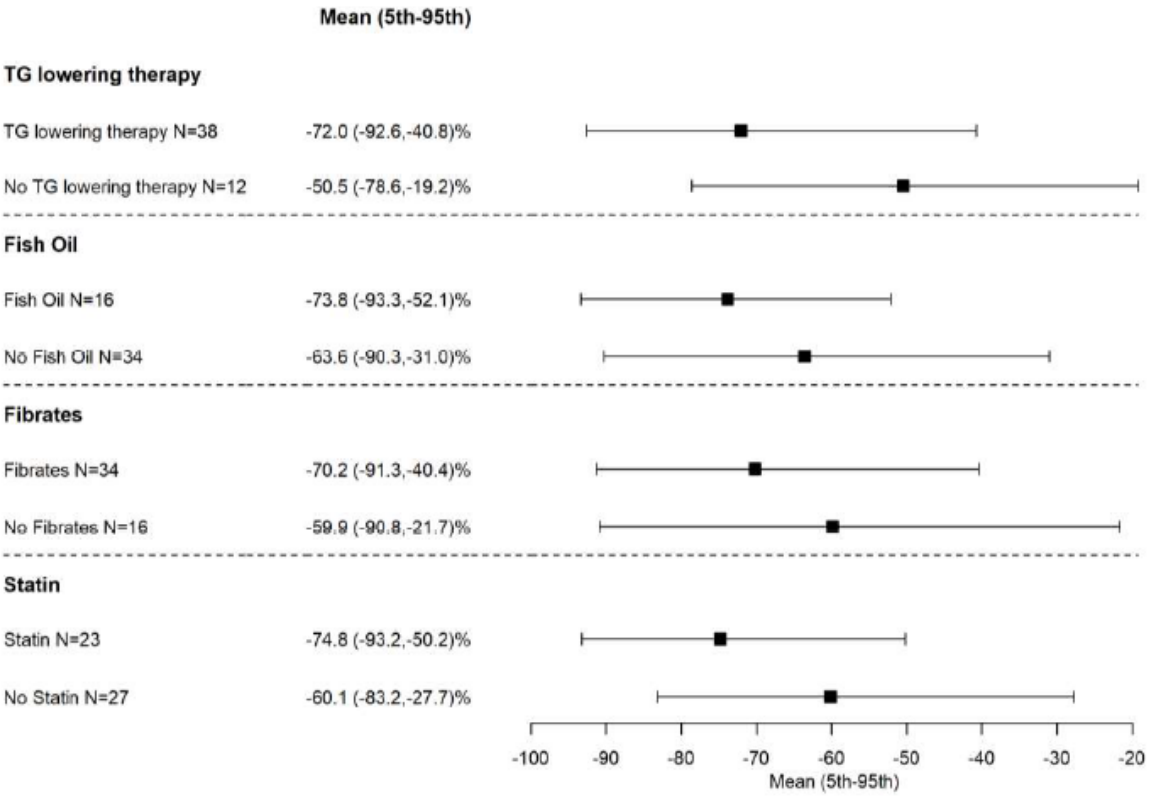


CI= confidence interval; FCS= familial chylomicronemia syndrome; LLOQ= lower limit of quantitation; Q3M= every 3 months; TG= triglycerides
Note: TG levels below 50 mg/dL were set to half of the LLOQ (i.e., ½ × 50 mg/dL)

Intrinsic and extrinsic factors were evaluated in subgroup analyses based on the individual time profiles of APOC3 and TG final K-PD model using posterior Bayes methodology obtained in the 50 subjects with FCS who received active doses of plozasiran in Study AROAPOC3-3001.

Figure 18: Post-hoc subgroup analysis of percent reduction in TG at steady state with 25 mg Q3M plozasiran treatment stratified by covariates of interest





Based on the final population K-PD model, Monte-Carlo simulations of serum APOC3 and TG levels in a virtual population of subjects (N=6000) with FCS were conducted by including inter-subject variabilities of the model parameters. The time profiles of serum APOC3 and TG levels were simulated for 4 doses of plozasiran 25 mg and 50 mg Q3M in subjects with FCS on stable background TG-lowering therapies (in study AROAPOC3-3001 majority of the patients were on at least one form of such therapies). Results are summarized in Table 20 below.

Table 17: Descriptive statistics of parameters APOC3 and triglycerides relative change from baseline after the last dose.

Regimens	Parameter	APOC3 (mg/dL) Mean (CV%) Median [95% PI]	Triglycerides (mg/dL) Mean (CV%) Median [95% PI]
Relative Change from Baseline (%)			
25 mg Q3M	Average	-84.2 (14.9%) -87.9 [-98.1 – -50.1]	-64.6 (32.7%) -68.6 [-93.6 – -16.2]
	Trough	-74.6 (25.4%) -79.7 [-96.9 – -26.6]	-57.0 (38.0%) -59.3 [-90.7 – -12.9]
	Nadir	-91.1 (8.4%) -93.4 [-98.9 – -70.1]	-70.2 (31.1%) -76.5 [-96.0 – -17.3]
50 mg Q3M	Average	-90.7 (9.8%) -93.6 [-99.0 – -65.4]	-69.8 (30.9%) -75.9 [-95.7 – -17.2]
	Trough	-84.0 (17.7%) -88.9 [-98.5 – -41.7]	-64.4 (33.5%) -68.8 [-94.0 – -15.3]
	Nadir	-95.2 (5.1%) -96.7 [-99.4 – -81.9]	-73.4 (30.3%) -81.1 [-97.3 – -18.0]

APOC3= apolipoprotein C3; CV=coefficient of variation; PI= percentile interval; Q3M= Q3M = every 3 months

5.2.5. Dose selection and therapeutic window

Dose justification is described under section 5.3.1.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Pharmacokinetics

Analytical methods

The method validation of plozasiran detection in plasma and urine was conducted in line with ICHM10 on bioanalytical method validation and study sample analysis. Assays on linearity, sensitivity, selectivity, stability, accuracy and precision, haemolysis- and hyperlipidaemic-effects, matrix factor, recovery, carry-over, and reinjection reproducibility were in line with the requirements described in this guideline. Accuracy and precision of QC samples was in line with values obtained during method validation. Samples were analysed within the window of the long-term sample stability. Incurred sample reanalysis was performed for all bioanalytical study reports and results were within the requirements as described in ICHM10.

PopPK model

The model provided is sufficient for the screening of covariates which potentially could impact the PK of plozasiran. Dense sampling has been performed in phase 1 studies, but also in a subset of subjects in phase 2 and 3 studies. The subset of FCS subjects in the model was relatively low (n=12, total subject n=146). Nevertheless, no significant PK differences for subjects with FCS compared to other subject populations and healthy volunteers is apparent form the popPK model and the phase 1 (healthy volunteers) v.s. phase 3 (subjects with FCS) PK data.

The model included two different rates of absorption, as double peaks were observed in individual PK profiles in multiple studies. Model parameters were estimated with sufficient precision (RSE<40.6%) and shrinkage values were acceptable. The exponent of body weight on V/F was estimated to be high and non-physiological (i.e., 1.81) and was therefore fixed to 1. This might be the reason that BMI was also identified as a significant covariate on V/F.

Bioequivalence

The formulation used in the clinical study and the intended commercial formulation cannot be considered bioequivalent regarding both AUC_{0-t} and Cmax (i.e. the commercial formulation v.s. study formulation GMR is 1.22 and 1.14 for AUC_{0-t} and Cmax, respectively). However, the increased exposure for the commercial formulation is not likely to influence efficacy responses based on 1. popPK-PD modelling (i.e. in a relatively flat part of dose response curve), 2. Similar PD results in the BE study between the formulations, and 3. efficacy and safety results from the phase 3 study at the 25 mg (proposed dose in SmPC) and 50 mg dose (additional dose tested). The increased exposure (~22%) for the proposed commercial formulation is not expected to be clinically relevant and the intended commercial formulation is considered acceptable.

ADME

Absorption: No human data on absolute bioavailability is available. From the pre-clinical cynomolgus monkey data it might be expected that part of plozasiran (~60%) will be degraded after SC administration before reaching the systemic circulation.

Distribution: Binding of plozasiran to plasma proteins was investigated at a single concentration in humans, above the expected Cmax at a dose of 25 mg (i.e. ~70ng/mL). The protein binding is not high (i.e. 22% unbound), however targeted delivery to the hepatocyte is expected to quickly reduce plasma plozasiran concentrations.

Subsequent to distribution in plasma and extracellular body water plozasiran is primarily delivered to the liver (mediated by the action of ASGPR expressed in hepatocytes) and that plozasiran is minimally redistributed back to plasma circulation. Distribution to other organs (e.g. kidney) might also occur.

Metabolism: Given the *in vitro* data provided and the nature of plozasiran, CYP/UGT mediated metabolism is not expected. Plozasiran is likely metabolized by ribonucleases (RNases) in the liver to shorter oligonucleotides of varying lengths. The parent plozasiran is the predominant molecule in the plasma and urine. Only trace amount can be quantified in plasma and urine for metabolites. The pharmacological activity of metabolites, if this would be of relevance, is expected to be low due to the low abundance. Pharmacological activity is therefore not expected to be relevant for metabolites.

Elimination: Although no mass-balance study has been performed, estimates on the relative contribution of elimination pathways are available. It is agreed that, when assuming that bioavailability would be 40% (similar to cynomolgus monkey), renal clearance is expected to be around 40% of total systemic clearance of plozasiran. Given the fact that the drug is targeted to the liver, it can be assumed that the remainder would be largely eliminated via the liver (although formally a contribution to elimination at other sites is not excluded). No mass balance study is considered necessary, due to slow excretion of the entire dose from the body.

The terminal half-life was supported by NCA and popPK modelling and estimates on PK parameters were largely similar between these methods.

Dose proportionality and time dependency

Dose-dependencies were not observed after single- or multiple-dosing, although number of subjects per dose group were small. Accumulation of plozasiran is not expected after multiple dosing. Given the short half-life and relatively long dosing interval plozasiran will completely be cleared from the systemic circulation before a new dose is given.

Special populations

A popPK forest plot based on individual exposure levels (i.e. Cmax and AUC from 0 to 48 hours postdose) after single SC administration of 25 mg plozasiran was provided for each subject with intensively collected PK samples included in the phase III study, as well as forest plot using the complete dataset (n=146 subjects). The covariates BW and BMI had the largest impact on exposure, which was expected. As BMI does also separately influence the PD effect, dose-adjustments are not required. The PK profile in different populations is sufficiently characterised. A relationship between exposure and weight is identified in the popPK model. Patients with higher body weight and BMI exhibited moderately lower AUC and Cmax values at a given dose. AUC decreased from 1121 ng·h/mL in the lowest weight tertile (47.2–61.7 kg) to 586 ng·h/mL in the highest tertile (70–99.2 kg), and Cmax decreased from 136 ng/mL to 42.4 ng/mL, respectively. The AUC values observed in the highest weight tertile (70–99.2 kg) partially overlap with the exposure range observed after administration of 10 mg plozasiran in healthy volunteers, which was considered to be below the exposure threshold for maximal pharmacodynamic effect. The lack of clinical relevance of this observation is further discussed in the PD section below.

No clinically significant ethnicity effect on plozasiran PK or PD was observed; however, the very small sample size of Asian subjects limits this conclusion.

No dedicated studies in renally impaired and hepatically impaired individuals have been performed. Renal impairment might influence the hepatic uptake based on increased systemic levels. A dedicated severe renal impairment study is ongoing, and results will be submitted in the post-authorisation phase (REC). In addition, as ~40% of the drug is expected to be renally cleared, the 50 mg dose, which was used in the phase III study, further confirm acceptable safety at elevated exposures. In addition, plozasiran specifically targets the liver. A dedicated PK-PD hepatic impairment study in moderate hepatic impairment is to be conducted in the post-authorisation phase (REC).

DDIs

Substrates and positive controls chosen are acceptable and in line with compounds mentioned in ICHM12. The *in vitro* data submitted indicate that plozasiran is not an inhibitor or inducer of CYP enzymes and transporter proteins. The concentration ranges studied are considerably above 50xCmax unbound concentration and are therefore sufficient.

Pharmacodynamics

Plozasiran is a first-in-class N-acetylgalactosamine (NAG) conjugated small interfering RNA (siRNA) designed to target messenger RNA (mRNA) from the apolipoprotein C-III (apoC3) gene in the liver. Reduced apoC3 levels enhances the activity of lipoprotein lipase (LPL) and hepatocyte uptake of triglyceride-rich lipoprotein remnants leading to decreases in serum triglycerides. Therefore, consistent with its mechanism of action, reductions from baseline in serum ApoC3 and TGs may be regarded as the on-target pharmacological response and treatment efficacy of plozasiran, respectively.

The PD effects of plozasiran were initially evaluated in the first-in-human study AROAPOC3-1001 after single and multiple dose administrations ((every 4 weeks [Q4W]) of 10 mg, 25 mg, 50 mg and 100 mg) in healthy volunteers, as well as in patients with severe hypertriglyceridemia (SHTG), genetically

confirmed and clinically diagnosed FCS. This study showed that the dose response for decrease in ApoC3 over time correlated well with the dose response for a decrease in TG. In healthy volunteers, a single dose of 10 mg, 25 mg and 100 mg resulted in dose-dependent decreases in the range of 82% to 94% for mean maximum serum ApoC3 and 62% to 69% for mean maximum TG, respectively. In the same population, multiple doses of 10 mg, 25 mg, and 50 mg (2 repeat doses administered 4 weeks apart) resulted in mean maximum reductions of 83% to 94% in ApoC3 and 67% to 76% in TG. In the subjects with SHTG, multiple doses of 10 mg, 25 mg, 50 mg and 100 mg resulted in generally dose-dependent mean maximum reductions of 83% to 98% in ApoC3 and 79% to 87% in TG. The patients with clinically diagnosed FCS and genetically confirmed FCS who received 2 repeated doses of 50 mg had mean maximum reductions of 97% and 99% in APOC3 and 92% and 89% in TG, respectively. For all the populations, the maximum effects in ApoC3 and TG were already observed at D15 post first dose and maintained up to week 16 following 1 or 2 doses of plozasiran, with the exception of the lowest 10 mg dose. Overall, in all populations the effect of plozasiran in mean serum ApoC3 and TG was rapid, substantial and persistent.

Any QT prolonging or other arrhythmic potential for plozasiran is unlikely, based on the absence of any pro-arrhythmic effect in 3-way crossover thorough QT/QTc study and phase 3 ECG data.

Plozasiran is neither a substrate nor inhibitor of major CYPs or drug transporters. Therefore, plozasiran has a low potential to be a precipitant or an object drug of DDIs caused by other concomitant medications capable of modulating CYP or transporter activity or expression. The reductions in APOC3 and TGs were consistent between subjects with genetically confirmed versus clinically diagnosed FCS.

Immunogenicity test results showed that treatment-emergent anti-drug antibodies (ADAs) incidence against plozasiran is very low with low titers between 10 and 40 (1 out of 65 subjects (1.5%) in the OLE period of the pivotal study AROAPOC3-3001, 3 out of 165 subjects (1.8%) in study AROAPOC3-2002 and 1 out of 264 subjects (0.4%) in study AROAPOC3-2002 developed ADAs against plozasiran.

PD model

The K-PD model developed is considered acceptable. The model structure is in line with the expected mechanism of action. The population of FCS subjects is accepted as the most relevant population. In addition, goodness-of-fit plots and pcVPCs indicated acceptable model predictions. The model is therefore considered suitable for the purpose of covariate analysis and to support the most optimal dose for labelling.

Plozasiran in the effect compartment is estimated to have a long t½ of ~48 days for a typical FCS patient. In addition, it was observed that, compared to the dose, a relatively low IC50ARO-APOC3 (the plozasiran dose to inhibit 50% of APOC3 synthesis rate, [estimated to be ~2.2 mg]) for subjects with FCS was observed. Responses are therefore expected to be in a relatively flat part of the dose-response curve. These factors explain prolonged action of plozasiran during the Q3M dosing interval.

From the covariate analysis it is apparent that high BMI is associated with faster elimination of plozasiran form the effect compartment. However, this is counteracted by inverse relationship between BMI and IC50APOC3 (the APOC3 concentration to inhibit 50% of TG degradation rate, possibly explained by higher baseline levels of APOC3 for indivuduals with higher BMI). From the post-hoc subgroup analysis it is apparent that the net effect will be a larger expected reduction in TG in subjects with a higher BMI. An additional analysis assessing the relationship between BMI and triglyceride response as a continuous variable was performed to clarify whether any trend exists across the full BMI range to confirm the appropriateness of flat dosing across full body weight range. While this assessment is largely descriptive and associated with substantial uncertainty due to limited sample size

and high variability of TG measurements, visual inspection of the BMI–TG response plots did not indicate a significant trend towards reduced TG lowering at higher BMI/body weight. The differences in effect on TG reduction for race, age, sex, FCS diagnosis in the post-hoc subgroup analysis are generally expected to be mediated via the differences in BMI, as these were not identified as independent significant covariates. The differences are low and do not require dose adjustment in sub-groups. The analysis also indicates that TG lowering therapy does not impede plozasiran response and might even slightly potentiate the plozasiran effect.

5.2.6.2. Conclusions

The pharmacokinetics have been described to a reasonable extent in the healthy population and FCS patients. In addition, the pharmacodynamics of plozasiran have been sufficiently evaluated.

5.3. *Clinical efficacy*

The efficacy of plozasiran to reduce TG levels in adult patients with FCS is based on data from the pivotal phase 3 study AROAPOC3-3001, which includes a completed double-blind (DB), placebo-controlled period and an ongoing open-label extension (OLE) period, and supported by 2 randomized dose-finding phase 2b studies (AROAPOC3-2001 and AROAPOC2-2002) and an open-label study (AROAPOC3-2003) in related populations, including severe hypertriglyceridaemia (SHTG) and mixed hyperlipidaemia (Table 21).

Table 18: Clinical studies supporting the use of plozasiran in patients with FCS

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria

AROAPOC3-3001 (PALISADE)	Ongoing First patient screened: 21-12-2021 123 patients	A randomized, double-blind, placebo-controlled to evaluate the efficacy and safety of ARO-APOC3 in adults with FCS	Randomized DB period, 12 months (completed) • Plozasiran 25 mg or PBO randomized 2:1 (n=26:13) • Plozasiran 50 mg or PBO randomized 2:1 (n=24:12) Total of 4 doses of plozasiran or matching placebo administered SC Q3M <u>OLE Period A (ongoing)</u> Subjects randomized to plozasiran continued to receive their assigned original treatment (blinded). Subjects who received placebo switched to the active treatment in the OLE based on the initial dosing group to which they were assigned. <u>OLE Period B (ongoing)</u> All subjects switched to the selected clinical dose (plozasiran 25 mg Q3M).	Adult subjects with genetically confirmed or clinically diagnosed FCS
AROAPOC3-2001 (SHASTA-2)	Completed First patient enrolled: 31-05-2021 Last patient completed: 31-07-2023 226 participants	A double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of ARO-APOC3 in adults with severe hypertriglyceridemia	<u>Randomized DB period (completed)</u> • Plozasiran 10 mg (n=54) or PBO (n=20) • Plozasiran 25 mg (n=55) or PBO (n=20) • Plozasiran 50 mg (n=57) or PBO (n=20) Total of 2 doses of plozasiran or matching placebo administered SC on Day 1 and Week 12 for each dose cohort.	Adult subjects with SHTG (including 5 subjects with FCS)
AROAPOC3-2002 (MUIR)	Completed First patient enrolled: 28-09-2021 Last patient completed: 14-07-2023 226 participants	A double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of ARO APOC3 in adults with mixed hyperlipidemia	<u>Randomized DB period (completed)</u> • Plozasiran 10 mg (n=67) or PBO (n=21) Day 1 and Week 12 • Plozasiran 25 mg (n=67) or PBO (n=22) Day 1 and Week 12 • Plozasiran 50 mg (n=66) or PBO (n=22) Day 1 and Week 12 • Plozasiran 50 mg (n=66) or PBO (n=22) Day 1 and Week 24 Total of 2 doses of plozasiran or matching placebo administered SC.	Adult subjects with mixed hyperlipidemia

AROAPOC3-2003	Ongoing 169 patients	A Phase 2 open-label extension study to evaluate the long-term safety and efficacy of ARO-APOC3 in adults with dyslipidemia	Open-label extension (ongoing) Initially all subjects received plozasiran at the same dose or PBO-matched dose. Up until protocol Amendment 2 (dated 22 Nov 2022), subjects were on their assigned dosing per respective protocols. As of 04 Dec 2023, all subjects who were not on the 25 mg Q12W were switched to 25 mg Q12W.	Adult subjects with hyperlipidemia from AROAPOC3 2001 and AROAPOC3-2002

5.3.1. Dose response studies

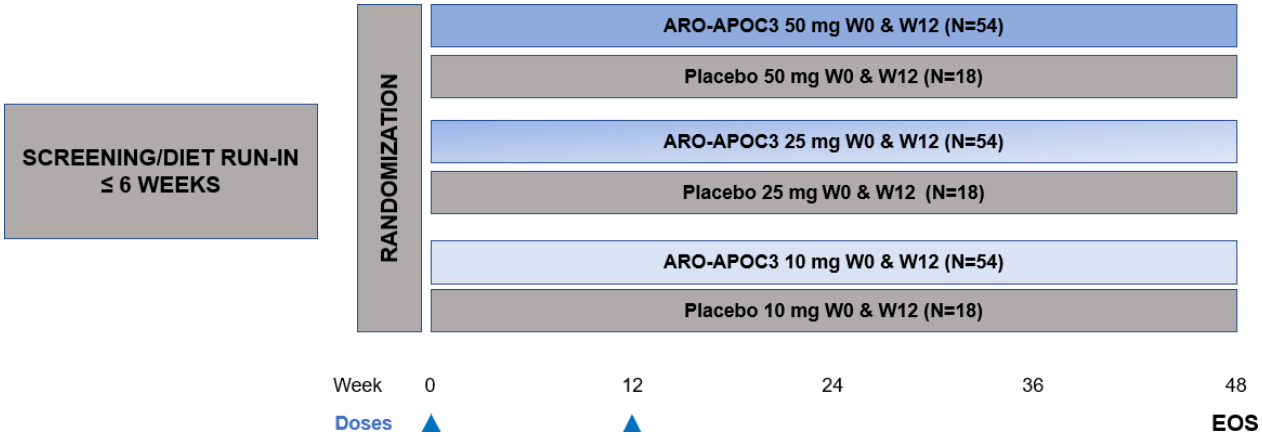
Two phase 2b dose-finding clinical studies (Study AROAPOC3-2001 and AROAPOC3-2002) have been conducted for plozasiran, which are separately described below.

Study AROAPOC3-2001 (SHASTA-2)

Design. This study was a double-blind, placebo-controlled, multiregional, phase 2b study conducted to evaluate the efficacy and safety of plozasiran in adult patients with SHTG.

Method. The study population included adults with SHTG, defined as mean fasting TG level ≥500 mg/dL (≥5.65 mmol/L) and ≤4000 mg/dL (45.2 mmol/L) at screening who were willing to follow diet counselling and maintain a stable diet as per investigator judgement based on local standard of care and maintain stable background medications. The study consisted of 2 study periods: a screening/diet run-in of ≤6 weeks and an acute treatment period of 48 weeks (Figure 21). A total of 229 eligible subjects were randomized to receive 1 of the 3 plozasiran treatments (2 doses of plozasiran 10, 25, or 50 mg on Day 1 and Week 12) or matched placebo. The allocation ratio was 3:1 (active: placebo) within each dose cohort, and all dose cohorts enrolled in parallel. The study doses were selected based on the population PD modeling results of phase 1 study AROAPOC31001, which suggested that clinically significant responses in APOC3 and TG reduction can be obtained starting from a plozasiran dose of 10 mg Q12 weeks (Q12W), while become saturated between 25 mg and 50 mg Q12W dose levels. The primary efficacy endpoint was the change of fasting TG from baseline to Week 24. The changes in serum APOC3 over the study time course was a key secondary endpoint indicating the primary clinical pharmacological activity of plozasiran.

Figure 19: Study Schema AROAPOC3-2001



Results. All subjects received study drug (ie, plozasiran or placebo) Q12W and most randomized subjects (93.0%) completed the study. All doses of plozasiran significantly reduced fasting TG levels at Week 24 compared with placebo. Repeat doses of plozasiran 10, 25, and 50 mg resulted in marked decreases at Week 24 in the mean percent changes from baseline in TG levels (-68.9%, -70.5%, and -74.0%, respectively), compared with a mean change of -18.2% in the placebo group. The median percent changes from baseline in TG levels were -74.9%, -76.0%, and -80.2%, respectively, compared with -29.4% for placebo. The between-group LS mean differences for the plozasiran 10, 25, and 50 mg dose groups versus placebo were -48.8%, -53.1%, and -57.0%, respectively (P<0.0001 for all comparisons). Most subjects who received plozasiran achieved greater reductions in TGs at Week 24 compared with placebo.

Plozasiran significantly decreased APOC3 levels, in comparison to APOC3 levels in placebo-treated subjects. Plozasiran treatment led to reductions in APOC3 levels at Week 4 following the first dose and reached a maximum (nadir) 4 weeks after the second dose (study Week 16) compared with no change in the placebo group (Figure 23). All doses showed durable effects through Week 48/EOS, waning slowly beyond Week 16. The between-group LS mean differences for the plozasiran 10, 25, and 50 mg dose groups versus placebo were -77.9%, -87.7%, and -89.1%, respectively, at Week 16; -67.7%, -71.5%, and -77.4%, respectively, at Week 24; and demonstrated notable durability with reductions of -38.7%, -52.6%, and -51.4%, respectively, at Week 48/EOS (P<0.0001 for all comparisons). Thus, differences between the peak (Week 16) and trough (Week 24) LS mean were relatively small at 10.2%, 16.2%, and 11.7% for the plozasiran 10, 25, and 50 mg doses, respectively.

Figure 20: Fasting Triglyceride Mean (±SD) Percent Changes from Baseline Over Time in Patients with SHTG

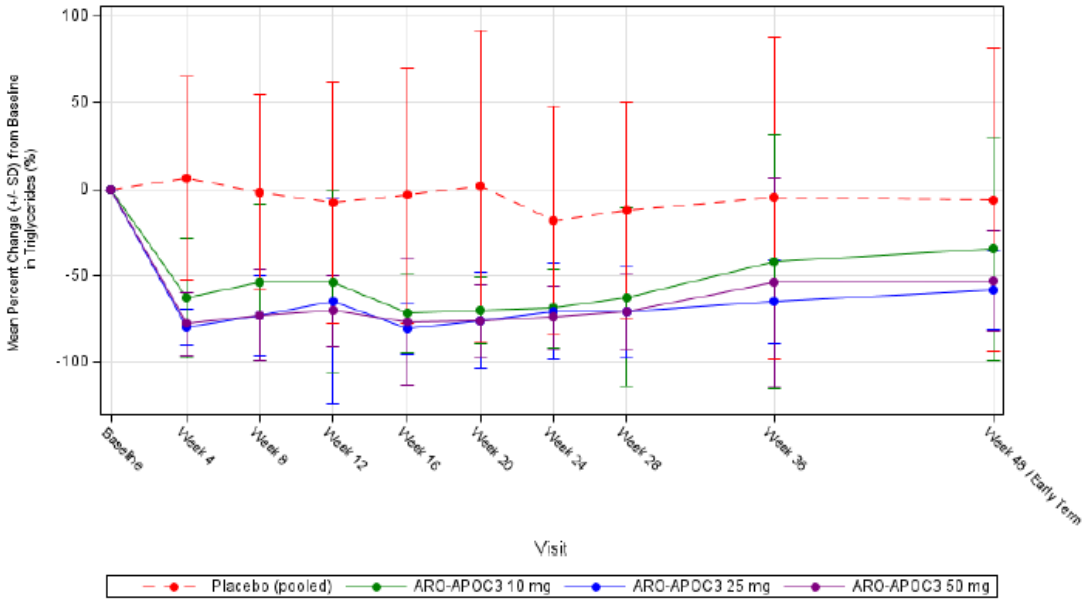
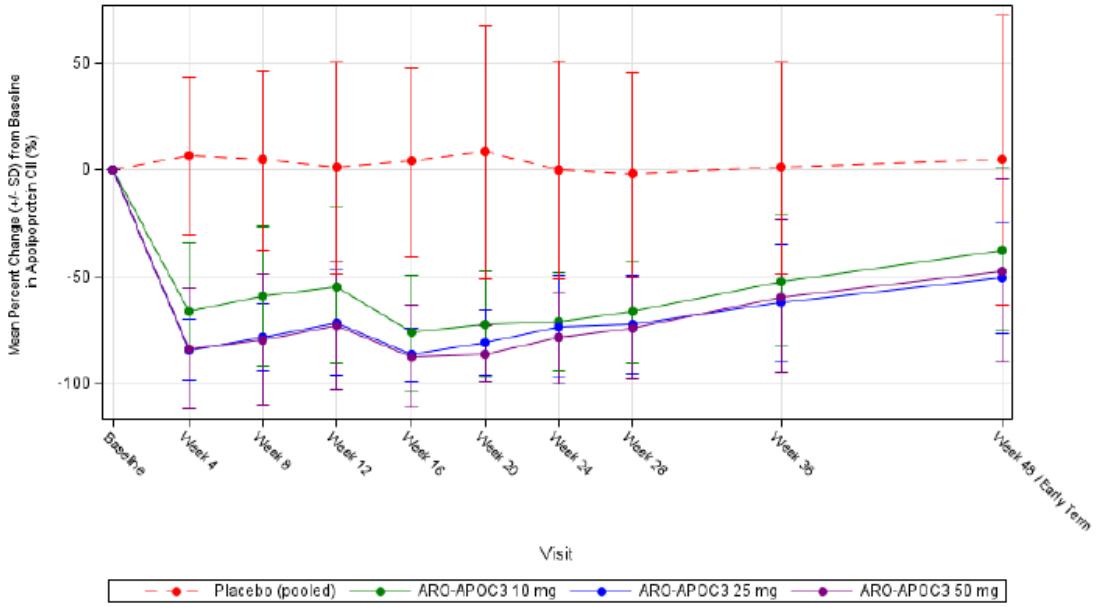


Figure 21: Mean ± SD Percent Changes from Baseline Over Time in APOC3 in Patients with SHTG



Study AROAPOC3-2002 (MUIR)

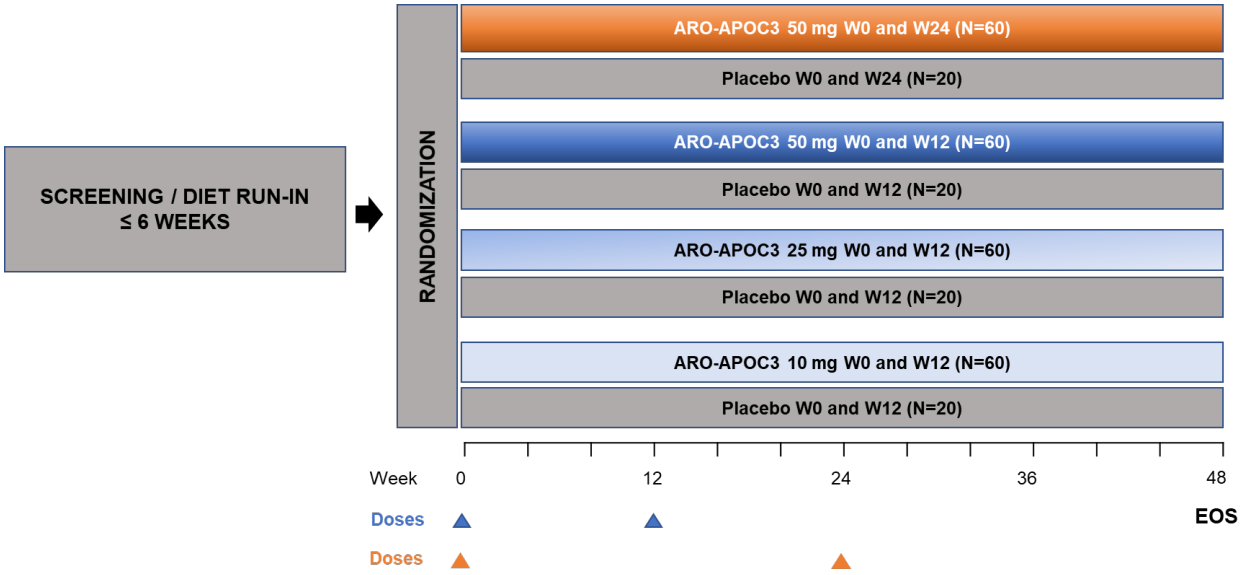
Design. This study was a double-blind, placebo-controlled, multiregional, phase 2b study to evaluate the efficacy and safety of plozasiran in adults with mixed dyslipidemia (MD).

Method. The study population included adult subjects with MD, defines as elevated mean fasting TG between 1.70 mmol/L and 5.64 mmol/L (150 mg/dL and 499 mg/dL) and either non-HDLC ≥2.59 mmol/L (≥100 mg/dL) or LDL C >1.81 mmol/L (>70 mg/dL) at screening. The primary efficacy

endpoint was the change of fasting TG from baseline to week 24. The changes in serum APOC3 over the study time course was a key secondary endpoint indicating the primary clinical pharmacological activity of plozasiran.

A total of 353 subjects were randomized to receive 1 of the 4 plozasiran treatments (2 doses of plozasiran 10, 25, or 50 mg on Day 1 and Week 12, or 2 doses of 50 mg on Day 1 and Week 24) or matched placebo. The allocation ratio was 3:1 (active: placebo) within each dose cohort, and all dose cohorts enrolled in parallel (Figure 24).

Figure 22: Study Schema AROAPOC3-2002

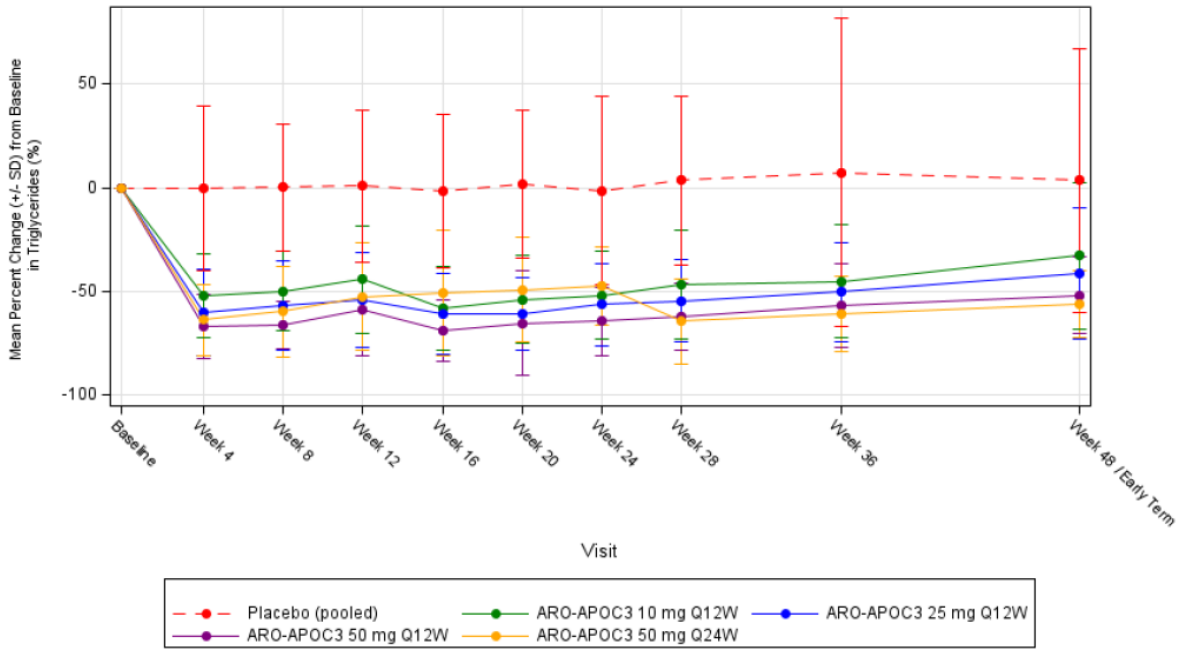


Results. All subjects received study drug (ie, plozasiran or placebo) and most randomized subjects completed study treatment (93.5%) and the study (91.8%). Twenty-three subjects (6.5%) discontinued study treatment and 29 subjects (8.2%) discontinued the study prematurely. The most common reasons for study treatment discontinuation were withdrawal by subject (9 subjects [2.5%]), TEAEs (4 subjects [1.1%]), death (3 subjects [0.8%]) and non-compliance/protocol violations (3 subjects [0.8%]). Plozasiran treatment resulted in rapid and durable reductions in TG levels from baseline (mean ranging from 2.68 to 2.86 mmol/L [237.22 to 253.15 mg/dL]), with all plozasiran dose groups demonstrating marked decreases in TG levels as early as 4 weeks after the initial dose and reaching a maximum (nadir) 4 weeks after the second dose, corresponding to Week 16 for the Q12W dosing groups and Week 28 for the Q24W dosing group (Figure 25). For the plozasiran 10, 25, and 50 mg Q12W dosing groups, the mean percent change from baseline in TG at Week 16 was -58.1%, -60.6%, and -68.9%, respectively, with TGs gradually increasing over time from Weeks 24 to 48 after administration of the second dose. Despite the last dose being administered at Week 12, all plozasiran Q12W doses (ie, 10, 25, and 50 mg) demonstrated prolonged PD response, in which the mean percent change from baseline in TG at Week 48/EOS were -32.8%, -41.5%, and -51.8%, respectively. The between-group LS mean difference between the Q12W groups versus placebo was -56.2%, -60.2%, and -66.5%, respectively, at Week 16, -49.8%, -56.0%, and -62.4%, respectively, at Week 24 and -34.9%, -44.5%, -51.9%, respectively, at Week 48/EOS. In the plozasiran 50 mg Q24W group, in which subjects had only received 1 dose at baseline and had not yet received a second dose, mean TGs were reduced to 124.62 mg/dL at Week 24, a mean percent

change from baseline of -47.4% was observed, with a between-group LS mean difference versus placebo of -44.2% (P<0.0001).

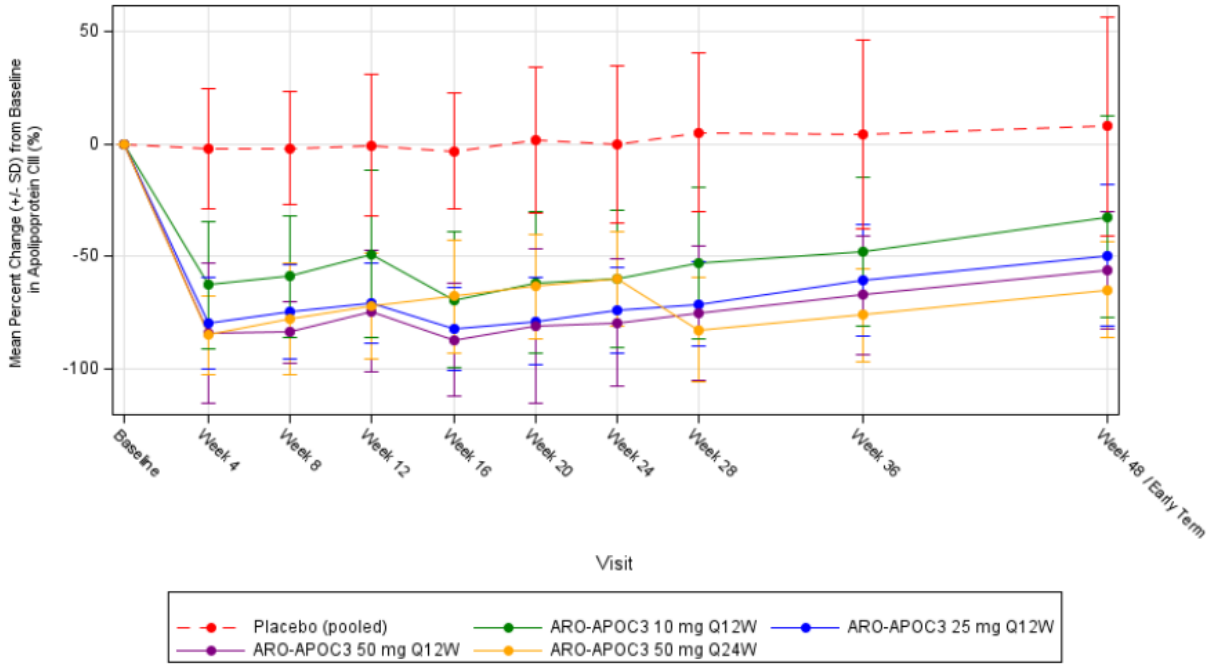
Although the plozasiran 50 mg Q12W dose showed the greatest and most durable TG-lowering effect, the differences between doses were not large. The plozasiran 10 mg Q12W dose was also effective at decreasing TG levels but the magnitude of the effect was less than that at higher doses. The plozasiran 50 mg Q24W dose was as effective as the plozasiran 25 mg Q12W and 50 mg Q12W doses early after the first dose but lost substantial efficacy between Weeks 12 and 24.

Figure 23: Fasting Triglyceride Mean (±SD) Percent Changes from Baseline Over Time in Subjects With Mixed Hyperlipidemia



Plozasiran significantly decreased APOC3 levels. Similar to TGs, APOC3 levels were reduced from baseline (mean ranging from 0.15 to 0.16 g/L [14.595 to 15.543 mg/dL]) in a dose-dependent manner with plozasiran. Plozasiran treatment led to reductions in APOC3 levels starting at Week 4 and reached a nadir 4 weeks after the second dose compared with no change in the placebo group (Figure 22). All doses showed durable effects through Week 48/EOS. Across all time points, placebo showed no effect on APOC3 levels. For the plozasiran 10, 25, 50 mg Q12W dosing groups, the mean percent change from baseline in APOC3 at nadir (Week 16) was -69.3%, -82.5%, and -87.3%, respectively; -60.1%, -74.0%, and -79.7%, respectively, at Week 24; and -32.5%, -49.7%, and -56.2%, respectively, at Week 48/EOS. The between-group LS mean difference for the plozasiran 10, 25, and 50 mg Q12W groups versus placebo was -66.4%, -79.1%, and -84.3%, respectively, at Week 16; -57.3%, -72.5%, and -78.5%, respectively, at Week 24; and demonstrated notable durability with reductions of -37.0%, -54.8%, and -59.8%, respectively, at Week 48/EOS. In the plozasiran 50 mg Q24W group, in which subjects had only received 1 dose at baseline and had not yet received a second dose, a mean percent change from baseline of -57.7 % at Week 24 was observed, with a between-group LS mean difference versus placebo of -56.1% (P<0.0001). The effect of plozasiran on APOC3 mirrors its effect on TG levels, with the 25 mg and 50 mg Q12W doses showing relatively similar reduction in APOC3. The plozasiran 50 mg Q24W dose was as effective as the plozasiran 25 mg Q12W and 50 mg Q12W at reducing APOC3 but was unable to maintain efficacy beyond 12 weeks after a single dose.

Figure 24: Mean ±SD Percent Changes from Baseline Over Time in APOC3 in Subjects With Mixed Hyperlipidemia



Recommended dose

Plozasiran 25 mg Q3M and 50 mg Q3M both produced significant reductions in triglycerides and ~80% of subjects in both dose groups achieved triglyceride reductions of 50% or more in the pivotal Phase 3 study in FCS (AROAPOC3-3001). The reductions in TG as well as ApoC3 were apparent at 1 Month (first postbaseline measurement) and remained consistent throughout the 12-month duration of the trial, with relatively small peak-to-trough differences in both parameters. The 25 mg and 50 mg doses of plozasiran produced similar efficacy results relative to placebo. Subgroup analyses in AROAPOC3-3001, AROAPOC3-2001, and AROAPOC3-2002 showed similar effects of plozasiran 25 mg Q3M regardless of age, sex, race, or other baseline characteristics, including the presence of genetically confirmed FCS.

Based on population PK and population PD analyses that included data from multiple studies, plozasiran 25 mg Q3M was shown to be appropriate for adult patients with FCS, with no adjustment recommended based on patient body weight, BMI, sex, age, race/ethnicity, baseline triglyceride level, mild or moderate renal impairment, or mild hepatic impairment. Population PD analysis also supported the use of plozasiran 25 mg Q3M for all patients with FCS, regardless of pathogenic variants, concomitant triglyceride-lowering or lipid lowering therapies, baseline apoC3 or triglyceride levels, or other demographic characteristics. The 25 mg dose was therefore selected as the recommended dose.

5.3.2. Main study

5.3.2.1. AROAPOC3-3001

5.3.2.1.1. Study title

A Phase 3 study to evaluate the efficacy and safety of AROAPOC3 in adults with familial chylomicronemia syndrome (Palisade)

Table 19: Study identifiers

Study code	AROAPOC3-3001
Other identifier(s)	PALISADE
Location in eCTD	5.3.5.1

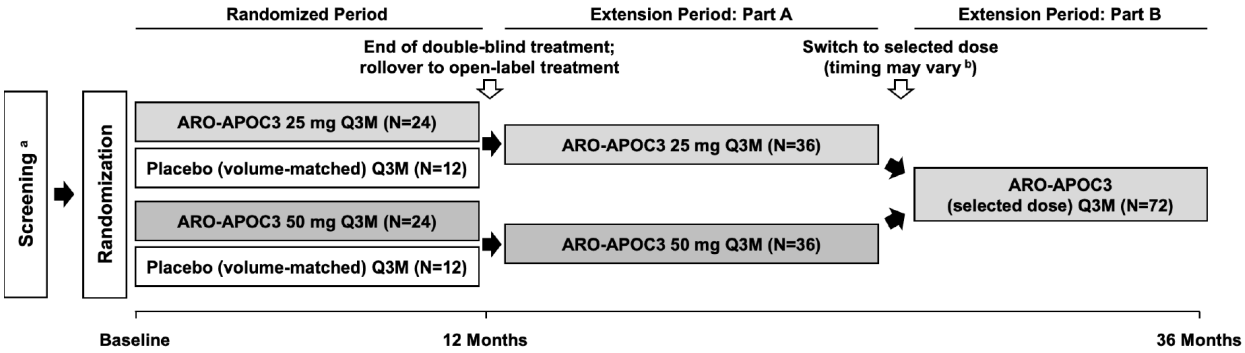
5.3.2.1.2. Study design

Treatment

Study AROAPOC3-3001 was a randomized, double-blind, placebo-controlled, phase 3 clinical study conducted in 75 adult subjects with genetically confirmed or clinical FCS. Eligible subjects with a diagnosis of FCS first initiated a treatment stabilization period for at least 4 weeks, during which diet, lifestyle, and medication regimen were stabilized at the Investigator's discretion and in accordance with the local standard of care. All other eligibility criteria assessments and laboratory sample collections required to confirm the subject's eligibility were completed within 6 weeks prior to Day 1.

In the 12-month randomized period, subjects who successfully passed eligibility requirements at screening were enrolled into the study. All dose cohorts enrolled in parallel with subjects randomly assigned 2:1:2:1 to the dose cohorts (plozasiran 25 mg, volume-matched placebo, plozasiran 50 mg, and volume matched placebo, respectively). Randomization was stratified by level of fasting TG at screening (≥2000 mg/dL versus <2000 mg/dL). In each cohort, a total of 5 doses were administered SC on Day 1 and Months 3, 6, 9, and 12, i.e. every 3 months (Q3M), and subjects were followed through Month 12. Subjects who completed the randomized, double-blind period of the study were invited to consent to continue in a 2-part open-label extension (OLE) period. Subjects received either plozasiran 25 mg or 50 mg as a subcutaneous injection Q3M during Part A of the OLE. Once the final clinical dose of 25 mg Q3M was chosen, all subjects transitioned to that dose for Part B. The OLE will ultimately provide an additional 24 months of plozasiran treatment (efficacy and safety) evaluation. In Part A of the OLE, subjects remained blinded to their treatment assignment from the randomized period and initially received open label plozasiran at the dose corresponding to their dose in the randomized period.

Figure 25: Study Schema AROAPOC3-3001



Abbreviations: Q3M=every 3 months.
a Screening: review and stabilization of diet, medications, and laboratory values.
b Dependent on when the subject entered Part A and timing of dose selection for Part B.

Randomisation

All potential participants who sign informed consent at screening received a unique identifier (ie, a screening number). For participants who are deemed eligible, this unique screening number became the participants permanent study ID number.

Eligible participants allocated a unique randomization number, in accordance with the randomization schedule. Each participant 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 administered per the randomized sequence generated by an Interactive Web Response System (IWRS). The allocation of active treatment or placebo performed using a block randomization algorithm. Randomization is stratified by level of TG at screening (≥2000 mg/dL versus <2000 mg/dL).

Blinding

Treatment assignment (active versus placebo) is blinded in this clinical study. Dose group assignments are not blinded due to required injection volume differences dictated by the respective dose group. Therefore, participants received an injection of either active or placebo volume matched to the assigned dose group. To mask for slight color differences between active and placebo, syringes were blinded in the pharmacy with translucent wrapping to mask the blinded staff and participants to the treatment assignment in accordance with instructions provided in the Pharmacy Manual.

Patient population

A total of 75 eligible subjects distributed across 54 different sites in 18 countries (Argentina, Australia, Austria, Belgium, Canada, Croatia, France, Germany, Ireland, Japan, Mexico, New Zealand, Oman, Poland, Serbia, Singapore, South Korea, Spain, Turkey, and the United States (US)) were included in the study.

Patients were eligible to be included in the trial only if all the following inclusion criteria apply:

- Males or nonpregnant (who do not plan to become pregnant), nonlactating females ≥18 years of age

- Able and willing to provide written informed consent prior to the performance of any study-specific procedures
- 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 Table 19). Two repeat tests are allowed to qualify.
- A diagnosis of FCS based on a documented history of fasting TG levels in excess of 11.3 mmol/L (1000 mg/dL) on repeated testing (for at least 3 prior occasions), and at least one of the following:
    a. 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
    b. Documented history of recurrent episodes of acute pancreatitis, not caused by alcohol or cholelithiasis; or
    c. Documented history of recurrent hospitalizations for severe abdominal pain without other explainable cause; or.
    d. Documented history of childhood pancreatitis; or
    e. Family history of hypertriglyceridemia-induced pancreatitis
- Willing to follow dietary counseling as per PI judgment based on local standards of care, consistent with an intake of ≤20 g of fat per day during the study
- If on medications for management of HTG, type 2 diabetes, or other medications specified in the Table 23 below, the dosing regimen must be stable before collection of qualifying lipid parameter at screening.

Table 20: Restricted concomitant medications

Restricted Background Medications	Time on Stable Regimen Before Qualifying Screening Laboratory Assessments
Lipid lowering therapies (including statins)	> 4 weeks
Fibrates	> 6 weeks
PCSK9 inhibitors	> 8 weeks
Beta-blockers, Thiazide diuretics	> 4 weeks
Retinoids	> 8 weeks
Atypical antipsychotics	> 12 weeks
Diabetes mellitus medications	> 12 weeks
Oral estrogens, tamoxifen, raloxifene	> 16 weeks
Immunosuppressants	> 24 weeks

- 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.

- Participants of childbearing potential must agree to use a highly effective form of contraception in addition to a male condom (Appendix 1), during the study and for at least 24 weeks after the last dose of IP. 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 IP.

The following exclusion criteria were employed:

- Current use or use within the last 365 days from Day 1 of any hepatocyte-targeted siRNA or antisense oligonucleotide molecule
- Diabetes mellitus with any of the following:
  - Newly diagnosed within 12 weeks of screening
  - HbA1c ≥9.0% at screening (or >75 mmol/mol International Federation of Clinical Chemistry [IFCC] units) at screening
- Active pancreatitis within 12 weeks before Day 1
- History of acute coronary syndrome events (myocardial infarction or unstable angina) or procedures (coronary revascularization, angioplasty, or stenting) within 24 weeks of Day 1
- History of major surgeries within 12 weeks of Day 1 (including cardiac and vascular surgeries, eg, coronary artery bypass graft)
- Any of the following laboratory values at screening:
  - ALT or AST ≥ 3xULN at screening
  - Total bilirubin ≥ 1.5xULN (if the participant has a prior diagnosis and documentation of Gilbert's syndrome, then total bilirubin must be ≤3 mg/dL at screening)
  - 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)
  - Spot urine protein/spot urine creatinine ratio greater than 3 grams per day
  - Clinically significant abnormality in prothrombin time, partial thromboplastin time, or INR
- Uncontrolled hypertension (blood pressure >160/100 mmHg at screening); if untreated, participant may be rescreened once hypertension is treated and controlled
- Use of any of the following:
  - Systemic use of corticosteroids or anabolic steroids within 4 weeks prior to Day 1 or planned use during the study
  - GLP-1 receptor agonists
  - Plasma apheresis within 4 weeks prior to Day 1 or planned during the study
  - 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

- On treatment with HIV antiretroviral therapy (Note: determination of HIV status is not a required study procedure)
- 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)
- New York Heart Association (NYHA) Class II, III, or IV heart failure or last known ejection fraction of <30%
- 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)
- History of stroke, transient ischemic attack, or peripheral artery disease within 24 weeks of first dose
- History of bleeding diathesis or coagulopathy
- Current diagnosis of nephrotic syndrome
- 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)
- 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 relapsing for recent cancer
- 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
- 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
- Clinical evidence of Cushing's syndrome

5.3.2.1.3. Objectives and estimands

Primary objective

The objectives of study AROAPOC3-3001 were to evaluate the efficacy and safety of plozasiran in adults with FCS. The primary endpoint was percent change from baseline at Month 10 in fasting triglycerides. Comparison was made of the plozasiran group to the placebo group, with the hypothesis that there is superiority of plozasiran over placebo over the primary endpoint.

Hypothesis testing

For each dose of plozasiran, the primary null hypothesis was that there was no difference in the median percent change from baseline in fasting triglycerides at Month 10 between plozasiran and placebo, and the alternative hypothesis was that a median difference exists.

Estimands for the primary objective

Table 21: Estimands for primary objective

Population	Adult FCS patients as defined by inclusion/exclusion criteria who would encounter the Intercurrent Event of noncompliance with the treatment use of prohibited medications if assigned to plozasiran.
Treatment condition<s>	Assignment to plozasiran (25 mg and 50mg), regardless of discontinuation and use of prohibited medications, compared to assignment to placebo, regardless of discontinuation and use of prohibited medications.
Endpoint (variable)	Fasting TG at month 10
Population-level summary	Difference in median percent change from baseline at Month 10
Treatment discontinuation	Treatment policy
Use of prohibited medication	Treatment policy

Statistical methods for estimation and sensitivity analysis on primary estimands

The efficacy analysis is performed on the FAS dataset. As sensitivity analysis PPS was also used.

For the analysis of primary endpoint, the Wilcoxon rank-sum test with Hodges-Lehman approach was used to estimate the median difference and its 95% CI for percent changes between ARO-APOC3 doses and placebo groups using a pattern mixture model for imputation. As sensitivity analyses primary analysis was performed on PPS without missing data imputation. Trimmed Hodge-Lehmann statistic was calculated to evaluate the robustness.

For the primary endpoint, an ANCOVA model with treatment as a factor and baseline TG as a covariate was performed on the FAS.

For change from baseline at Month 10 in fasting TG, an ANCOVA model with treatment as a factor and baseline TG as a covariate was performed using FAS.

A MMRM using FAS based on the missing at random (MAR) assumption was also performed. A tipping point analysis using FAS to investigate the robustness of the departures from MAR assumption in the multiple imputation model was performed using a prespecified sequence of shift

parameters.

Another sensitivity analysis that used ANHECOVA is also performed and included treatment group as factor and the stratification factor of baseline TG level as a covariate and interaction of the treatment group by stratification factor.

Covariate adjusted analyses were also performed using the MMRM that included treatment arm, study visit, baseline value and treatment by visit interaction in the model.

To control the family-wise Type I error at a 0.05 level, a fixed sequential testing procedure was implemented in a hierarchical step-down manner on a prespecified order of endpoints. The hypothesis testing procedure started with the primary efficacy endpoint and moved to key secondary endpoints using a fixed-sequence stepping-down procedure. For a strong control of the family-wise overall Type-I error, conclusions about the efficacy endpoints needed to be statistically significant for both dose levels of the previous endpoint.

Secondary objectives

Key secondary endpoints included:

- Percent change from baseline at Months 10 and 12 (averaged) in fasting triglycerides
- Percent change from baseline at Month 10 in fasting apoC3
- Percent change from baseline at Month 12 in fasting apoC3
- Incidence of positively adjudicated events of acute pancreatitis during the randomized period defined as meeting 2 of the following 3 criteria (according to the 2013 Atlanta definition):
    a. Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
    b. Serum lipase activity (or amylase activity) ≥ 3x ULN
    c. Characteristics findings of acute pancreatitis on CECT, MRI, or transabdominal

Other secondary endpoints included:

- Percent change from baseline at Month 10 in non-HDL-C and HDL-C
- Percent change from baseline at Month 12 in fasting triglycerides, non-HDL-C, and HDL-C
- Proportion of subjects achieving triglycerides of <500, 880, and 1000 mg/dL at Month 10
- Proportion of subjects achieving triglycerides of <500, 880, and 1000 mg/dL at Month 12
- Proportion of subjects achieving ≥40%, ≥70% reduction in fasting triglycerides from baseline over time
- Change and percent change from baseline at each scheduled assessment in fasting triglycerides up to Month 12
- Subject incidence of treatment-emergent AEs (TEAEs)

Exploratory endpoints included:

- Change and percent change from baseline at each scheduled assessment in fasting lipid parameters (total cholesterol, LDL-C, HDL-C, non-HDL-C, VLDL-C, total apoB, apoB-48, lipoprotein(a) [Lp(a)], apolipoprotein B 100 [apoB-100], apoC2, apoC3, apolipoprotein A-I [apoA1], and apoA5), with all values drawn after at least a 10-hour fast; LDL-C was measured using ultracentrifugation methodology, preferentially, as well as Martin-Hopkins methodology.
- Changes from baseline at each scheduled assessment in fasting serum blood glucose, glycosylated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide
- Area under the curve in fasting triglyceride from baseline to Month 12
- Incidence of positively, probably, or possibly adjudicated events of acute pancreatitis during the randomized period.
- Time to the first positively adjudicated events of acute pancreatitis
- Time to the first positively, probably, or possibly adjudicated events of acute
- Pancreatitis
- Incidence of hospitalizations for abdominal pain
- Subject incidence of abdominal pain
- Subject incidence of emergent apheresis
- Population pharmacokinetics (PK) of plozasiran, with assessment of the covariates of country (Japan) and race (Asian) for any significant effect on plozasiran PK (randomized period only)
- Incidence of anti-drug antibodies (ADA) to plozasiran
- Change from baseline at each scheduled assessment in European Organisation for them 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

Estimands for the secondary objectives

The Applicant has specified the secondary estimands for the secondary endpoints as treatment policy similarly to the primary estimand.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The Applicant described that the same statistical methods as used for the primary endpoint.

Tertiary objective

Not applicable

Estimand for the tertiary objective

Not applicable

Statistical methods for estimation and sensitivity analysis on the tertiary estimand

Not applicable

5.3.2.1.4. Results

Participant flow and numbers analysed

Participant flow

The date first participant enrolled was 21 December 2001 and the last subject last visit before database lock for the primary analysis was 29 April 2024.

Among 123 individuals who were screened, 75 subjects met the eligibility criteria and were randomized 1:1:1 to receive placebo (n=25), plozasiran 25 mg (n=26), or plozasiran 50 mg (n=24). Reasons occurring in >5% for individuals failing screening were inclusion criterion 3 for triglycerides ≥ 10 mmol/L (14.6%) or inclusion criterion 4 for FCS diagnosis (10.6%).

Of the 75 randomized subjects, 64 (85.3%) completed 12 months of randomized study treatment. The number of subjects who discontinued the randomized period was higher in the placebo group (6 subjects total, 3 due to acute pancreatitis and 3 due to withdrawal from treatment) compared to the plozasiran groups (3 subjects in the plozasiran 25 mg group and 2 subjects in the plozasiran 50 mg group).

In the plozasiran 25 mg group, 2 (7.7%) subjects discontinued study due to a treatment-emergent adverse event (TEAE) and 1 (3.8%) subject discontinued due to pregnancy. In the plozasiran 50 mg group, 1 (4.2%) subject discontinued the study due to a TEAE and 1 (4.2%) subject discontinued for "other" reason (left the country) (Table 21). No subject discontinued treatment or the study due to Coronavirus Disease 2019 (COVID-19).

The protocol was amended to allow subjects who were deemed to have experienced acute pancreatitis by the Investigator to be unblinded and then early transitioned to the OLE period. Due to the timing of Amendment 4 and respective required approvals, only 3 subjects who experienced a suspected acute pancreatitis event were unblinded and were early transitioned to the OLE. All 3 of these subjects had an event that was ultimately positively adjudicated as pancreatitis by the blinded adjudication committee. These 3 patients did not go on to have recurrent episodes of adjudicated pancreatitis after they transitioned to unblinded treatment with plozasiran (through 26 May 2025).

Table 22: Subject Disposition (Randomized Period)

	Placebo (pooled) n (%)	Plozasiran 25mg n (%)	Plozasiran 50mg n (%)	Plozasiran (pooled) n (%)	Total n (%)
Screened[a]					123
Screen failures[a]					48 (39.0)
Randomized subjects[b]	25 (100.0)	26 (100.0)	24 (100.0)	50 (100.0)	75 (100.0)
Completed 12-month treatment in randomized period[b]	19 (76.0)	23 (88.5)	22 (91.7)	45 (90.0)	64 (85.3)
Discontinued treatment during randomized period[b]	6 (24.0)	3 (11.5)	2 (8.3)	5 (10.0)	11 (14.7)
Due to acute pancreatitis[b]	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.0)
Due to other adverse event	0 (0.0)	2 (7.7)	1 (4.2)	3 (6.0)	3 (4.0)
Withdrawal from treatment by subject	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.0)
Pregnancy	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	1 (1.3)
Other	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	1 (1.3)
Completed randomized period[b]	19 (76.0)	23 (88.5)	22 (91.7)	45 (90.0)	64 (85.3)
Early terminated during randomized period due to acute pancreatitis but continued in Open-Label Extension[b]	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.0)

a Denominator=screened subjects. More than one criterion can be provided for not eligible subject and, as such, the percentage may total more than 100%.
b Denominator=randomized subjects.

Treatment compliance

Overall study treatment compliance was 92.0%. The mean total number of injections received was 3.7, with 1, 2, 3, and 4 injections received by 5 (6.7%), 2 (4.0%), 3 (4.0%), and 64 (85.3%) subjects, respectively.

Table 23: Study Drug Administration (Randomized Period) – Safety analysis set

Parameter Category/Statistic	Placebo (pooled) (N=25) n (%)	ARO-APOC3 25mg (N=26) n (%)	ARO-APOC3 50mg (N=24) n (%)	ARO-APOC3 (pooled) (N=50) n (%)	Total (N=75) n (%)
Number of injections received, n(%)					
1	2 (8.0)	1 (3.8)	2 (8.3)	3 (6.0)	5 (6.7)
2	1 (4.0)	2 (7.7)	0 (0.0)	2 (4.0)	3 (4.0)
3	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.0)
4	19 (76.0)	23 (88.5)	22 (91.7)	45 (90.0)	64 (85.3)
Total number of injections received					
n	25	26	24	50	75
Mean (SEM)	3.6 (0.18)	3.7 (0.15)	3.8 (0.17)	3.7 (0.11)	3.7 (0.10)
SD	0.92	0.78	0.85	0.80	0.84
Median	4.0	4.0	4.0	4.0	4.0
Q1, Q3	4.0, 4.0	4.0, 4.0	4.0, 4.0	4.0, 4.0	4.0, 4.0
Min, Max	1, 4	1, 4	1, 4	1, 4	1, 4
Overall compliance (%) [1]					
n	25	26	24	50	75
Mean (SEM)	89.0 (4.58)	93.3 (3.81)	93.8 (4.32)	93.5 (2.84)	92.0 (2.43)
SD	22.91	19.44	21.17	20.08	21.02
Median	100.0	100.0	100.0	100.0	100.0
Q1, Q3	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0
Min, Max	25, 100	25, 100	25, 100	25, 100	25, 100
Study exposure during randomized period (months) [2]					
n	25	26	24	50	75
Mean (SEM)	10.5 (0.55)	11.8 (0.14)	11.4 (0.50)	11.6 (0.25)	11.2 (0.25)
SD	2.74	0.71	2.43	1.75	2.18
Median	11.8	11.8	11.8	11.8	11.8
Q1, Q3	11.6, 11.9	11.8, 12.0	11.8, 11.8	11.8, 12.0	11.8, 12.0
Min, Max	1, 12	9, 13	1, 15	1, 15	1, 15

[1] Overall compliance at randomized period is defined as total number of injections received at randomized period * 100 / 4.
[2] Study exposure during randomized period (months) = (end of randomized period date - Day 1 date + 1) / 365.25*12
Abbreviation: SD = Standard deviation. SEM = Standard error of the mean. Q1 = 1st quartile. Q3 = 3rd quartile.

Data sets analysed

All 75 subjects (100.0%) were included in the Full Analysis Set, the Safety Analysis Set, and the PRO Analysis Set. The PPS included the 64 (85.3%) subjects who received all 4 injections of study drug and who provided Month 10 fasting triglyceride measurements. The PK Analysis Set included 25 (96.2%) subjects in the plozasiran 25 mg group and 23 (95.8%) subjects in the plozasiran 50 mg group.

Table 24: Analysis Population (Randomized Period) – All randomised subjects

	Placebo (pooled) (N=25) n (%)	ARO-APOC3 25mg (N=26) n (%)	ARO-APOC3 50mg (N=24) n (%)	ARO-APOC3 (pooled) (N=50) n (%)	Total (N=75) n (%)
Full Analysis Set [1]	25 (100.0)	26 (100.0)	24 (100.0)	50 (100.0)	75 (100.0)
Safety Analysis Set [2]	25 (100.0)	26 (100.0)	24 (100.0)	50 (100.0)	75 (100.0)
PRO Analysis Set [3]	25 (100.0)	26 (100.0)	24 (100.0)	50 (100.0)	75 (100.0)
Per-protocol Analysis Set [4]	19 (76.0)	23 (88.5)	22 (91.7)	45 (90.0)	64 (85.3)
Reason for exclusion from PPS					
Missing Month 10 fasting TG measurements	6 (24.0)	2 (7.7)	2 (8.3)	4 (8.0)	10 (13.3)
Not completing all 4 injections of the study drug	6 (24.0)	3 (11.5)	2 (8.3)	5 (10.0)	11 (14.7)
PK Analysis Set [5]	0 (0.0)	25 (96.2)	23 (95.8)	48 (96.0)	48 (64.0)

% = 100 x n/N. PRO = Patient-Reported Outcomes.
[1] Full Analysis Set (FAS) includes all randomized subjects regardless of adherence to the treatment.
[2] Safety Analysis Set includes all subjects who receive at least 1 dose of IP.
[3] PRO Analysis Set includes all subjects who are randomized and have at least one PRO assessment.
[4] Per-protocol Set (PPS) includes all randomized subjects who completed the study without major protocol deviations.
[5] PK analysis set include all FAS participants who have sufficient plasma concentration data to facilitate determination of PK parameters.

Baseline data

Demographics and characteristics

Subject demographics were generally comparable across the treatment groups (Table 28). Mean age at screening was 46.0 years and approximately half of the subjects in each treatment group were

male. Most subjects were White (73.3%) or Asian (21.3%). Region was balanced across North America (36.0%), Europe (30.7%), and other areas (33.3%). Five (6.7%) subjects were from Japan. The mean body mass index (BMI) was 25.5 kg/m2 and 53.3% of subjects were overweight (BMI ≥25 kg/m2).

Table 25: Subject Demographics and Baseline Characteristics - Full Analysis Set

Demographics/Characteristics Statistic/Category	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)	Plozasiran (pooled) (N=50)	Total (N=75)
Age (years)[a]					
Mean (SD)	47.4 (13.93)	47.9 (14.41)	42.6 (10.85)	45.4 (12.98)	46.0 (13.24)
Median	44.0	46.5	40.5	43.5	44.0
Min, Max	26, 71	22, 76	24, 68	22, 76	22, 76
Age group, n (%)					
<50 years	14 (56.0)	15 (57.7)	20 (83.3)	35 (70.0)	49 (65.3)
50 to <65 years	8 (32.0)	7 (26.9)	2 (8.3)	9 (18.0)	17 (22.7)
≥65 years	3 (12.0)	4 (15.4)	2 (8.3)	6 (12.0)	9 (12.0)
Sex at birth, n (%)					
Male	14 (56.0)	12 (46.2)	11 (45.8)	23 (46.0)	37 (49.3)
Female	11 (44.0)	14 (53.8)	13 (54.2)	27 (54.0)	38 (50.7)
Race, n (%)					
White	19 (76.0)	19 (73.1)	17 (70.8)	36 (72.0)	55 (73.3)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	1 (1.3)
Asian	4 (16.0)	7 (26.9)	5 (20.8)	12 (24.0)	16 (21.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (8.0)	0 (0.0)	1 (4.2)	1 (2.0)	3 (4.0)
Ethnicity, n (%)					
Hispanic or Latino	1 (4.0)	0 (0.0)	1 (4.2)	1 (2.0)	2 (2.7)
Not Hispanic or Latino	24 (96.0)	26 (100.0)	22 (91.7)	48 (96.0)	72 (96.0)
Unknown	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	1 (1.3)
Region, n (%)					
North America	11 (44.0)	9 (34.6)	7 (29.2)	16 (32.0)	27 (36.0)

Demographics/Characteristics Statistic/Category	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)	Plozasiran (pooled) (N=50)	Total (N=75)
Europe	6 (24.0)	8 (30.8)	9 (37.5)	17 (34.0)	23 (30.7)
Other	8 (32.0)	9 (34.6)	8 (33.3)	17 (34.0)	25 (33.3)
Region - Japan, n (%)					
Yes	2 (8.0)	2 (7.7)	1 (4.2)	3 (6.0)	5 (6.7)
No	23 (92.0)	24 (92.3)	23 (95.8)	47 (94.0)	70 (93.3)
BMI (kg/m^2)					
Mean (SD)	24.95 (4.098)	26.09 (3.923)	25.43 (4.763)	25.78 (4.314)	25.50 (4.234)
Median	25.00	26.15	24.55	25.15	25.00
Min, Max	18.5, 33.4	19.8, 32.7	19.1, 35.9	19.1, 35.9	18.5, 35.9
BMI group, n (%)					
<25 kg/m^2	12 (48.0)	11 (42.3)	12 (50.0)	23 (46.0)	35 (46.7)
≥25 kg/m^2	13 (52.0)	15 (57.7)	12 (50.0)	27 (54.0)	40 (53.3)

Abbreviations: BMI=body mass index; SD=standard deviation.
[a] Age at time of consent.

Baseline lipids and lipoproteins

Mean values for lipids and lipoproteins were reasonably balanced across treatment groups at baseline given the sample size of this trial. Consistent with expected entry values for a population with FCS, the median triglyceride level at baseline was 23.1 mmol/L (2043.9 mg/dL). Mean values for other key lipids at baseline were as follows: non-HDL-C, 7.1 mmol/L (272.7 mg/dL); apoC3, 0.37 g/L (37.0 mg/dL); HDL-C, 0.44 mmol/L (16.9 mg/dL); and LDL-C (by ultracentrifugation), 0.67 mmol/L (25.9 mg/dL).

Table 26: Baseline Lipids - Full Analysis Set

Demographics/Characteristics Statistic/Category	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)	Plozasiran (pooled) (N=50)	Total (N=75)
Triglycerides at baseline (mg/dL) [1]					
Mean (SD)	2271.91 (1141.426)	2349.53 (1374.542)	2491.45 (1523.200)	2417.65 (1434.621)	2369.07 (1337.965)
Median	2052.60	2007.95	1902.36	2007.95	2043.89
Min, Max	746.7, 4425.1	826.4, 5596.5	798.4, 6597.3	798.4, 6597.3	746.7, 6597.3
Triglycerides at baseline category, n (%)					
< 2000 mg/dL	12 (48.0)	13 (50.0)	12 (50.0)	25 (50.0)	37 (49.3)
>= 2000 mg/dL	13 (52.0)	13 (50.0)	12 (50.0)	25 (50.0)	38 (50.7)

Demographics/Characteristics Statistic/Category	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)	Plozasiran (pooled) (N=50)	Total (N=75)
apoC3 at baseline (mg/dL)					
Mean (SD)	39.899 (17.5576)	38.519 (17.1285)	32.470 (19.7976)	35.615 (18.5197)	37.043 (18.1995)
Median	38.770	38.935	30.125	33.570	35.440
Min, Max	10.00, 71.52	13.08, 88.00	14.24, 88.00	13.08, 88.00	10.00, 88.00
non-HDL-C at baseline (mg/dL)					
Mean (SD)	267.6 (150.22)	278.7 (135.28)	271.7 (146.34)	275.3 (139.29)	272.7 (142.05)
Median	234.0	243.0	250.0	243.0	240.0
Min, Max	89, 776	99, 624	53, 708	53, 708	53, 776
HDL-C at baseline (mg/dL)					
Mean (SD)	18.0 (8.96)	18.1 (6.41)	14.6 (5.46)	16.4 (6.17)	16.9 (7.20)
Median	15.0	18.0	13.5	15.0	15.0
Min, Max	9, 51	7, 40	6, 33	6, 40	6, 51
LDL-C at baseline by ultracentrifugation (mg/dL)					
Mean (SD)	28.4 (18.93)	23.8 (13.91)	25.8 (19.35)	24.7 (16.60)	25.9 (17.37)
Median	24.0	21.5	21.5	21.5	22.0
Min, Max	6, 81	8, 53	4, 80	4, 80	4, 81
LDL-C at baseline category by ultracentrifugation, n (%)					
<22 mg/dL (median)	11 (44.0)	13 (50.0)	12 (50.0)	25 (50.0)	36 (48.0)
≥22 mg/dL (median)	14 (56.0)	13 (50.0)	12 (50.0)	25 (50.0)	39 (52.0)

Abbreviations: HDL-C=high density lipoprotein cholesterol; IWRS=Interactive Web Response System; LDL-C=low density lipoprotein cholesterol; non-HDL-C=non-high density lipoprotein cholesterol; SD=standard deviation.
[1] Mean triglyceride value at baseline is defined as the geometric mean of the last 2 non-missing values prior to the first dose or the last non-missing value prior to the first dose if only a single value is available.

HbA1c and diabetes status at baseline

Patients with FCS often have accompanying metabolic disorders. Based on medical history, use of diabetic medications, and HbA1c or fasting glucose, 21.3% of subjects had diabetes, with a higher prevalence in the placebo group (32.0%, 15.4%, and 16.7% for placebo, plozasiran 25 mg, and plozasiran 50 mg, respectively), and 16.0% had prediabetes at study entry with higher prevalence in the 25 mg group (12.0%, 23.1%, and 12.5%, for placebo, plozasiran 25, and plozasiran 50 mg. respectively).

Table 27: HbA1c and Diabetes Status at Baseline - Full Analysis Set

Demographics/Characteristics Statistic/Category	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)	Total (N=75)
HbA1c at baseline (%)				
Mean (SD)	6.12 (1.326)	5.73 (0.896)	5.59 (1.154)	5.82 (1.143)
Median	5.60	5.30	5.25	5.30
Min, Max	4.4, 8.9	4.8, 7.9	4.4, 8.5	4.4, 8.9
HbA1c category (and diabetes status) at baseline, n (%)				
<5.7% (normoglycemia)	14 (56.0)	16 (61.5)	17 (70.8)	47 (62.7)
5.7% to <6.5% (prediabetes)	3 (12.0)	6 (23.1)	3 (12.5)	12 (16.0)
≥6.5% (diabetes)	8 (32.0)	4 (15.4)	4 (16.7)	16 (21.3)

Abbreviations: SD=standard deviation.

Prior and concomitant lipid-lowering therapy

Background triglyceride-lowering therapy at study entry included fibrates (66.7% of subjects), statins (45.3%), and oils (omega-3 fatty acid or fish oil; 29.3%); 26.7% of subjects were receiving no background triglyceride-lowering therapy at baseline. Only 4 subjects experienced an addition or change in lipid-lowering therapy during the study. In one case, TG lowering medication was started after a suspected episode of acute pancreatitis. In the other three cases, the changes were made on the basis of a pre-existing medical history and not in response to an adverse event or a receipt of a blinded TG or low-density lipoprotein-cholesterol (LDL-C) alert.

Table 28: Background Triglyceride-Lowering Therapy - Full Analysis Set

Therapy	Placebo (pooled) (N=25) n (%)	Plozasiran 25mg (N=26) n (%)	Plozasiran 50mg (N=24) n (%)	Total (N=75) n (%)
Fibrates	16 (64.0)	19 (73.1)	15 (62.5)	50 (66.7)
Icosapent ethyl, omega-3 fatty acid, or fish oil	6 (24.0)	9 (34.6)	7 (29.2)	22 (29.3)
Statin	11 (44.0)	11 (42.3)	12 (50.0)	34 (45.3)
None	8 (32.0)	5 (19.2)	7 (29.2)	20 (26.7)

Prior and concomitant diabetic therapy

All subjects with diabetes (based on HbA1c ≥6.5% baseline) were treated with diabetes medications at baseline, most commonly metformin (and combinations) or insulin.

Table 29: Diabetic Medication Use at Baseline - Full Analysis Set

Demographics/Characteristics Statistic/Category	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)	Total (N=75)
Diabetic subjects at baseline, N' [1]	8	4	4	16
Diabetic medications use at baseline, n/N'(%) [2]				
Metformin/combo	7 (87.5)	3 (75.0)	5 (125.0)	15 (93.8)
Insulin	5 (62.5)	4 (100.0)	4 (100.0)	13 (81.3)
Glucagon-like peptide (GLP1) receptor agonists	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dipeptidyl peptidase-4 (DPP-4) inhibitors	3 (37.5)	1 (25.0)	0 (0.0)	4 (25.0)
Sodium-glucose transporter (SGLT) 2 inhibitors	3 (37.5)	3 (75.0)	3 (75.0)	9 (56.3)
Other	4 (50.0)	0 (0.0)	2 (50.0)	6 (37.5)
None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: SD=standard deviation.
[1] Based on HbA1c ≥6.5% at baseline.
[1] % = 100 x n/N', N' is the number of diabetic subjects at baseline.

Pancreatitis history

Pancreatitis history was reasonably balanced across treatment groups. Most subjects (89.3%) had a history of pancreatitis, with 80.0% reporting pancreatitis within the last 10 years (Table 33).

Table 30: Pancreatitis History – Safety Analysis Set

Category	Placebo (pooled) (N=25) n (%)	Plozasiran 25mg (N=26) n (%)	Plozasiran 50mg (N=24) n (%)	Total (N=75) n (%)
History of Pancreatitis, n (%)	22 (88.0)	23 (88.5)	22 (91.7)	67 (89.3)
History of Recurrent Pancreatitis, n (%)	18 (72.0)	19 (73.1)	22 (91.7)	59 (78.7)
Pancreatitis within the Last 10 Years, n (%)	20 (80.0)	18 (69.2)	22 (91.7)	60 (80.0)
Pancreatitis within the Last 5 Years, n (%)	17 (68.0)	14 (53.8)	18 (75.0)	49 (65.3)
Pancreatitis within the Last 2 Years, n (%)	14 (56.0)	9 (34.6)	11 (45.8)	34 (45.3)
Pancreatitis within the Last 1 Year, n (%)	9 (36.0)	4 (15.4)	8 (33.3)	21 (28.0)

Clinical versus genetically confirmed FCS

Demographic and baseline characteristics were analyzed separately in subjects with genetically confirmed FCS versus those with clinical FCS (Table 34). Generally, FCS with genetic confirmation subjects tended to have higher median baseline triglyceride values, lower BMI, lower mean LDL-C and ApoB values, a lower tendency to display components of metabolic syndrome, and were more

likely to be female than their clinical FCS counterparts. However, both groups had similarly high rates of prior pancreatitis and a high prevalence of recurrent pancreatitis.

Table 31: Demographics and Baseline Characteristics: Subjects with Genetically Confirmed vs Clinical FCS

	Subjects with on-study genetic confirmation of FCS	Subjects without on-study genetic confirmation of FCS
Number of Subjects (%) in Study	41 (54.7)[a]	34 (45.3)[a]
Age (years) mean	44.3	46.7
Age of symptom onset (years) mean	Data not available	Data not available
Sex, % females	26 (63.4)	12 (35.3)
BMI (kg/m²) (mean)	23.79	27.57
Race - Asian (%)	11 (26.8)	5 (14.7)
Baseline TG (mmol/L)[b]		
Mean	27.027	26.461
Median	26.458	19.124
Baseline TG/TC ratio (mean)[b]	4.01	3.14
Baseline apoB (g/L) (mean)	0.5547	0.8890
Baseline LDL-C (Ultracentrifugation) (mmol/L) (mean)	0.488	0.893
Baseline HDL-C (mmol/L) (mean)	0.387	0.501
History of pancreatitis (%)	36 (87.8)	31 (91.2)
History of recurrent pancreatitis (%)	29 (70.7)	30 (88.2)
Type 2 diabetes mellitus (%)	2 (4.9)	13 (38.2)
Hypertension (%)	9 (22.0)	18 (52.9)
Smoking history (%)	7 (17.1)	10 (29.4)
Cardiovascular disease history (%)	13 (31.7)	22 (64.7)
Ever on statin treatment (%)	14 (34.1)	20 (58.8)
Ever on fibrate treatment (%)	26 (63.4)	24 (70.6)
Ever on fibrate + another lipid lowering medication (%)	26 (63.4)	24 (70.6)

Abbreviations: ApoB=apolipoprotein B; BMI=body-mass index; EDC=electronic data capture; FCS=familial chylomicronemia syndrome; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglyceride.
[a] Percentage (%) = number of subjects in each group/number of randomized subjects in total.
[b] Mean TG value at baseline is defined as the geometric mean of the last 2 non-missing values prior to the first dose or the last non-missing value prior to the first dose if only a single value is available.

Genotype

At database lock, genotypes consistent with a diagnosis of genetically confirmed FCS were documented at baseline in 41 (54.7%) subjects, as follows:

- Pathogenic *LPL* variants: 33/41 subjects (80.5%), including 20/41 subjects (48.8%) with homozygous *LPL* variants (biallelic identical), and 13/41 subjects (31.7%) with heterozygous *LPL* variants, all of which would be considered heterozygous for 2 pathogenic variants (biallelic different variant same gene or biallelic plus)
- Pathogenic *GPIHBP1* variants: 4/41 subjects (9.8%)
- Pathogenic *LMF1* variants: 3/41 subjects (7.3%)
- Pathogenic *APOC2* variants: 1/41 subjects (2.4%)

The other 34 (45.3%) subjects had clinical FCS per the enrollment criteria in the study protocol and were shown to have genotypes that could not be defined as genetically confirmed FCS. These included pathogenic gene variants in one copy (heterozygous) and single or biallelic variants of unknown significance or non-pathogenic variants (including homozygous variants that were intronic or of unclear clinical significance) in genes associated with FCS.

Outcomes and estimation

Primary endpoint

Change in fasting TG from baseline at Month 10

The primary efficacy endpoint was reduction in fasting triglycerides at Month 10 following plozasiran compared with placebo. Median changes from baseline at Month 10 in fasting triglycerides in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were -17.1%, -80.1%, and -77.6%, respectively. Between-group median differences versus placebo were -58.7% for plozasiran 25 mg (P<0.0001) and -52.5% for plozasiran 50 mg (P=0.0002).

Among subjects with fasting triglyceride measurements at Month 10, all subjects in the plozasiran groups experienced decreases from baseline, and ~80% experienced a >50% decrease from baseline. Deep reductions in triglycerides were apparent at 1 month (the first postbaseline measurement) and remained consistent throughout the 12-month duration of the trial, with relatively small peak-to-trough differences.

All subjects were instructed to consistently follow a diet very low in fat at baseline and then during every monthly visit. The difficulty subjects find in following such a restrictive diet, as reported broadly in the literature, is evident from median triglyceride measurements and interquartile ranges in the placebo group as shown in Figure 28. Approximately 40% of placebo subjects had an increase in triglycerides at Month 10, with the remainder showing a decrease. Plozasiran-treated subjects on the other hand showed more consistency in response and tighter interquartile ranges in spite of the challenges following dietary advice.

Table 32: Primary Efficacy Endpoint: Median Difference in Percent Change From Baseline at Month 10 in Fasting Triglycerides - Nonparametric Analysis With Pattern-Mixture Model - Full Analysis Set

	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)
Baseline (mmol/L)			
N	25	26	24
Mean (SD)	25.672 (2.5796)	26.550 (3.0463)	28.153 (3.5134)
Median	23.195	22.688	21.500
Q1, Q3	16.216, 31.131	13.606, 37.975	16.207, 33.311

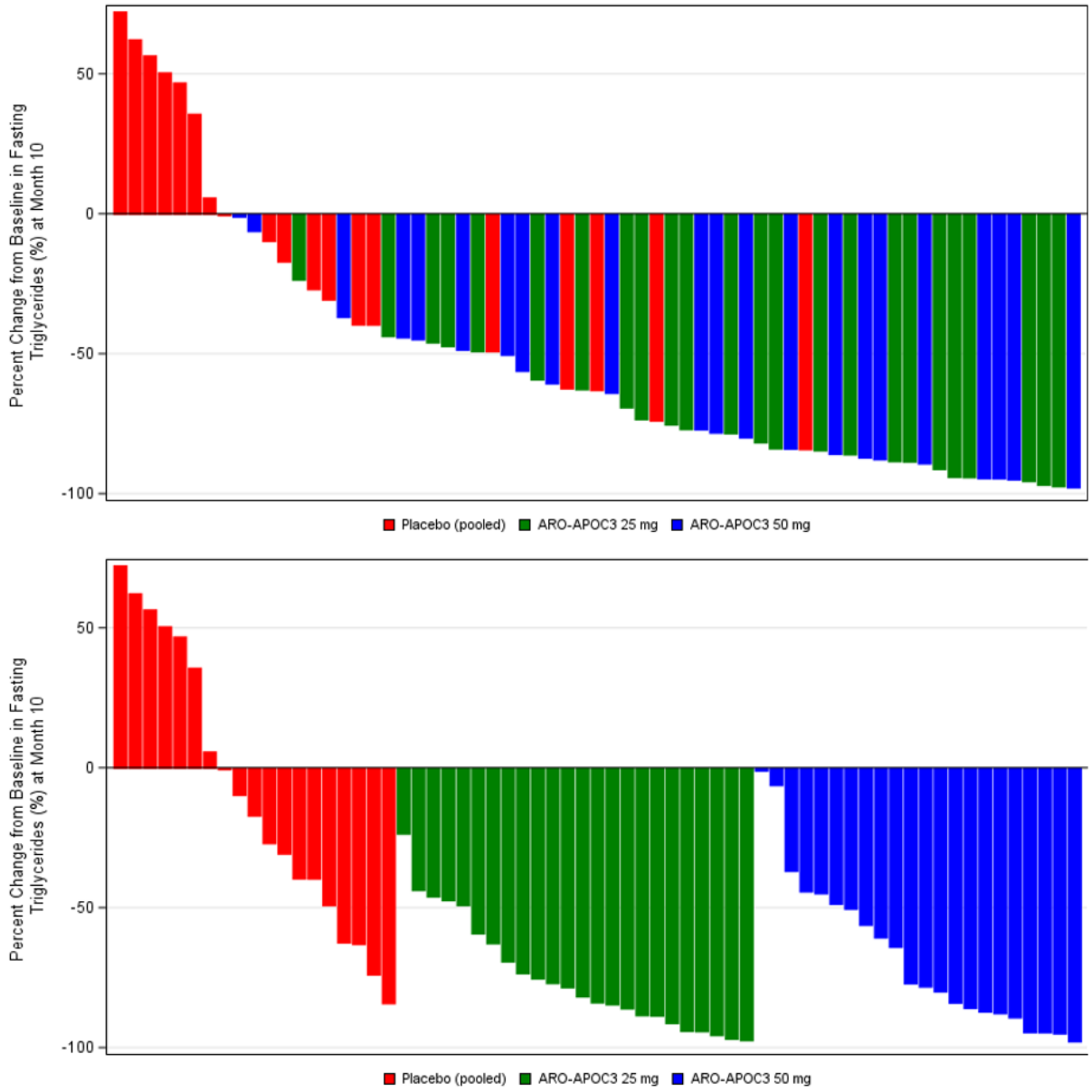
	Placebo (pooled) (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)
Month 10 (mmol/L)			
N	19	24	22
Mean (SD)	22.76	7.18	9.40
Median	18.24	5.01	7.50
Q1, Q3	9.96, 36.71	1.55, 9.01	1.94, 16.57
% Change from baseline at Month 10			
N	19	24	22
Median	-17.10	-80.07	-77.62
Q1, Q3	-49.12, 46.95	-89.90, -60.95	-87.73, -48.58
Median difference between plozasiran and placebo (pooled) at Month 10[a]			
Estimate		-58.72	-52.47
95% CI		[-89.57, -27.87]	[-83.06, -21.88]
P-value		<0.0001	0.0002
Adjusted *P*-value[b]		<0.0001	0.0002

Abbreviations: Q1=first quartile; Q3=third quartile; SD=standard deviation; SEM=standard error of the mean.

[a] Hodges-Lehmann method was used to estimate the median difference (location shift) and its corresponding 95% confidence interval for percent changes between plozasiran doses and placebo (pooled). *P*-values were from the Wilcoxon rank-sum test.

[b] The adjusted p-value was calculated using the Holm method for multiplicity adjustment.

Figure 26: Waterfall Plots of Percent Change From Baseline in Fasting Triglycerides at Month 10 (Full Analysis Set) - AROAPOC3-3001



Sensitivity analyses

An analysis of the primary efficacy endpoint data in the PPS without missing data imputation showed similar results as the FAS, with the between-group median differences versus placebo in percent change in fasting triglycerides at Month 10 were -59.5% for plozasiran 25 mg (P<0.0001) and -53.8% for plozasiran 50 mg (P=0.0001).

Sensitivity analysis using an ANCOVA model with treatment as a factor and baseline triglycerides as a covariate was performed for the FAS instead of non-parametric analysis. At Month 10, the between-group mean differences versus placebo in percent changes in fasting triglycerides were -63.9% (*P*=0.0004) for plozasiran 25 mg and -57.2% (*P*=0.0013) for plozasiran 50 mg. Shapiro-Wilk Normality Test indicated the normality assumption was not met. The ANCOVA results were consistent with results from the primary analysis. The normality test indicated that the choice of using median instead of mean triglyceride reductions in assessing the primary endpoint had been correct.

Additional sensitivity analysis with an MMRM model was performed for the FAS based on the MAR assumption. The MMRM model included treatment arm, study visit, and baseline value as model terms. The model also included treatment by visit as interaction terms. At Month 10, the between-group mean differences versus placebo in fasting triglycerides were -69.7% (*P*<0.0001) for plozasiran 25 mg and -62.0% (*P*<0.0001) for plozasiran 50 mg.

Key secondary endpoints

Change in fasting TG from baseline at Month 10 and 12 (averaged)

Both doses of plozasiran significantly reduced fasting triglycerides at Months 10 and 12 (averaged) compared with placebo. Median changes from baseline at Months 10 and 12 in fasting triglycerides in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were -2.6%, -77.7%, and -71.0%, respectively. Between-group median differences versus placebo were -59.6% for plozasiran 25 mg (P<0.0001) and -50.8% for plozasiran 50 mg (P=0.0007).

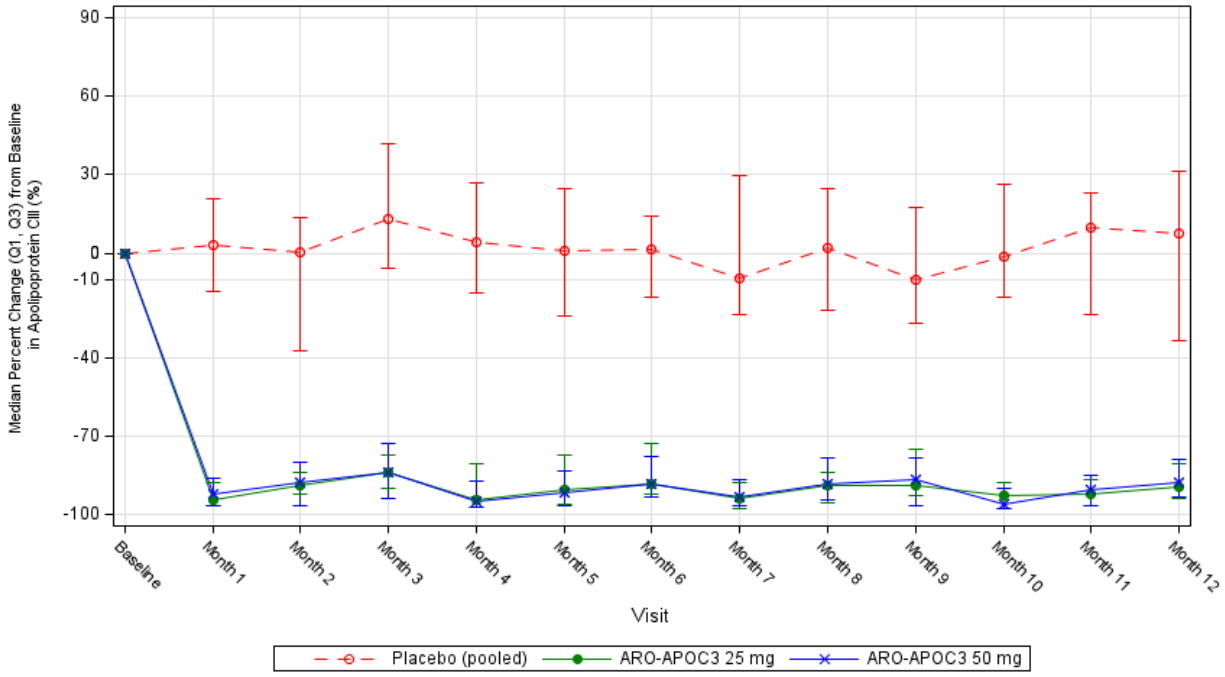
Change in fasting ApoC3 from baseline at Month 10 and at Month 12

Plozasiran significantly reduced fasting apoC3 at Month 10 and at Month 12 compared with placebo.

At Month 10, median changes from baseline in fasting apoC3 in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were -1.3%, -93.0%, and -96.2%, respectively. Between group median differences versus placebo at Month 10 were -90.5% for plozasiran 25 mg (P<0.0001) and -93.4% for plozasiran 50 mg (P<0.0001).

At Month 12, median changes from baseline in fasting apoC3 in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were 7.7%, -89.3%, and -87.7%, respectively. Between group median differences versus placebo at Month 12 were -87.0% for plozasiran 25 mg (P<0.0001) and -87.5% for plozasiran 50 mg (P<0.0001).

Figure 27: Plot of Median Percent Change (Q1, Q3) from Baseline in Fasting APOC3



Abbreviations: ARO-APOC3=plozasiran; CSR=clinical study report; Q1=first quartile; Q3=third quartile; SEM=standard error of the mean

Acute pancreatitis (positively adjudicated events)

Plozasiran reduced the odds of positively adjudicated events of acute pancreatitis. Thirteen adverse events of potential acute pancreatitis that met prespecified criteria for adjudication were sent to the blinded Pancreatitis Adjudication Committee of independent experts. The Committee positively adjudicated 9 total events in 7 subjects as definite acute pancreatitis: 7 positively adjudicated events occurred in 5 (20.0%) subjects in the placebo group and 2 positively adjudicated events occurred in 2 (4.0%) subjects in the pooled plozasiran groups (pooling of the 2 plozasiran groups was prespecified in the SAP). The odds of acute pancreatitis were 83% lower (OR=0.169; P=0.0292) in the pooled plozasiran groups compared with the placebo group. In the placebo group, most of the positively adjudicated events were severe; in the plozasiran groups, none of the positively adjudicated events were severe.

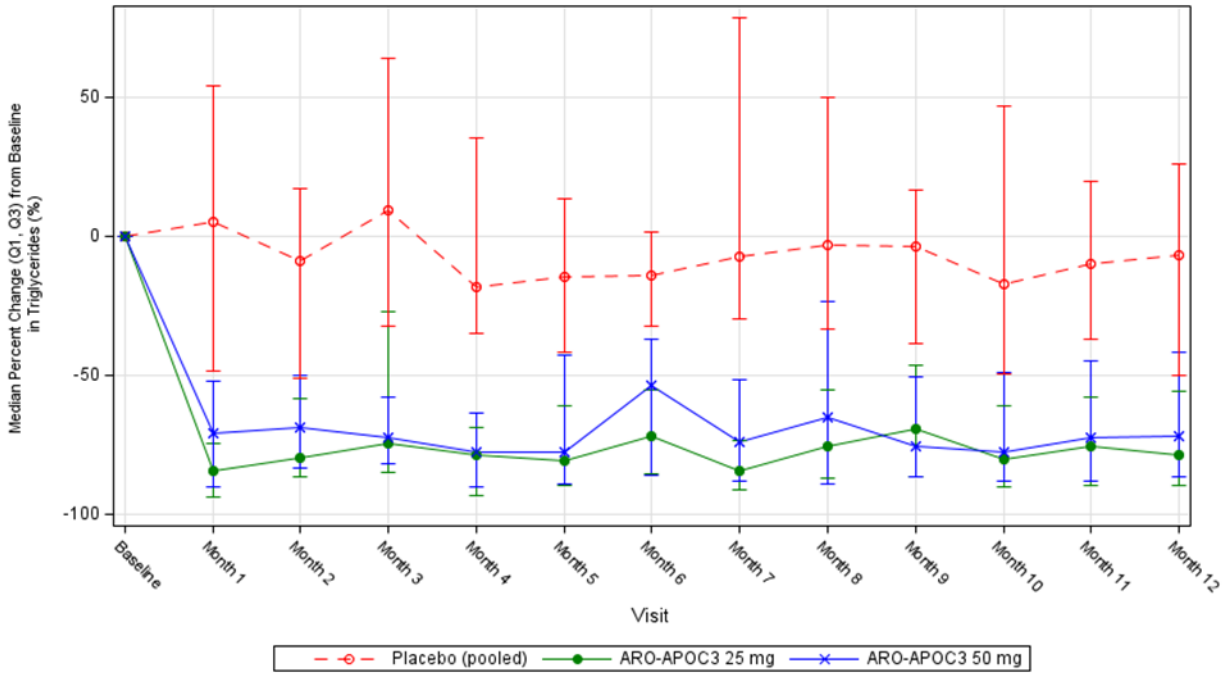
The positively adjudicated acute pancreatitis events were relatively evenly distributed between genetic and clinical familial chylomicronaemia syndrome (FCS) patients with 5 cases occurring in 3 genetically confirmed patients and 4 cases occurring in 4 clinically diagnosed patients.

Other secondary endpoints

Change in fasting TG from baseline at Month 12

Median percent changes in fasting triglycerides (Figure 30) favored the plozasiran groups versus placebo at each visit through Month 12. The ratio between each plozasiran group and the placebo group in area under the curve from baseline to Month 12 for fasting triglycerides was 0.295 for plozasiran 25 mg (P<0.0001) and 0.342 for plozasiran 50 mg (P<0.0001).

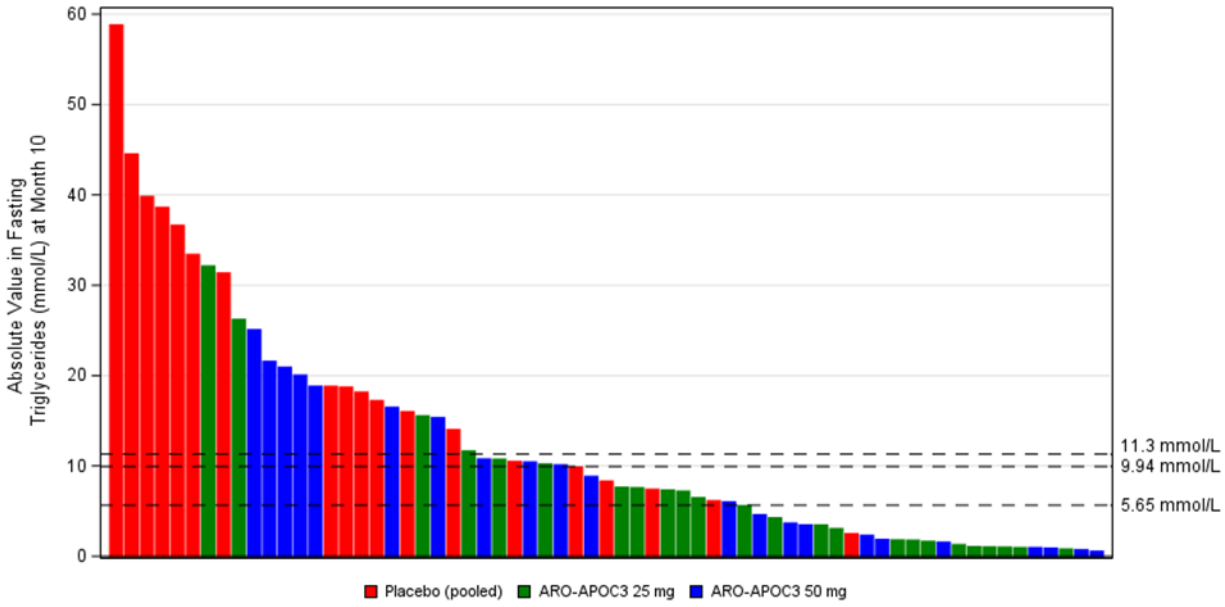
Figure 28: Plot of Median Percent Change From Baseline in Fasting Triglycerides - Full Analysis Set - AROAPOC3-3001



Proportion of subjects with TG< 5.65 mmol/L (< 500 mg/dL)

Additional non-alpha controlled secondary efficacy endpoints included the proportion of subjects who achieved triglycerides of <5.65 mmol/L (<500 mg/dL) at Month 10, a threshold associated with increased risk of acute pancreatitis (Yang 2020). This threshold was achieved in 50.0% and 45.5% of subjects randomized to 25 mg and 50 mg of plozasiran compared to 5.3% in the placebo group, respectively (Figure 27). The OR versus placebo for achieving this endpoint at Month 10 was 21.1 (95% CI, 2.3-190.4; P=0.0066) for plozasiran 25 mg and 18.0 (95% CI, 2.0-164.4; P=0.0106) for plozasiran 50 mg. At the end of the randomized period (Month 12), the odds ratio versus placebo for achieving triglycerides of <5.65 mmol/L (<500 mg/dL) was 9.1 (95% CI, 1.6-52.1; P=0.0131) for plozasiran 25 mg and 7.4 (95% CI, 1.3-43.4; P=0.0257) for plozasiran 50 mg.

Figure 29: Waterfall Plot of Absolute Value in Fasting Triglycerides at Month 10 (Full Analysis Set)



Proportion of subjects with TG< 9.94 mmol/L (< 880 mg/dL)

At Month 10, the proportion of subjects achieving fasting triglycerides of <9.94 mmol/L (<880 mg/dL) in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups was 21.1%, 75.0%, and 54.5%, respectively (Figure 27). The OR versus placebo for achieving this endpoint at Month 10 was 15.5 (P=0.0005) for plozasiran 25 mg and 5.7 (P=0.0194) for plozasiran 50 mg.

Other lipid parameters

Non-HDL-C

Both doses of plozasiran substantially reduced non-HDL-C compared with placebo at Month 10 and at Month 12.

At Month 10, LS mean changes from baseline in fasting non-HDL-C in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were 3.7%, -38.7%, and -36.1%, respectively. Between-group LS mean differences versus placebo at Month 10 were -42.4% for plozasiran 25 mg (P=0.0007) and -39.8% for plozasiran 50 mg (P=0.0018).

At Month 12, LS mean changes from baseline in fasting non-HDL-C in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were 6.7%, -38.2%, and -25.5%, respectively. Between-group LS mean differences versus placebo at Month 12 were -44.9% for plozasiran 25 mg (P=0.0003) and -32.2% for plozasiran 50 mg (P=0.0114).

HCL-C

Both doses of plozasiran increased HDL-C compared with placebo at Month 10 and at Month 12.

At Month 10, LS mean changes from baseline in fasting HDL-C in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were 2.9%, 65.5%, and 72.0%, respectively. Between-group LS mean differences versus placebo at Month 10 were 62.6% for plozasiran 25 mg (P=0.0002) and 69.1% for plozasiran 50 mg (P<0.0001).

At Month 12, LS mean changes from baseline in fasting HDL-C in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were 20.6%, 61.9%, and 74.5%, respectively. Between-group LS mean differences versus placebo at Month 12 were 41.3% for plozasiran 25 mg (*P*=0.0669) and 53.9% for plozasiran 50 mg (*P*=0.0256).

Exploratory endpoints

LDL-C, ApoB, and VLDL-C

As expected for this patient population, mean fasting LDL-C values by ultracentrifugation at baseline in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups were very low (0.73 mmol/L [28.4 mg/dL], 0.62 mmol/L [23.8 mg/dL], and 0.67 mmol/L [25.8 mg/dL], respectively), well below the standard clinical treatment thresholds of <1.4 mmol/L (55 mg/dL) or <1.8 mmol/L (70 mg/dL), and they remained low throughout the study. As expected, given large decreases in triglycerides, percent increases from baseline for LDL-C in each plozasiran group were larger than the percent increase from baseline in the placebo group, but mean fasting LDL-C at Month 10 and 12 in each treatment group was <1.4 mmol/L (<55 mg/dL). Total apoB did not increase from baseline for plozasiran 25 mg vs placebo (P=0.3420 at Month 10, P=0.2409 at Month 12) or for 50 mg vs placebo (P=0.8545 at Month 10, P=0.9328 at Month 12, indicating that plozasiran treatment did not increase atherogenic lipoproteins despite an increase in LDL-C. Similarly, both doses of plozasiran reduced fasting VLDL-C compared with placebo at Month 10 and at Month 12.

Patient reported outcomes

Absolute changes in various domain scores of the selected patient reported outcome questionnaires (European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ]-C30, EORTC QLQ-PAN-26, and EuroQol 5-dimension instrument [EQ-5D-5L]) correlated with improvements. Clinically meaningful improvements were shown for appetite loss, insomnia, cognitive functioning, emotional functioning, and role functioning in the plozasiran treated subjects compared to placebo (nominal P-values of <0.05).

Hospitalizations for abdominal pain

Hospitalizations for abdominal pain was included as an exploratory endpoint to support the pancreatitis endpoint. Because the etiology of abdominal pain complaints are inherently more uncertain than the etiology of pancreatitis, for which the Atlanta criteria provide convincing assurance regarding specificity, this endpoint was not alpha-controlled and the plozasiran dose groups were not pooled. However, this endpoint trended similarly to the pancreatitis endpoint (Table 36), offering support to the significant benefit seen on the pancreatitis endpoint.

Table 33: Proportion of Subjects with Hospitalization for Abdominal Pain (Full Analysis Set)

	Placebo (pooled) (N=25)	**Plozasiran 25 mg (N=26)**	**Plozasiran 50 mg (N=24)**
Subjects with hospitalization for abdominal pain, n (%)	5 (20.0)	1 (3.8)	1 (4.2)
--------vs Placebo-------			
Odds ratio[a]		0.175	0.193
95% CI[a]		(0.020, 1.543)	(0.022, 1.652)

	Placebo (pooled) (N=25)	Plozasiran 25 mg (N=26)	Plozasiran 50 mg (N=24)
P-value[a]		0.0858	0.0987

Abbreviations: CMH=Cochran-Mantel-Haenszel.

Notes: %=100*n/N.

Hospitalizations for abdominal pain are not dependent on pancreatitis.

a Odds ratio, 95% CI, and P-value were based on CMH test stratified by baseline triglyceride category.

Pre-defined and post-hoc subgroup analyses

Subgroup analysis of primary endpoint (pre-defined)

Percent changes from baseline in fasting triglycerides at Month 10 in each subgroup are presented in the table below.

Table 34: Subgroup Analyses of Median (Q1, Q3) Percent Change from Baseline in Fasting Triglycerides at Month 10 (Full Analysis Set) – AROAPOC3-3001

	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)
Overall study population	-80.1 (-89.9, -61.0)	-77.6 (-87.7, -48.6)
Triglycerides at screening		
<22.6 mmol/L	-84.18 (-92.63, -65.94); N'=14	-85.81 (-94.51, -44.19); N'=12
≥22.6 mmol/L	-76.87 (-87.28, -54.15); N'=12	-60.64 (-83.94, -48.58); N'=12
Age		
<65 years	-76.93 (-91.21, -59.21); N'=22	-70.51 (-86.46, -46.71); N'=22
≥65 years [a]	-83.83 (-84.54, -81.71); N'=4	-96.17 (-97.79, -94.55); N'=2
Sex at birth		
Male	-89.89 (-94.83, -72.60); N'=12	-67.16 (-94.52, -44.20); N'=11
Female	-74.36 (-80.08, -54.34); N'=14	-77.62 (-86.77, -58.38); N'=13

	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)
Race		
White	-83.83 (-91.21, -69.19); N'=19	-77.62 (-91.13, -52.36); N'=17
Asian [a]	-75.31 (-84.54, -45.98); N'=7	-79.93 (-85.81, -50.36); N'=5
Other [a]	-; N'=0	-36.85 (-36.85, -36.85); N'=2
BMI		
<25 kg/m^2 [a]	-79.57 (-88.39, -59.21); N'=11	-56.12 (-78.19, -44.20); N'=12
≥25 kg/m^2	-80.08 (-91.21, -62.69); N'=15	-87.73 (-94.55, -60.64); N'=12
Geographic region		
North America	-87.19 (-94.08, -64.91); N'=9	-87.11 (-94.55, -48.59); N'=7
Europe	-73.40 (-88.58, -62.69); N'=8	-58.38 (-79.25, -25.18); N'=9
Other	-76.93 (-84.54, -59.21); N'=9	-79.93 (-85.81, -77.05); N'=7
Geographic region - Japan		
Yes [a]	-65.92 (-84.54, -47.31); N'=2	-85.81 (-85.81, -85.81); N'=1
No	-80.08 (-91.21, -62.69); N'=24	-77.05 (-87.73, -48.59); N'=23
LDL-C by ultracentrifugation		
<Baseline median	-76.93 (-83.83, -69.19); N'=13	-78.19 (-87.73, -56.12); N'=12
≥Baseline median	-88.39 (-94.03, -47.31); N'=13	-63.97 (-94.52, -44.20); N'=12
Background triglyceride-lowering therapy		
Yes	-83.83 (-91.21, -73.40); N'=21	-79.93 (-94.52, -56.12); N'=17
No	-47.31 (-49.09, -45.98); N'=5	-48.59 (-87.11, -36.85); N'=7
Genetic confirmation of FCS		
Yes	-82.77 (-87.19, -76.12); N'=12	-63.97 (-85.81, -44.83); N'=15
No	-65.94 (-94.08, -48.20); N'=14	-94.52 (-94.96, -60.64); N'=9

Abbreviations: BMI=body mass index; FAS=full analysis set; FCS= Familial Chylomicronemia Syndrome; LDL C=low-density lipoprotein cholesterol; N=the number of subjects in the analysis population; N'=number of subjects in the subgroup; SD=standard deviation.
a Subgroups with <5 subjects in 1 or more treatment groups.

Covariate-adjusted observed cases and subgroup-adjusted observed cases were analyzed using mixed models for repeated measures that included treatment arm, study visit, and baseline value as

model terms. Both models also included treatment by visit as interaction terms and the subgroup model included treatment by subgroup as an interaction term. In the covariate-adjusted model, age, sex, race, BMI, region, LDL-C at baseline, background triglyceride-lowering therapy, and genetic confirmation of FCS were added as covariates, one covariate at a time. The result indicated that the genetic confirmation of FCS could be the only potential covariate.

Table 35: Analysis of Percent Change from Baseline at Month 10 in Fasting Triglycerides: Subgroup-adjusted MMRM with Observed Cases (Full Analysis Set) - AROAPOC3-3001

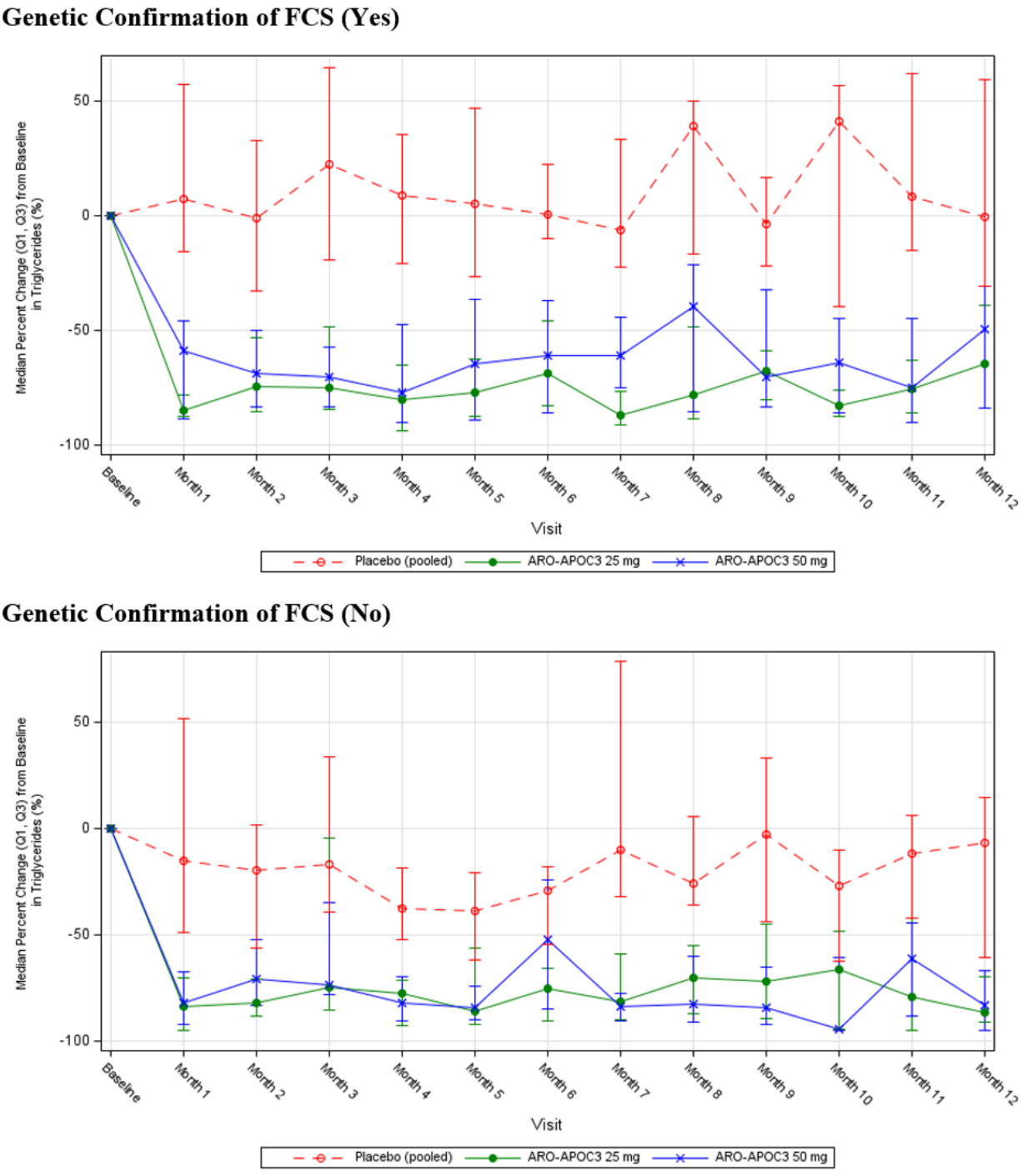
Covariate	P-value
Triglycerides at screening (<22.6 vs ≥22.6 mmol/L)	0.7781
Age (<65, ≥65)	0.9985
Sex (Female, Male)	0.9519
Race (White, Asian, and Other)	0.3407
BMI (<25 vs ≥25 kg/m^2)	0.1117
Region (North America, Europe, Other)	0.3600
Region – Japan (Japan: Yes or No)	0.7366
LDL-C by ultracentrifugation (< baseline median, ≥ baseline median)	0.6364
Background triglyceride-lowering therapy (Yes, No)	0.0514
Genetic confirmation of FCS (Yes, No)	0.0280

Abbreviations: FCS=familial chylomicronemia syndrome; LDL-C=low-density lipoprotein cholesterol; MMRM=mixed model for repeated measures.
MMRM includes treatment arm, study visit, and baseline value as model terms. The model also includes treatment by visit and treatment by subgroup as interaction terms. Observed cases of the data from baseline through Month 12 are included
Baseline value is defined as the geometric mean of the last 2 non-missing values prior to the first dose or the last non-missing value prior to the first dose if only a single value is available. Month 10 values are calculated by the geometric mean of two values collected 2 to 7 days apart. If only one value is available, then this value will be used for endpoint analysis at that Month 10. Month 10 and Month 12 (Averaged) values are calculated by the geometric mean of Month 10 and Month 12.
P-value is for each subgroup from the MMRM model.

Genetically confirmed FCS vs clinically confirmed FCS

Results of the covariate-lowering model indicate that the genetic confirmation of FCS could be the only potential covariate (see above). Given these findings, triglyceride responses were analyzed separately in subjects with genetically confirmed FCS versus those with clinical FCS (Figure 32). Baseline triglyceride values were somewhat higher in the genetically confirmed FCS subgroup and triglyceride changes from baseline were more variable as expected from the smaller samples in the subgroups. Interestingly, whether subjects fell into the genetically confirmed FCS or clinical FCS category, the response to plozasiran was similar, with large reductions from baseline in median triglycerides for both doses in both subgroups, beginning at Month 1. For the 25 mg dose at Month 10, the median % reduction in triglycerides was -82.8% and -65.9% for the genetically confirmed and clinical FCS subgroups, while the reduction at the same time point for the 50 mg dose was -64.0% and -94.5%, respectively. Importantly, while there were some numerical differences in median triglyceride reductions between the 2 subgroups, interquartile ranges were largely overlapping.

Figure 30: Median Percent Change (Q1, Q3) From Baseline in Fasting Triglycerides With or Without Genetic Confirmation of FCS, Full Analysis Set (Randomized Period) - AROAPOC3 3001



Abbreviations: FCS=familial chylomicronaemia syndrome; Q1=first quartile; Q3=third quartile.

5.3.3. Clinical studies in special populations

No dedicated clinical studies have been conducted at this stage to ascertain the effect of renal/hepatic impairment on plozasiran PK, PD and safety.

Generally, in the 5 clinical studies (AROAPOC31001, AROAPOC3-1002, AROAPOC3-2001, AROAPOC3-2002, and AROAPOC3-3001), 23 subjects (15.8%), 4 subjects (2.7%), and 1 subject (0.7%) had Mild, Moderate, or Severe RI, respectively, at baseline based on their eGFR assessment. Additionally, 4 subjects (2.7%) and 1 subject (0.7%) had Mild or Moderate degrees of hepatic impairment, respectively, at baseline according to the NCI's Organ Dysfunction Working Group (NCI-ODWG) criteria.

Table 36: Clinical studies in special populations

	Controlled Trials					
Study Number	1001	1002	2001	2002	3001	**Overall**
Renal Impairment Patients (Subjects number/total number)	50/112	4/36	108/226	239/353	16/75	417/802
Hepatic Impairment Patients (Subjects number/total number)	7/112	1/36	12/226	23/353	0/75	43/802
Age Category						
Paediatric patients <18 years (Subjects number/total number)	0/112	0/36	0/226	0/353	0/75	0/802
Age 65-74 (Subjects number /total number)	6/112	0/36	35/226	121/353	7/75	169/802
Age 75-84 (Subjects number /total number)	0/112	0/36	7/226	24/353	2/75	33/802
Age 85+ (Subjects number /total number)	0/112	0/36	0/226	2/353	0/75	2/802

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.3.5. Supportive studies

Study AROAPOC3-3001 OLE period

Design

Adult subjects with genetically confirmed or clinical FCS who completed the randomized, double-blind period of AROAPOC3-3001 were invited to consent to continue in a 2-part ongoing OLE period. Subjects received either plozasiran 25 mg or 50 mg as a subcutaneous injection Q3M during Part A of the OLE, based on their randomized dose (or matching placebo) in the blinded phase. Once the final clinical dose of 25 mg Q3M was chosen, all subjects transitioned to that dose for Part B.

Results

Dispositions of patients

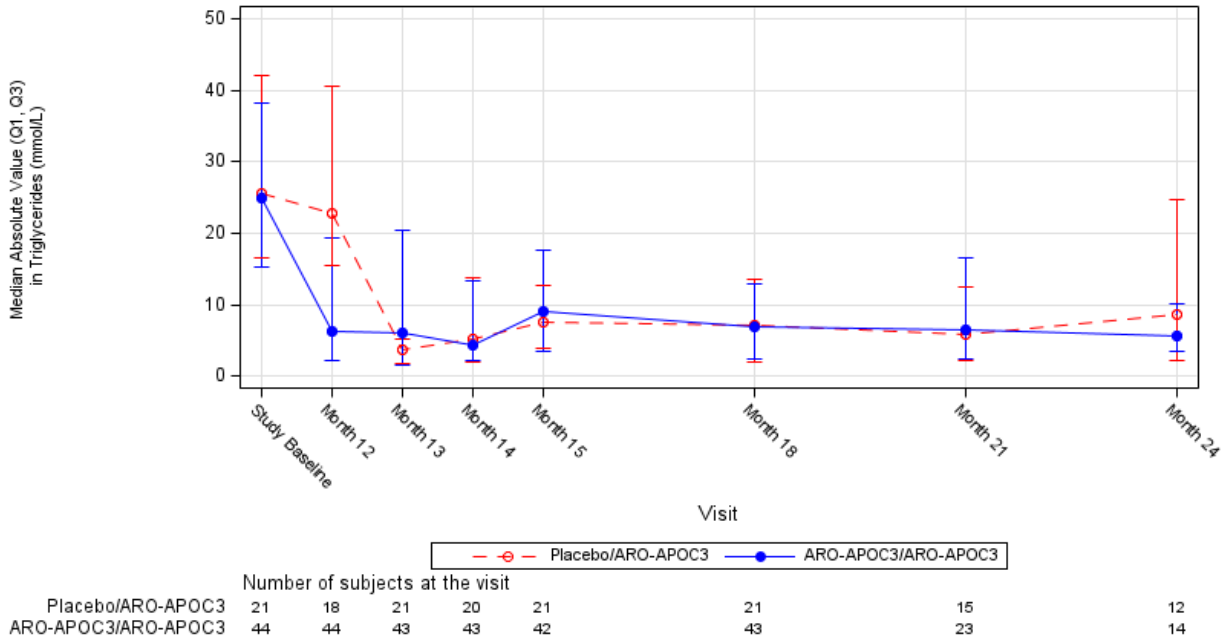
Of the 65 subjects who completed 12 months of randomized study treatment, 62 (97%) entered the OLE period. Of these subjects, 18 (29%) received placebo (placebo/plozasiran group) and 44 (71%) received plozasiran (plozasiran/plozasiran group) during the randomized period. In addition, 3 subjects who were unblinded after having a pancreatitis event during the randomized period prematurely entered the OLE period; these subjects had received placebo (placebo/plozasiran group) in the randomized period.

Of the 65 total subjects who entered the OLE period, 60 (92.3%) subjects were ongoing in the study as of the data cutoff date of 01 November 2024 (21 and 39 subjects in the placebo/plozasiran and plozasiran/plozasiran groups, respectively).

Fasting TG levels

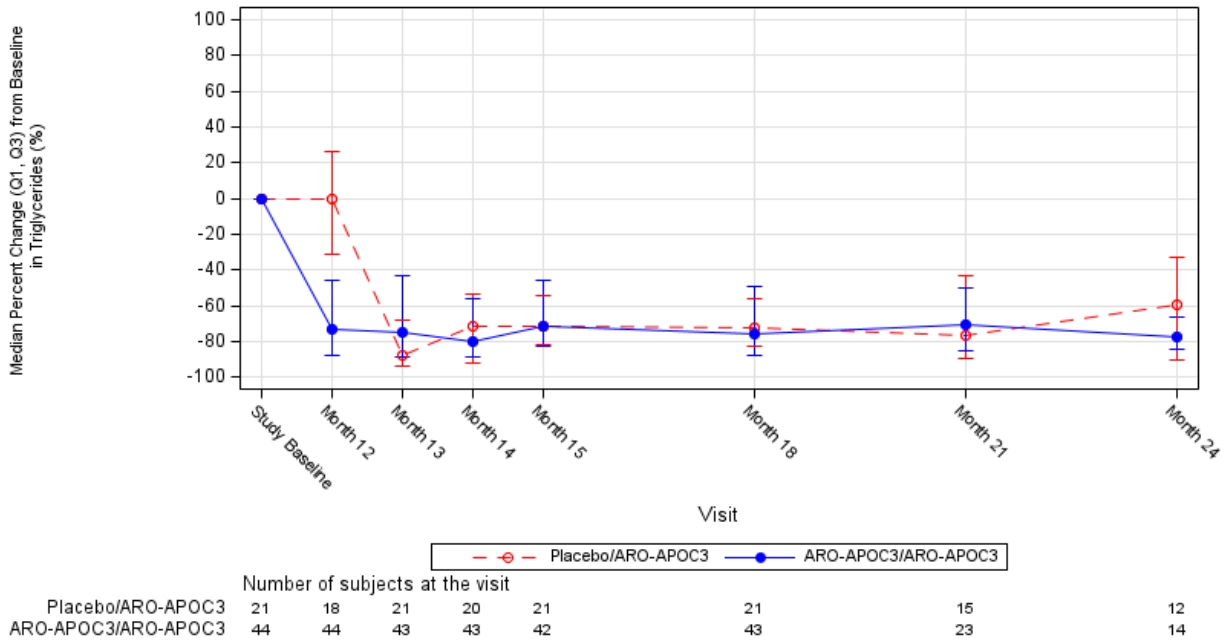
The results from the interim data analysis from the OLE period of AROAPOC3-3001 (cutoff date of 01 November 2024) are generally confirmatory with respect to the effects on median triglyceride levels and other important lipoproteins observed in the randomized period of the study, with the added insight that these effects appear to be durable over time. In subjects receiving plozasiran in both the randomized period and in the OLE (plozasiran/plozasiran group), reductions in fasting TGs were sustained through Month 18 of the OLE period (the last time point before subject numbers fall substantially). As expected, median absolute values of fasting TGs at OLE baseline (Month 12) were higher in subjects who received placebo in the randomized period (placebo/plozasiran group; 23.76 mmol/L [2103 mg/dL]) compared to the plozasiran/plozasiran group (6.31 mmol/L [558 mg/dL]). For subjects in the placebo/plozasiran group, median TGs had already fallen to a level similar to the plozasiran/plozasiran group after the first month of plozasiran treatment (Month 13; 3.67 mmol/L [325 mg/dL; -87.96%] and 6.0 mmol/L [531 mg/dL; -75.23%] in the placebo/plozasiran and plozasiran/plozasiran groups, respectively); allowing for the expected variability in fasting TGs and measurements taken at trough, these reductions were sustained through Month 18 of the OLE period. This first month response in the placebo/plozasiran group mirrors the rapid onset of action for plozasiran seen in active treatment subjects during the randomized period. Interim data beyond 12 months of treatment from the AROAPOC3-3001 OLE period support persistence of plozasiran efficacy (Figure 33 and Figure 34). At Month 18, the proportion of subjects achieving fasting TGs of <500 mg/dL (5.65 mmol/L) in the placebo/plozasiran and plozasiran/plozasiran groups was 38.1% and 38.6%, respectively, and 66.7% and 65.9% for a ~10 mmol/L (880 mg/dL) threshold, respectively.

Figure 31: Median Absolute Value (Q1, Q3) of Fasting Triglycerides (SI) (AROAPOC3-3001 OLE Period) - Full Analysis Set



Abbreviations: ARO-APOC3=plozasiran; OLE=open-label extension; Q1=first quartile; Q3=third quartile.
Notes: Baseline value is defined as the geometric mean of the last 2 nonmissing values prior to the first dose or the last nonmissing value prior to the first dose if only a single value is available in randomized period.
Data cutoff date: 01 Nov 2024.

Figure 32: Median Percent Change (Q1, Q3) from Study Baseline in Fasting Triglycerides (OLE Period) - Full Analysis Set



ApoC3

Also the reductions in fasting apoC3 observed in the randomized period with plozasiran treatment were sustained out to Month 18 of the OLE period (plozasiran/plozasiran group). At Month 15, plozasiran reduced mean fasting apoC3 in the placebo/plozasiran group to similar levels as those observed in the plozasiran/plozasiran group (0.064 g/L [6.40 mg/dL] and 0.063 g/L [6.31 mg/dL] in the placebo/plozasiran and plozasiran/plozasiran groups, respectively), representing reductions of ~85% relative to pre-treatment baseline levels.

Other endpoints

Lipid parameters

The reductions in fasting non-HDL-C observed in the randomized period with plozasiran treatment were sustained out to Month 18 of the OLE period (plozasiran/plozasiran group). By Month 13, plozasiran reduced mean fasting non-HDL-C levels in the placebo/plozasiran group to similar levels as those observed in the plozasiran/plozasiran group (3.56 mmol/L [137.3 mg/dL] and 4.04 mmol/L [156.1 mg/dL]) in the placebo/plozasiran and plozasiran/plozasiran groups, respectively).

The increases in fasting HDL-C observed in the randomized period with plozasiran treatment were sustained out to Month 18 of the OLE period (plozasiran/plozasiran group). By Month 13, plozasiran increased mean fasting HDL-C levels in the placebo/plozasiran group to similar levels as those observed in the plozasiran/plozasiran group (0.73 mmol/L [28.2 mg/dL] and 0.73 mmol/L [28.1 mg/dL]) in the placebo/plozasiran and plozasiran/plozasiran groups, respectively).

Adjudicated acute pancreatitis

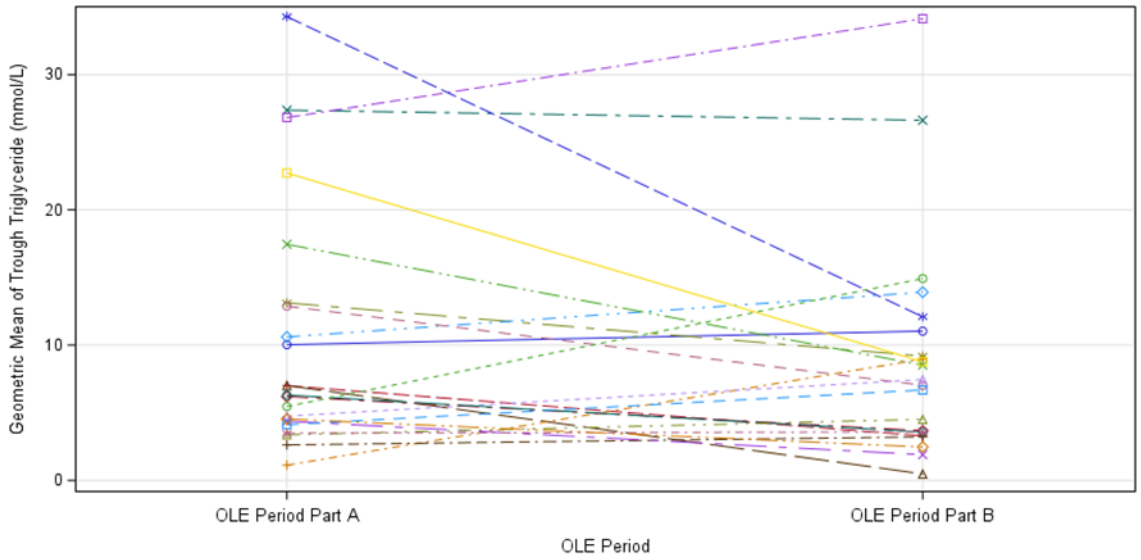
Two subjects were hospitalized for severe abdominal pain consistent with possible pancreatitis during the OLE prior to the data cutoff, 1 subject at the plozasiran 25 mg dose and 1 subject at the plozasiran 50 mg dose.

As of the data cutoff date of 01 November 2024, 2 events that were considered potentially consistent with an event of acute pancreatitis were adjudicated by the PAC in the OLE period. The committee positively adjudicated 1 event in 1 subject as definite acute pancreatitis.

Patients who switched from the 50 mg dose (OLE part A) to the 25 mg plozasiran dose (OLE part B)

For most subjects, TG levels remained stable or decreased slightly post-switch, indicating consistent responses between plozasiran 25 mg and 50 mg doses. Mean and median TG values were 10.71 and 6.65 mmol/L in Part A and 8.91 and 7.24 mmol/L in Part B, respectively, across these subjects. Since Part B reflects a longer duration of treatment, these findings also support sustained reductions in TG levels with continued plozasiran treatment (Figure 35).

Figure 33: Geometric Mean of Trough Triglyceride (mmol/L) in OLE period A and B for Each Subject (Full Analysis Set) - Subjects With Dose Switching in OLE Period



Study AROAPOC3-2003

Design

AROAPOC3-2003 is an ongoing OLE Phase 2b clinical study conducted in adult subjects who completed the 48-week study treatment period in the respective randomized, double blind, placebo-controlled parent studies (AROAPOC3-2001 or AROAPOC3-2002). All eligible subjects enrolling from the parent studies received open label plozasiran administered SC. The duration of the OLE study is approximately 2 years.

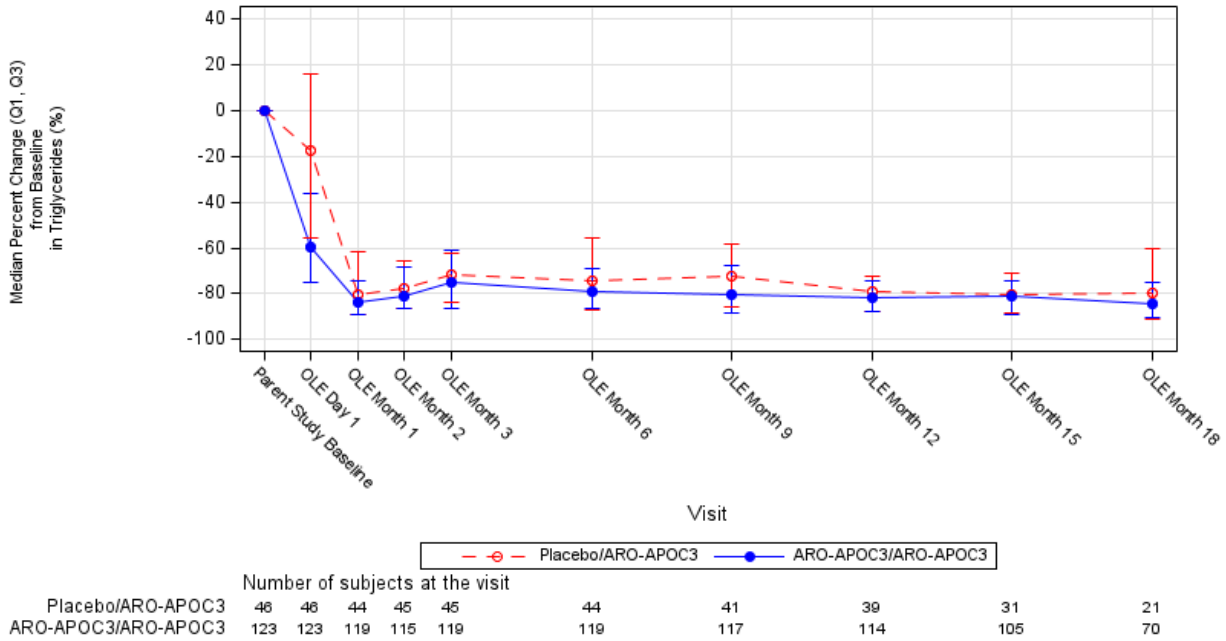
Results

Results from the interim analysis of AROAPOC3-2003 (cut off date of 08 November 2024) supports the efficacy conclusions from the Phase 2 parent studies (AROAPOC3-2001 and AROAPOC3-2002) and maintains confidence in sustained efficacy with longer term exposure to Month 18. In those subjects receiving plozasiran in both the parent studies and in the OLE study (plozasiran/plozasiran group), reductions in fasting TGs like those seen at the primary endpoint were sustained in the OLE study. Plozasiran substantially reduced triglyceride levels in the placebo/plozasiran group to similar levels as those observed in the plozasiran/plozasiran group.

For study AROAPOC3-2001, the median percent changes from parent study baseline at Month 15 in fasting TGs in the placebo/plozasiran and plozasiran/plozasiran groups were -80.64% and -81.08%, respectively.

For study AROAPOC3-2002, the edian percent changes from parent study baseline at Month 18 in fasting TGs in the placebo/plozasiran and plozasiran/plozasiran groups were -69.38% and 69.04%, respectively.

Figure 34: Median Percent Change (Q1, Q3) from Parent Study Baseline in Fasting Triglycerides, Subjects from Parent Study AROAPOC3-2001 - Full Analysis Set, AROAPOC3-2003

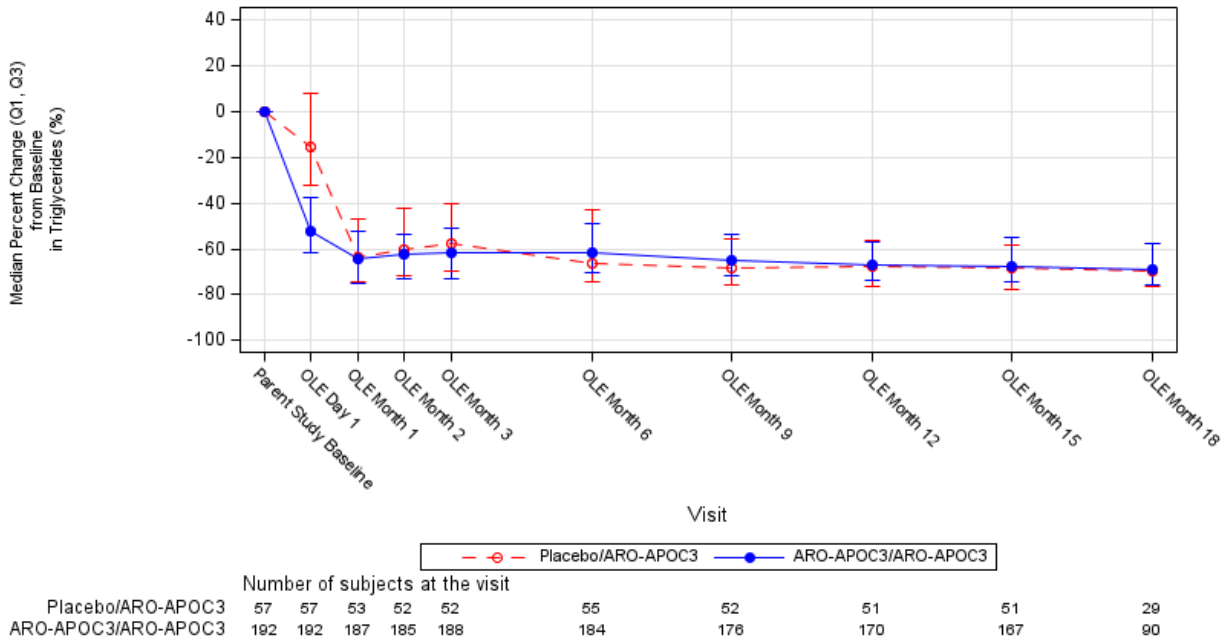


Number of subjects at the visit

Placebo/ARO-APOC3	46	46	44	45	45	44	41	39	31	21
ARO-APOC3/ARO-APOC3	123	123	119	115	119	119	117	114	105	70

Abbreviations: OLE=open-label extension; Q1=first quartile, Q3=third quartile.
Note: Baseline value is defined as the geometric mean of the last 2 nonmissing values prior to the first dose or the last nonmissing value prior to the first dose if only a single value is available in randomized period.
Data cutoff date: 08 November 2024.

Figure 35: Median Percent Change (Q1, Q3) from Parent Study Baseline in Fasting Triglycerides, Subjects from Parent Study AROAPOC3-2002 - Full Analysis Set, AROAPOC3-2003



Number of subjects at the visit

Placebo/ARO-APOC3	57	57	53	52	52	55	52	51	51	29
ARO-APOC3/ARO-APOC3	192	192	187	185	188	184	176	170	167	90

Abbreviation: Q1 = 1st quartile, Q3 = 3rd quartile.
Note: Baseline value is defined as the geometric mean of the last 2 non-missing values prior to the first dose or the last non-missing value prior to the first dose if only a single value is available in randomized period.
Data cutoff date: 08 November 2024.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Comparison of efficacy results of studies AROAPOC3-2001, AROAPOC3-2002, and AROAPOC3-3001

In the plozasiran clinical development program, 3 related patient populations were studied within the continuous spectrum of hypertriglyceridemia, namely, FCS (fasting TG ≥9.94 mmol/L [≥880 mg/dL]) in AROAPOC3-3001, SHTG (fasting TG between 5.65 to 45.2 mmol/L [500 and 4000 mg/dL]) in AROAPOC3-2001 and HTG (fasting TG between 1.70 and 5.65 mmol/L [150 and 500 mg/dL]) in AROAPOC3-2002. A comparison of plozasiran PD performance (% reduction in serum APOC3), treatment efficacy (% reduction in fasting TG) and acute pancreatitis is presented below.

TG and ApoC3 levels

In this comparison, 1 time point each is chosen to represent the maximum (nadir) and minimum (trough) PD responses, estimated to occur at 4 weeks and 12 weeks post the second dose administration, respectively, i.e. Month 4 and Month 6. While the baseline levels of APOC3 and TG were quite different in the 3 patient populations due to different severities in TG abnormality in these studies, plozasiran demonstrated a robust and consistent effect on the primary efficacy and pharmacodynamic parameters, namely the consistent reduction in apoC3 by approximately 80% to 90% and triglycerides by approximately 70% to 80% during peak pharmacodynamic response across subjects with FCS, SHTG, or mixed hyperlipidemia (Table 40). The similar plozasiran PD and efficacy performance demonstrated in SHTG and HTG populations in the well-controlled Phase 2 studies (AROAPOC3-2001 and AROAPOC3-2002) provided confirmatory evidence for the observed clinical efficacy of plozasiran in the FCS patient population.

Table 37: Consistent Effect of Plozasiran on ApoC3 and Triglycerides in Different Patient Populations

	AROAPOC3-3001 Familial Chylomicronemia Syndrome			AROAPOC3-2001 Severe Hypertriglyceridemia			AROAPOC3-2002 Mixed Hyperlipidemia		
Dose	Placebo Q3M×4 (N=25)	25 mg Q3M×4 (N=26)	50 mg Q3M×4 (N=24)	Placebo Q12W×2 (N=60)[c]	25 mg Q12W×2 (N=55)	50 mg Q12W×2 (N=57)	Placebo Q12W×2 (N=87)	25 mg Q12W×2 (N=67)	50 mg Q12W×2 (N=66)
ApoC3, mean (SD)									
Baseline, g/L	0.399 (0.176)	0.385 (0.171)	0.325 (0.198)	0.306 (0.159)	0.345 (0.168)	0.316 (0.161)	0.146 (0.047)[a]	0.155 (0.054)[a]	0.150 (0.057)[a]
% change at Month 4[b]	8.0% (36.8)	-89.2% (11.2)	-91.4% (6.6)	4.1% (44.4)	-86.3% (12.7)	-87.1% (23.9)	-3.2% (25.7)[a]	-82.5% (18.4)[a]	-87.3% (25.1)[a]
% change at Month 6[b]	6.1% (36.5)	-80.0% (19.0)	-80.1% (24.1)	0.3% (51.1)	-73.2% (24.1)	-78.5% (21.9)	-0.3% (35.0)[a]	-74.0% (19.2)[a]	-79.7% (28.4)[a]
% change at Month 10	0.8% (34.1)	-87.6% (17.4)	-93.6% (5.5)	-	-	-	-	-	-
Triglycerides, median (Q1, Q3)									
Baseline, mmol/L	23.2 (16.2, 31.1)	22.7 (13.6, 38.0)	21.5 (16.2, 33.3)	7.67 (6.1, 10.5)	6.75 (5.85, 11.1)	7.49 (5.99, 11.6)	2.45 (2.06, 3.12)	2.42 (2.04, 3.11)	2.59 (2.12, 3.35)
% change at Month 4[b]	-18.4% (-35.0, 35.3)	-78.5% (-93.1, -68.5)	-77.3% (-90.1, -63.3)	-19.2% (-50.4, 19.7)	-85.2% (-90.5, -73.9)	-85.5% (-89.3, -80.0)	-4.6% (-24.8, 14.0)	-67.2% (-72.1, -53.2)	-73.1% (-77.4, -62.6)
% change at Month 6[b]	-14.1% (-32.1, 1.6)	-71.7% (-85.4, -54.9)	-53.6% (-85.8, -37.1)	-29.4% (-55.5, 5.2)	-76.0% (-86.9, -62.5)	-80.2% (-85.2, -70.1)	-8.9% (-23.6, 7.0)	-59.1% (-70.5, -50.6)	-66.6% (-75.1, -58.5)
% change at Month 10	-17.1% (-49.1, 47.0)	-80.1% (-89.9, -61.0)	-77.6% (-87.7, -48.6)	-	-	-	-	-	-

Abbreviations: ApoC3=apolipoprotein C3; Q1, Q3=first and third quartiles; Q3M=every 3 months; Q12W=every 12 weeks; Q4W=every 4 weeks.
a 1 subject each in placebo, 25 mg, and 50 mg dose groups excluded due to baseline values of below level of quantification (BLOQ).
b Month 4=Week 16 and Month 6=Week 24 in AROAPOC3 2001 and AROAPOC3 2002.
c For ApoC3 N=58 for the pooled placebo group

5.3.7. Overall discussion and conclusions on clinical efficacy

5.3.7.1. Discussion

The main body of evidence supporting the efficacy of plozasiran in patients with FCS is the pivotal Phase 3 study AROAPOC3-3001, which included a completed double-blind, placebo-controlled (DBPC) period and an ongoing open-label extension (OLE) period. Supportive efficacy data are obtained from the 2 randomized dose-finding Phase 2b studies (AROAPOC3-2001 and AROAPOC2-2002) and an open-label study (AROAPOC3-2003) in related populations, including severe hypertriglyceridaemia (SHTG) and mixed hyperlipidaemia.

Dose finding

Two phase 2b dose-finding clinical studies (Study AROAPOC3-2001 and AROAPOC3-2002) have been conducted for plozasiran. The doses selected for these studies were based on the study results and population PD modeling results of the first-in-human study AROAPOC3-1001, which showed that the lowest dose of 10 mg Q3M dose is pharmaceutical active, while the efficacy response may be saturated between the 25 mg and 50 mg Q3M dose levels.

Study AROAPOC3-2001 was a randomized, double-blind Phase 2b dose-finding study to evaluate the efficacy and safety of 2 doses of plozasiran 10 mg, 25 mg, 50mg on Day 1 and Week 12 compared with placebo in 229 patients with SHTG (fasting TG ≥ 5.65 mmol/L and ≤ 45.2 mmol/L). Repeat doses of 10 mg, 25 mg, and 50 mg Q12W resulted in substantial decreases in TG levels (between-group LS mean difference of 49%, 53%, and 57%, respectively) and in ApoC3 levels (between-group LS mean difference of 68%, 72%, and 77%) compared with placebo at Week 24.

Study AROAPOC3-2002 was a double-blind, placebo-controlled, multiregional, Phase 2b dose-finding study to evaluate the efficacy and safety of 2 doses of plozasiran 10 mg, 25 mg, 50 mg on Day 1 and Week 12, or 2 doses of plozasiran 50 mg on Day 1 and Week 24 compared with placebo in 353 adults with mixed dyslipidemia (fasting TG ≥1.7 mmol/L and ≤ 5.64 mg/dL and either non-HDLC ≥2.59 mmol/L or LDL-C >1.81 mmol/L). Repeat doses of 10 mg, 25 mg, and 50 Q12W resulted in substantial decreases in TG levels (between-group LS mean difference of 50%, 56%, and 62%, respectively) and in ApoC3 levels (between-group LS mean differences of 57%, 73%, and 79%) compared with placebo at Week 24. In the plozasiran 50 mg Q24W group, in which subjects had only received 1 dose at baseline and had not yet received a second dose, the between-group LS mean difference versus placebo was of -44% in TG and in -56% in ApoC3 at Week 24. The results indicate that the 50 mg Q24W was as effective as the 25 mg and 50 mg Q12W early after the first dose but lost substantial efficacy between weeks 12 and 24, supporting the Q12W (Q3M) interval.

In both studies, the decreases in TG and ApoC3 were observed as early as 4 weeks and were persistent up to Week 48, since the TG and ApoC3 returned back to baseline very slowly beyond Week 16, i.e. 4 weeks after the last dose.

Overall, treatment with plozasiran 25 mg and 50 mg Q12W resulted in rapid, substantial and persistent reductions in TG and ApoC3 levels regardless of the study population, i.e. SHGT or mixed lipidaemia levels, supporting the Q12W (Q3M) interval. Further, although the plozasiran 50 mg Q12W dose showed the greatest and most durable TG-lowering effect, the differences between the 25 mg and 50

mg Q12W doses were negligible. A modest incremental improvement in TG reduction comparing the 25 mg and 50 mg Q12W was also predicted by population PD modeling.

Since no major differences in the safety profile between the 25 mg and 50 mg Q3M has been observed, it is considered appropriate that both dose levels were selected to be evaluated in the pivotal Phase 3 study AROAPOC3-3001 in patients with FCS.

Based on the results of the pivotal study AROAPOC3-3001 and the population PK and population PD analyses that included data from multiple studies, selection of the 25 mg Q3M dose as the recommended dose is acceptable.

Design and conduct of the pivotal study AROAPOC3-3001

Study AROAPOC3-3001 was a randomized, double-blind, placebo-controlled Phase 3 study conducted in adult subjects with genetically confirmed or clinical FCS. The design of AROAPOC3-3001 is appropriate to achieve the primary objective of the study. The study included three periods i.e. a screening period, a 12-month randomized DBPC period and a 24-month 2-part OLE period. The screening period of up to 6 weeks is acceptable since eligible subjects with a diagnosis of FCS initiated a treatment stabilization period for at least 4 weeks, during which diet, lifestyle, and background medication regimen were stabilized in accordance with the local standard of care. In the randomized DBPC period, eligible subjects were randomized (2:1:2:1) to the dose cohorts plozasiran 25 mg, volume-matched placebo, plozasiran 50 mg, and volume matched placebo and received 5 doses Q3M. Randomization was stratified by level of fasting TG at screening (≥2000 mg/dL versus <2000 mg/dL), which is considered acceptable. Population PD modelling using the results of AROAPOC3-3001 indicated that genetic confirmation of FCS was not a statistically significant covariate to influence the efficacy of plozasiran. Therefore, it is acceptable that FCS diagnosis (genetically/clinical) was not a stratification factor. The duration of the DBPC treatment period of 12 months is considered appropriated to assess the primary study objective of improvement in fasting TG levels. After completion of this DBPC period, the subjects had the option to enroll in a 2-part OLE period in which subjects received either plozasiran 25 mg or 50 mg SC Q3M (part A) and all switched to 25 mg Q3M once the final clinical dose of 25 mg Q3M was chosen (part B). The duration of the OLE period of 24 Months is sufficient to evaluate maintenance of effect. In Part A of the OLE, subjects remained blinded to their treatment assignment from the randomized DBPC period and initially received open-label plozasiran at the dose corresponding to their dose in the randomized period, which is considered appropriate.

After all subjects were randomized, amendment 4 was introduced that allowed unblinding in case a subject experienced acute pancreatitis in the randomized period. In such cases if the subject was assigned to receive placebo, they were re-assigned to receive active plozasiran in the open-label extension period of the study and if the subject was assigned to receive plozasiran, they were assigned to receive active plozasiran in the open-label extension period of the study.

The inclusion/exclusion criteria are considered appropriate. Key inclusion criteria included men and nonpregnant (who do not plan to become pregnant), nonlactating females, age ≥18 years, fasting triglycerides ≥10 mmol/L at screening that was refractory to standard lipid lowering therapy, a diagnosis of FCS based on a documented history of fasting triglyceride levels >11.3 mmol/L on repeated testing (≥3 prior occasions), and at least 1 of the following: a supportive genetic test or known LPL deficiency, history of recurrent episodes of acute pancreatitis not caused by alcohol or cholelithiasis, history of recurrent hospitalizations for severe abdominal pain without other explainable cause, history of childhood pancreatitis, or family history of HTG-induced pancreatitis. Given that the risk of pancreatitis is clinically significant if TGs are >10 mmol/L (2019 ESC guideline), the TG threshold of ≥10 mmol/L at screening is acceptable. Furthermore, the selected method of genetically

diagnosis of FCS is in line with the 2019 ESC guideline and with previous studies with genetically confirmed FCS. The inclusion criteria to identify clinical FCS are in line with the American Heart Association and the Endocrine Society which stated that clinical FCS can be diagnosed based on fasting TG (>750mg/dL) in combination with one of the following: history of acute pancreatitis, history of childhood pancreatitis, history of recurrent abdominal pain, or family history of hypertriglyceridemia, Although criteria for diagnosis of clinical FCS are not present in the 2019 ESC guideline, reference can be made to the article of Moulin et al. (2018) and Stroes et al. (2017) in which a clinical rating scale and a diagnostic algorithm for FCS, respectively, has been defined by European lipid experts, endocrinologists, gastroenterologists, pancreatologists, and general practitioners. In the review article of Moulin et al. (2018), a panel of European experts proposed a diagnostic scoring system for identification of FCS patients. Features included in this FCS score comprise: severe elevation of plasma TGs (fasting TG levels >10 mmol/L [885 mg/dL] on multiple occasions), refractory to standard TG-lowering therapies, a young age at onset, the lack of secondary factors (except for pregnancy and oral oestrogens), unexplained recurrent abdominal pain, and a history of episodes of acute pancreatitis. In the article of Stroes et al. (2017), a board of European experts proposed a diagnostic algorithm for identification of patients with FCS. In this algorithm, patient in a non-acute setting are pre-selected based on TG> 10 mmol/L for 3 consecutive blood analyses, onset of symptoms at age < 40 years, history of pancreatitis, no secondary lifestyle factor (except pregnancy and ethinyl oestradiol) and no history of familial combined hyperlipideamia (FCH). This patient pre-selection is followed by "clinical suspect" based on TG/TC ratio 2.2 (mmol/L/mmol/L), normal/low ApoB level (<100 mg/dL), and no positive effect of fibrate therapy. Eventually, once the patient is considered possibly affected by LPL deficiency, genetic analysis could be considered.

Based on above, it can be concluded that the inclusion criteria of the pivotal study to identify clinical FCS, resembles the features included in the clinical rating scale and diagnostic algorithm for identification of FCS recommended by European expert panels while excluding the broader typical severe hypertriglyceridemia (SHTG) patients and are considered appropriate. More specifically, clinical FCS subjects enrolled in the pivotal study likely met the FCS score ≥10: "FCS very likely" of Moulin et al (2018) based on the baseline characteristics of these subjects. Furthermore, it is acknowledged that SHTG patients are sufficiently excluded from the pivotal study based on the inclusion criteria persistent TGs in the chylomicronaemic range (>10 mmol/L and often considerably higher) and resistance to classical therapies that improve TG levels such as statins, fibrates and fish oils. Exclusion of SHTG patients from the pivotal study has also been sufficiently demonstrated been sufficiently demonstrated by and by the high prevalence of prior pancreatitis in both the genetically confirmed and clinical FCS groups (71% and 88%, respectively) and the consistency in terms of observed TG lowering from baseline, despite prior refractoriness to traditional SHTG therapies.

Moreover, at the enrolment and during the study patients were allowed to continue the use of TG-lowering therapy and they had to follow a diet comprising ≤ 20 g fat per day. The adjunction to diet has already been reflected in the proposed indication, whereas TG-lowering background therapy has not. However, since most of the patients are refractory to standard lipid lowering therapy, it is considered acceptable not to reflect this in the indication.

Appropriate blinding principles were applied. Dose group assignment was not blinded, due to required injection volume differences dictated by the respective dose group, which is acceptable as it is expected not to have an impact on the outcome since both dose groups are placebo controlled.

The methods used for the assessment of efficacy is considered appropriate and consistent in both treatment arms. Specifically, the incidence of acute pancreatitis was adjudicated by a blinded, independent committee (Acute Pancreatitis Adjudication Committee (PAC)). PAC was to adjudicate

events suggestive of acute pancreatitis using the criteria using Atlanta Classification according to the 2013 Atlanta definition meeting 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; and 3.) characteristic findings of acute pancreatitis on CECT, MRI, or transabdominal (Banks et al 2013), which is acceptable.

The primary endpoint of percent change from baseline at Month 10 in fasting triglycerides is considered appropriate to establish the TG lowering effect of plozasiran, since the maximum effect is already achieved at Month 1. The key secondary endpoint of TG and ApoC3 levels at different time points and the incidence of positively adjudicated events of acute pancreatitis during the randomized period are supportive to the primary analysis. The other secondary and exploratory efficacy endpoints to also evaluate the effect of plozasiran on other lipid parameters, responder analysis, (hospitalization for) abdominal pain and QoL provide further insight on the effects of plozasiran. The endpoints that are not Type I error controlled (other than the primary and key secondary endpoints) should only be considered exploratory.

Regarding statistical methods, for the analysis of primary endpoint, the Wilcoxon rank-sum test with Hodges-Lehman approach was used to estimate the median difference and its 95% CI for percent changes between plozasiran doses and placebo groups. As sensitivity analyses the same analysis was performed on PPS dataset without missing data imputation. To evaluate the robustness of the conclusion, trimmed Hodge-Lehman statistics was calculated. Additional sensitivity analyses are also performed using an ANCOVA model where treatment group and baseline was included in the model on the FAS dataset. Another sensitivity analysis was performed by using MMRM on the FAS dataset based on the MAR assumption. The model included treatment group, study visit and treatment by visit interaction and the baseline value of the endpoint. A tipping point was used to assess the robustness of departures from MAR in the multiple imputation model by using a prespecified sequence of shift parameters. Another sensitivity analysis was also performed on the FAS dataset using ANHECOVA model that included treatment group and stratification factor of baseline TG level and the interaction of treatment by stratification factor.

Covariates and subgroups were also tested in the MMRM one by one by adding as a covariate (for covariate analyses) and by adding treatment by covariate interaction (for subgroup analyses).

Efficacy data and additional analyses

The date first participant enrolled was 21 December 2001 and the last subject last visit before database lock for the primary analysis was 29 April 2024. A total of 75 subjects were randomized (n=26, n=24, and n=25, respectively, in, plozasiran 25 mg, plozasiran 50 mg, and the pooled placebo group) and all subjects received at least one dose of study drug. The percentage of subjects who completed study treatment was higher in the plozasiran groups (89% and 92%, for 25 mg and 50 mg respectively) compared with placebo (76%), which is reassuring. Similarly, the percentage of subjects who completed the study was higher in the plozasiran groups (89% and 92%, respectively) compared with the placebo group (76%). The imbalance in percentage of subjects who completed study treatment can be explained by the lower number of subjects who discontinued due to acute pancreatitis (0% in both plozasiran groups vs. 12% (n=3) in the placebo group) and withdrawal from treatment by subject (0% in both plozasiran groups vs. 12% (n=3) in the placebo group). The three patients in the placebo group who discontinued due to acute pancreatitis entered the extension phase of the study. These 3 patients did not go on to have recurrent episodes of adjudicated pancreatitis after they transitioned to unblinded treatment with plozasiran (through 26 May 2025; ~1.5 years exposure), which supports the beneficial effect of plozasiran in reducing the risk for acute pancreatitis.

The percentage of discontinuation of study treatment due to other adverse events is low (8% (n=2) and 4% (n=1) in the 25 mg and 50 mg plozasiran groups vs. 0% in the placebo).

Protocol deviations were reportable for 29 (38.7%) subjects: 14 (56.0%), 7 (26.9%), and 8 (33.3%), respectively, in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, which had minimal impact on the overall study outcome. Treatment compliance was relatively high (92% and well balanced between the plozasiran 25 mg and 50 mg group (93.3% and 93.8%) and higher than the placebo group (89%).

The recruited subjects reflect a population of FCS regarding demographics, medical history and background medications for FCS, which are generally well distributed across the treatments groups. Overall, the mean age at screening was 46.0 years and the majority was female (50.7%), white (73.3%), and not Hispanic or Latino (96.0%). Considering that 30.7% of the subjects were from Europe, the population is sufficiently representative for Europe. The median values for TG and ApoC3 at baseline were also well balanced across treatment groups. Consistent with expected values for a population with FCS, the median fasting triglyceride levels at baseline were 22.7 mmol/L, 21.5 mmol/L, and 23.2 mmol/L for plozasiran 25 mg, 50 mg, and placebo, respectively. The median fasting apoC3 levels at baseline were 38.9 mg/dL, 30.1 mg/dL, and 38.8 mg/dL, respectively. Most subjects (89.3%) has a history of pancreatitis at baseline (88.5%, 91.7% and 88.0% for plozasiran 25 mg, 50 mg, and placebo, respectively) of which the majority had a history of recurrent pancreatitis at baseline (73%, 92%, and 72%, respectively). This indicates a slightly higher percentage of subjects with recurrent pancreatitis in the 50 mg plozasiran compared with the plozasiran 25 mg and placebo group. Since it can be expected that this imbalance will more likely underestimate the effect of plozasiran on the risk reduction for acute pancreatitis event than overestimate it, since the risk increases upon each acute pancreatitis event, this issue is not further pursued. A higher percentage of diabetic subjects were found in the placebo group (32%) compared with the plozasiran 25 mg and 50 mg group (15% and 17%, respectively). At baseline, the majority of subjects were taking fibrates (67%) followed by statins (45%) and icosapent ethyl, omega-3 fatty acid or fish oil (29%). A relatively high percentage of the subjects (27%) did not receive concomitant lipid-lowering therapy, probably since these patients were refractory to standard lipid lowering therapy.

Genetically confirmed FCS was documented at baseline in 41 subjects (54.7%), of which 80.5% had pathogenic LPL variants, 9.8% had pathogenic GPIHBP1 variants, 7.3% had pathogenic MF1 variants and 2.4% pathogenic ApoC2 variants, which were not well distributed across the treatment groups (see table "genotype"). No subgroups analyses for genotypes were prespecified, which can be acceptable given the small numbers of patients with pathogenic variants other than LPL variants. Additionally, considering that plozasiran induced robust and durable reductions in TGs in almost all patients, this issue is not pursued. The other 34 subjects (45.3%) had clinical FCS according to the inclusion criteria and were shown to have genotypes that could not be defined as genetically confirmed FCS.

In the primary efficacy analyses, both the 25 mg and 50 mg plozasiran Q3M dose demonstrated a substantial median fasting TG reduction of -80% and -78%, respectively, compared to -17% in placebo at Month 10, resulting in a between-group LS median difference vs placebo of -59% and -52% ($p< 0.0001$ and $p< 0.0002$, respectively). This corresponded to an absolute median TG reduction of -17.7 mmol/L and -14.0 mmol/L to 5.01 mmol/L and 7.5 mmol/L levels at Month 10 for 25 mg and 50 mg Q3M plozasiran, respectively, so below the TG target level of 10 mmol/L of reduced risk of pancreatitis (ESC 2019). Results of the sensitivity analyses were consistent with the primary analysis. These substantial reductions in TG and ApoC3 maintained up to Month 24 as indicated by the interim data of the OLE part of the pivotal AROAPOC3-3001 study (cutoff date of 01 November 2024; see also below).

Strikingly, approximately 50% of the placebo subjects showed also a decrease in TG at Month 10, which can be explained by the difficulty to consistently follow a very restrictive diet in normal life and as also shown by the high fluctuations in TG levels over time. Nevertheless, considering that across the entire clinical development program, there has been consistent evidence of the persistence efficacy in TG reduction (> 50%) after each dose of 25 mg and 50 mg plozasiran Q3M, the TG lowering effect of plozasiran is not questioned.

The results of the key (alpha-controlled) secondary endpoint of median reduction in TG levels from baseline at Month 10 and 12 (averaged) is similar to the primary analysis, with between-group differences versus placebo of -60% ($p<0.0001$) and -51% ($p=0.0007$) for 25 mg and 50 mg plozasiran Q3M, respectively, indicating that the substantial reduction in TG is maintained over the period of the maximum (nadir) and minimum (trough) effect. Further, a numerically higher proportion of subjects reached the target TG level of < 10 mmol/L of reduced risk of pancreatitis (ESC 2019) of 75% and 55% in the 25 mg and 50 mg plozasiran Q3M groups, respectively, compared with 21% in the placebo group at Month 10. Moreover, also the target TG level of < 5.65 mmol/L at Month 10 was reached by a numerically higher proportions of subjects in the 25 mg and 50 mg plozasiran Q3M groups compared with placebo (50% and 46% vs. 5%, respectively). Additionally, the mechanism of action was also reflected by the substantial decrease in fasting ApoC3, which showed a between-group difference of -91% and -93% at Month 10 and -87% and -88% at Month 12 for 25mg and 50 mg Q3M plozasiran, respectively ($p<0.0001$ for all comparisons). Treatment with plozasiran also resulted in numerically favourable outcomes in other lipid parameters including non-HDL-C, ApoB, and VLDL-C along with increases in HDL-C and LDL-C. The increases in LDL-C, which remained below the ULN (<1.4mmol/L), was accompanied by a decrease in non-HDL-C, suggesting an overall anti-atherogenic effect, which is reassuring. As indicated above, the differences between the 25 mg and 50 mg plozasiran Q12W doses were negligible or even a higher effect size with the 25 mg plozasiran dose has been observed, whereas no differences in safety profile between both doses were observed. Therefore, it is acceptable to select the lowest dose of 25 mg Q3M as the trwatment dose.

The assessment of the clinical impact of the TG effect of plozasiran is often challenging, mainly due to the limited data available on relevant clinical outcomes including acute pancreatitis, abdominal pain and patient reported outcome (PRO) assessment. Nevertheless, for the key (alpha-controlled) secondary endpoint of acute pancreatitis, a significant reduction in the risk for these events was shown, with 2 positively adjudicated events in 2 patients in the pooled plozasiran groups compared with 7 positively adjudicated events in 5 patients in the placebo group (OR=0.169; $p=0.0292$). Additionally, in the placebo group, most of the positively adjudicated events were severe, whereas in the plozasiran groups, none of the positively adjudicated events were severe. The positively adjudicated acute pancreatitis events were relatively evenly distributed between genetic and clinical familial chylomicronaemia syndrome (FCS) patients with 5 cases occurring in 3 genetically confirmed patients and 4 cases occurring in 4 clinically diagnosed patients, which is reassuring, as it confirms the similarity between genetic and clinical FCS patients.

Although the numbers of acute pancreatitis are limited and observed in a limited time frame of assessment on-treatment, i.e. 12 months, these results are suggestive for the clinical relevance of reducing TG. However, in the pivotal study these acute pancreatitis events were only observed in subjects with a history of acute pancreatitis of which the majority had a history of recurrent pancreatitis (n=6 out of 7). The risk of acute pancreatitis increases relative to the elevation in serum triglycerides, with the incidence of acute pancreatitis increasing 3% to 4% for every 1.13 mmol/L (100 mg/dL) increase in triglycerides (Murphy 2013; Rashid 2016). Further, already the first episode of acute pancreatitis can be life threatening (Frosmark 2016, Nawaz 2015). In this respect, it is

considered appropriate to extrapolate the significant reduction in the risk for acute pancreatitis observed in FCS patients with a history of acute pancreatitis to FCS patients without a history of acute pancreatitis and to accept the broad indication "FCS patients", i.e. without the restriction to "patients with FCS and at high risk for pancreatitis". No clear or robust effects on other clinically relevant outcomes have been shown. For abdominal pain, only a trend toward less frequent occurrence of hospitalization for abdominal pain was observed with 1 patient in each 25 mg and 50 mg plozasiran Q3M group compared with 5 patients in the placebo group (OR (95%CI): 25 mg 0.175 (0.020, 1.54); 50 mg 0.193 (0.022, 1.65). For patient reported outcomes (PROs: EORTC QLQ-C30, EORTC QLQ-PAN26, and EQ-5D-5L), numerically improvements were shown for appetite loss, insomnia, cognitive functioning, emotional functioning, and role functioning in the plozasiran treated subjects compared to placebo. However, since the PROS were exploratory endpoints, firm conclusions cannot be drawn.

A consistent TG-lowering effect was observed in all prespecified subgroups, including TG at screening (< 22.6 and ≥ 22.6 mmol/L), age, gender, race, BMI, region, LDL-C (< and ≥ baseline median), background TG-lowering therapy (yes/no), and genetic confirmation of FCS (yes/no). Regarding the subgroup analysis of background TG-lowering therapy, a lower effect size was observed in patients not receiving background therapy (-47% and -49% for 25 mg and 50 mg plozasiran, respectively) compared with patients receiving TG-lowering background therapy (-84% and -80%, respectively). This difference is considered a chance finding at the Month 10 timepoint and there is no expected biological basis for this difference. The number of patients in the subgroup of no background therapy is relatively small (n=8 in placebo, n=5 in the 25 mg group and n=7 in the 50 mg group). This small sample size in combination with an artifact related to dietary compliance around that sampling time might have resulted in this difference. Further, results of covariate-adjusted modeling indicated genetic confirmation of FCS as the only potential covariate. However, persistent substantial median reduction of TG was observed for the 25 mg and 50 mg plozasiran Q3M dose regardless of whether the subject had genetically confirmed FCS (-83% vs. -64%, respectively) or clinical FCS (-66% vs -95%, respectively).

Supportive data was obtained the OLE period of the pivotal study AROAPOC3-3001. Of the 62 total subjects who entered the OLE period, 60 (92.3%) subjects were ongoing in the study as of the data cutoff date of 01 November 2024 (21 and 39 subjects in the placebo/plozasiran and plozasiran/plozasiran groups, respectively). The majority of subjects had exposure durations in the OLE of >10 months: >10 to 13 months (18.5% subjects), >13 to 16 months (20.0% subjects), >16 to 19 months (13.8% subjects), and >19 to 22 months (3.1% subjects). The results of the interim data analysis of the OLE period showed that in subjects who received plozasiran in the DBPC period (plozasiran/plozasiran group) the substantial reduction in TG and ApoC3 observed at month 12 (primary analysis) maintained up to Month 24. For subjects in the placebo/plozasiran group, fasting TG and ApoC3 already decreased to the levels similar as observed in the plozasiran/plozasiran group at month 13 and 15, respectively. Overall, at Month 18 (the last time point before subject numbers reduced substantially), the proportion of subjects achieving fasting TGs of <10 mmol/L threshold in the placebo/plozasiran and plozasiran/plozasiran groups was 66.7% and 65.9%, respectively.

Additional supportive data was obtained from AROAPOC3-2003 an ongoing 2-year OLE Phase 2b clinical study conducted in adult subjects who completed the phase 2b dose-finding studies AROAPOC3-2001 or AROAPOC3-2002 conducted in patients with severe hypertriglyceridaemia (SHTG) and mixed hyperlipidaemia, respectively. The results of the interim data analyses of this OLE study (cutoff date of 08 November 2024) showed maintenance of effect in fasting TG levels up to Month 18, which was similar as those seen at the primary endpoint. Furthermore, the reductions in TG and ApoC3

in the subjects who received placebo in the parent study (placebo/plozasiran group) was similar to those observed in the subjects who received plozasiran in the parent study (plozasiran/plozasiran).

Regarding special populations, separate efficacy studies were not conducted in patients with renal or hepatic impairment (HI). The number of patients across the clinical studies were 417 for renal and 43 for hepatic impairment. Regarding heptic impairment, mild HI (according to the NCI-ODWG criteria) does not appear to have an influence on PD, as it is not detected as a covariate in PPD analysis. However, there is insufficient data for moderate- and severe-HI. The SmPC section 4.2 states that plozasiran has not been studied in patients with moderate or severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk. For elderly, a limited number of FCS patients ≥ 65 years of age was included (n=9 (12%)). These limited data show a similar efficacy in patients ≥ 65 years of age compared with patients ≤ 65 years of age (subgroup analyses).

5.3.7.2. Conclusions on the clinical efficacy

Treatment with plozasiran resulted in a substantial reduction in TG which was maintained up to at least 18 months. The improvement in TG was further supported by a significant reduction in the risk for acute pancreatitis, although the results should be interpreted with caution due to the limited cases observed. The primary result was in line with the sensitivity analyses, consistent in subgroup analyses, including genetically confirmed FCS and clinical FCS and as well as consistent to results observed in the 2 Phase 2b dose-finding studies.

5.4. *Clinical safety*

Please refer to the table of studies in section 5.3.2

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The overall clinical safety database supporting the Marketing Authorisation Application (MAA) for the treatment of FCS includes 654 subjects from 3 Phase 2/3 studies, including subjects with FCS and

related conditions as follows:

- AROAPOC3-3001: A pivotal Phase 3 study in 75 adult subjects with FCS, which includes a completed randomized, DB, placebo-controlled period, of which 65 subjects continued participation in an ongoing OLE period.
- Two supportive DB, placebo-controlled Phase 2b studies in adult subjects with related populations:
    - AROAPOC3-2001: A Phase 2 study in 226 adult subjects with SHTG.
    - AROAPOC3-2002: A Phase 2 study in 353 adult subjects with moderate HTG and elevated LDL-C or elevated non-HDL C. This subject population is also referred to as mixed hyperlipidemia or by the older term, mixed dyslipidemia.
- AROAPOC3-2003: A long-term Phase 2b OLE study in 418 adult subjects with dyslipidemia, including subjects from AROAPOC3-2001 and AROAPOC3-2002.

There are 3 groupings of safety data from the Phase 2/3 studies based on the Integrated Summary of Safety (ISS) and Statistical Analysis Plan (SAP). The groupings and general sets of analyses performed for each grouping are

- Pool 1 (Phase 3 Pivotal Study, Double-Blind Period): Safety data from the randomized placebo-controlled DB period of the pivotal study, AROAPOC3-3001.
- Pool 2 (Phase 2/3 Double-Blind [Placebo-Controlled] Studies): Integrated placebo-controlled safety data from the placebo-controlled double-blind period of AROAPOC3-3001 and AROAPOC3-2001 (SHTG) and AROAPOC3-2002 (moderate HTG), to analyse potential safety signals in the pivotal Phase 3 study.
- Pool 3 (Open-Label Extension Portion): Integrated open-label safety data from the OLE period of AROAPOC3-3001 (data cutoff date, 01 November 2024) and from AROAPOC3-2003 (data cutoff date, 08 November 2024) to identify any late safety signals that might not have been observed during the ~1 year of follow-up in randomized, placebo-controlled studies.

5.4.2. Patient exposure

Pool 1 (Phase 3 Pivotal Study, Double-Blind Period)

Exposure parameters are summarized in Table 41. A total of 50 subjects were exposed to at least a single dose of plozasiran in Pool 1. The median total number of plozasiran injections received was 4 injections across the dose groups in the randomized, DB period of Study AROAPOC3-3001. Mean doses received varied from 3.6 to 3.8 doses across treatment groups.

The median study duration was similar across the treatment groups. The large majority of subjects had plozasiran exposure >10 months . Although the mean exposure was slightly lower in the placebo-treated subjects compared to the plozasiran groups, median exposure was similar across treatment groups.

Table 38: Study Drug Administration, Duration of Study and Study Drug Exposure: Pool 1 - Randomized Period (Safety Set)

	AROAPOC3-3001			
	Placebo (N=25)	**Plozasiran 25 mg (N=26)**	**Plozasiran 50 mg (N=24)**	**Plozasiran (25 mg+ 50 mg) (N=50)**
Number of injections received n (%)				
1	2 (8.0)	1 (3.8)	2 (8.3)	3 (6.0)
2	1 (4.0)	2 (7.7)	0 (0.0)	2 (4.0)
3	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	19 (76.0)	23 (88.5)	22 (91.7)	45 (90.0)
Total number of injections received				
n	25	26	24	50
Mean (SEM)	3.6 (0.18)	3.7 (0.15)	3.8 (0.17)	3.7 (0.11)
SD	0.92	0.78	0.85	0.80
Median	4.0	4.0	4.0	4.0
Study duration (days)				
n	25	26	24	50
Mean (SEM)	320.3 (16.69)	360.3 (4.01)	341.9 (14.41)	351.5 (7.27)
SD	83.46	20.47	70.59	51.37
Median	358.0	360.0	359.0	360.0
Study duration category, n (%)				
≤4 months (≤122 days)	1 (4.0)	0 (0.0)	1 (4.2)	1 (2.0)
>4-10 months (>122-304 days)	5 (20.0)	1 (3.8)	1 (4.2)	2 (4.0)
>10 months (>304 days)	19 (76.0)	25 (96.2)	22 (91.7)	47 (94.0)
Treatment exposure (days)				
n	25	26	24	50
Mean (SEM)	319.0 (17.29)	346.1 (9.81)	336.3 (16.60)	341.4 (9.39)
SD	86.47	50.01	81.35	66.38
Median	358.0	359.5	359.0	359.0
Treatment Exposure category, n (%)				
≤4 months (≤122 days)	2 (8.0)	1 (3.8)	2 (8.3)	3 (6.0)
>4-10 months (>122-304 days)	4 (16.0)	2 (7.7)	0 (0.0)	2 (4.0)
>10-12 months (>304-365 days)	19 (76.0)	23 (88.5)	22 (91.7)	45 (90.0)

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Abbreviations: Max=maximum; Min=minimum; SEM=standard error of the mean; Q1=1st quartile; Q3=3rd quartile. %=100 x n/N. Note: "On-Study" duration is defined as study completion date minus randomization date + 1 day per each individual subject. For "on-treatment" study drug exposure for the randomized double-blinded period, the study drug exposure is calculated as follows: for subjects taking 1 dose (Q3M or Q6M) only during the double-blinded studies, the planned exposure is 4 months (122 days); for subjects taking 2 doses (Q3M or Q6M) during the double-blinded studies, the planned exposure is 10 months (304 days); for subjects taking 3 or 4 doses during the double-blinded studies, the planned exposure is 12 months (365 days). With both planned exposure and study duration available for individual subjects, their actual "on-treatment" study drug exposure was determined as the shorter time of the planned study drug exposure and study duration. For subjects with dose interruption or missing dose, actual exposure was determined based on medical review and documented.

Pool 2 (Phase 2/3 Double-Blind [Placebo-Controlled] Studies)

Exposure parameters are summarized in Table 42. Across the 3 studies, 481 subjects with FCS or related indications have been exposed to at least a single injection of plozasiran. Because the Phase 2b studies were designed to administer only 2 plozasiran injections and, in comparison to the Phase 3 study, Pool 2 contributed more subjects to the overall Safety Set. The median total number of injections for Pool 2 was 2 injections compared to 4 injections in Pool 1.

In comparison to Pool 1, Pool 2 had similar study durations because the Phase 2b studies included a long follow-up period after the last dose. The majority of subjects in Pool 2 had plozasiran exposure >10 months (>304 days). Median exposure was 304.0 days across all plozasiran groups in Pool 2, compared to 358.0 days in the placebo group and 359.5 days in the plozasiran 25 mg group in Pool 1.

Table 39: Study Drug Administration, Duration of Study and Study Drug Exposure: Pool 2 - Randomized Period (Safety Set)

Category	Placebo (N=173)	Plozasiran 10 mg (N=121)	Plozasiran 25 mg (N=148)	Plozasiran 50 mg Q12W (N=146)	Plozasiran 50 mg Q24W (N=66)	Plozasiran (25 mg+ 50 mg) (N=360)	Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)
Number of injections received, n(%)							
1	8 (4.6)	6 (5.0)	6 (4.1)	8 (5.5)	6 (9.1)	20 (5.6)	26 (5.4)
2	143 (82.7)	114 (94.2)	119 (80.4)	116 (79.5)	60 (90.9)	295 (81.9)	409 (85.0)
3	3 (1.7)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
4	19 (11.0)	0 (0.0)	23 (15.5)	22 (15.1)	0 (0.0)	45 (12.5)	45 (9.4)
Total number of injections received							
n	173	121	148	146	66	360	481
Mean (SEM)	2.2 (0.05)	2.0 (0.02)	2.3 (0.06)	2.2 (0.06)	1.9 (0.04)	2.2 (0.04)	2.1 (0.03)
SD	0.68	0.24	0.77	0.78	0.29	0.72	0.64
Median	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Study duration (days)							
n	173	121	148	146	66	360	481
Mean (SEM)	330.4 (4.02)	327.2 (4.92)	340.8 (3.20)	332.9 (4.26)	330.7 (5.59)	335.7 (2.40)	333.6 (2.19)
SD	52.86	54.13	38.91	51.42	45.38	45.60	47.97
Median	342.0	341.0	344.0	343.0	342.0	343.0	343.0
≤4 months (≤122 days)	4 (2.3)	4 (3.3)	2 (1.4)	4 (2.7)	1 (1.5)	7 (1.9)	11 (2.3)
>4-10 months (>122-304 days)	12 (6.9)	7 (5.8)	3 (2.0)	4 (2.7)	4 (6.1)	11 (3.1)	18 (3.7)
>10 months (>304 days)	157 (90.8)	110 (90.9)	143 (96.6)	138 (94.5)	61 (92.4)	342 (95.0)	452 (94.0)
Exposure (days)							
n	173	121	148	146	66	360	481
Mean (SEM)	297.6 (3.99)	291.0 (4.25)	303.2 (3.96)	298.7 (4.66)	287.0 (6.67)	298.4 (2.79)	296.6 (2.35)
SD	52.49	46.77	48.14	56.36	54.22	52.89	51.47
Median	304.0	304.0	304.0	304.0	304.0	304.0	304.0
Exposure category, n (%)							
≤4 months (≤122 days)	8 (4.6)	6 (5.0)	6 (4.1)	8 (5.5)	6 (9.1)	20 (5.6)	26 (5.4)
>4-10 months (>122-304 days)	146 (84.4)	115 (95.0)	119 (80.4)	116 (79.5)	60 (90.9)	295 (81.9)	410 (85.2)
>10-12 months (>304-365 days)	19 (11.0)	0 (0.0)	23 (15.5)	22 (15.1)	0 (0.0)	45 (12.5)	45 (9.4)

Abbreviations: SEM=standard error of the mean; Q1=1st quartile; Q3=3rd quartile; Q12W=every 12 weeks; Q24W=every 24 weeks; Q3M=every 3 months; Q6M=every 6 months. %=100 x n/N. Planned doses were used in the analysis for these subjects. Study duration was defined as study completion date minus randomization date plus 1 day per each individual subject. For randomized period, the planned drug exposure was calculated as: for subjects taking 1 dose (Q3M or Q6M) only during the double-blinded studies, the planned exposure was 4 months (122 days); for subjects taking 2 doses (Q3M or Q6M) during the double-blinded studies, the planned exposure was 10 months (304 days); for subjects taking 3 or 4 doses during the double-blinded studies, the planned exposure was 12 months (365 days). Study duration was calculated by study completion date minus randomization date plus 1 day per each individual subject. With both planned exposure and study duration available for individual subjects, their actual study drug exposure was determined as the shorter time of the planned drug exposure and study duration. For subjects with dose interruption or missing dose, actual exposure was determined based on medical review and documented.

Pool 3 (Open-Label Extension Portion)

Study drug administration, duration of study, and study drug exposure parameters for Pool 3 are presented in Table 43.

Of the 657 subjects initially randomized in the Phase 2/3 studies, as of the data cutoff dates for AROAPOC3-3001 (01 Nov 2024) and AROAPOC3-2003 (08 Nov 2024), 483 (73.5%) subjects received at least 1 dose of plozasiran in the OLE studies. In the plozasiran 25 mg group (which includes subjects transitioned from the 10 and 50 mg doses), the majority of subjects had exposure durations in the OLE of >16 months.

The median cumulative treatment exposure in the combined randomized and OLE periods was 797.0 days in the plozasiran 25 mg group (25.7% of subjects had >25 to 28 months exposure). Sixty-six subjects (14.0%) have been treated with plozasiran 25 mg for greater than 31 months.).

Table 40: Study Drug Administration, Study Drug Exposure, and Study Drug Exposure Combined both Randomized Period and OLE: Pool 3 – OLE Portion (Safety Set)

	Plozasiran 10 mg (N=8)	**Plozasiran 25 mg (N=471)**	**Plozasiran 50 mg (N=4)**	**Plozasiran (25 mg+ 50 mg) (N=475)**	**Plozasiran (10 mg+ 25 mg+ 50 mg) (N=483)**
Number of injections received, n (%) – OLE Portion					
1	5 (62.5)	14 (3.0)	4 (100.0)	18 (3.8)	23 (4.8)
2	1 (12.5)	5 (1.1)	0 (0.0)	5 (1.1)	6 (1.2)
3	1 (12.5)	42 (8.9)	0 (0.0)	42 (8.8)	43 (8.9)
4	0 (0.0)	19 (4.0)	0 (0.0)	19 (4.0)	19 (3.9)
5	0 (0.0)	61 (13.0)	0 (0.0)	61 (12.8)	61 (12.6)
6	0 (0.0)	144 (30.6)	0 (0.0)	144 (30.3)	144 (29.8)
7	0 (0.0)	98 (20.8)	0 (0.0)	98 (20.6)	98 (20.3)
8	1 (12.5)	88 (18.7)	0 (0.0)	88 (18.5)	89 (18.4)
Total number of injections received – OLE Portion					
n	8	471	4	475	483
Mean (SEM)	2.3 (0.86)	5.9 (0.08)	1.0 (0.00)	5.9 (0.08)	5.8 (0.08)
SD	2.43	1.72	0.00	1.77	1.84
Median	1.0	6.0	1.0	6.0	6.0
Q1, Q3	1.0, 2.5	5.0, 7.0	1.0, 1.0	5.0, 7.0	5.0, 7.0
Min, Max	1, 8	1, 8	1, 1	1, 8	1, 8
Exposure (days)– OLE portion					
n	8	471	4	475	483
Mean (SEM)	218.9 (75.21)	516.7 (6.73)	168.3 (50.51)	513.8 (6.85)	508.9 (7.04)

SD	212.72	146.14	101.03	149.19	154.80
Median	160.0	529.0	186.5	529.0	527.0
Q1, Q3	75.0, 306.5	463.0, 617.0	107.0, 229.5	460.0, 616.0	457.0, 614.0
Min, Max	1, 667	39, 754	29, 271	29, 754	1, 754
Exposure category, n (%)– OLE Portion					
≤4 months (≤122 days)	3 (37.5)	9 (1.9)	1 (25.0)	10 (2.1)	13 (2.7)
>4-7 months (>122-213 days)	2 (25.0)	15 (3.2)	2 (50.0)	17 (3.6)	19 (3.9)
>7-10 months (>213-304 days)	1 (12.5)	27 (5.7)	1 (25.0)	28 (5.9)	29 (6.0)
>10-13 months (>304-395 days)	1 (12.5)	24 (5.1)	0 (0.0)	24 (5.1)	25 (5.2)
>13-16 months (>395-487 days)	0 (0.0)	88 (18.7)	0 (0.0)	88 (18.5)	88 (18.2)
>16-19 months (>487-578 days)	0 (0.0)	146 (31.0)	0 (0.0)	146 (30.7)	146 (30.2)
>19-22 months (>578-669 days)	1 (12.5)	99 (21.0)	0 (0.0)	99 (20.8)	100 (20.7)
>22 months (>669 days)	0 (0.0)	63 (13.4)	0 (0.0)	63 (13.3)	63 (13.0)
Exposure (days)– Combined both randomized period and OLE portion					
n	8	471	4	475	483
Mean (SEM)	408.9 (89.06)	747.9 (9.15)	423.8 (89.46)	745.2 (9.20)	739.6 (9.35)
SD	251.91	198.54	178.91	200.42	205.59
Median	464.0	797.0	467.5	797.0	792.0
Q1, Q3	227.0, 610.5	591.0, 894.0	287.0, 560.5	586.0, 894.0	582.0, 890.0
Min, Max	1, 667	174, 1058	185, 575	174, 1058	1, 1058
Exposure category, n (%)– Combined Both Randomized Period and OLE Portion					
≤4 months (≤122 days)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
>4-7 months (>122-213 days)	0 (0.0)	3 (0.6)	1 (25.0)	4 (0.8)	4 (0.8)
>7-10 months (>213-304 days)	0 (0.0)	10 (2.1)	0 (0.0)	10 (2.1)	10 (2.1)
>10-13 months (>304-395 days)	1 (12.5)	14 (3.0)	1 (25.0)	15 (3.2)	16 (3.3)
>13-16 months (>395-487 days)	2 (25.0)	33 (7.0)	0 (0.0)	33 (6.9)	35 (7.2)
>16-19 months (>487-578 days)	1 (12.5)	50 (10.6)	2 (50.0)	52 (10.9)	53 (11.0)
>19-22 months (>578-669 days)	2 (25.0)	36 (7.6)	0 (0.0)	36 (7.6)	38 (7.9)
>22-25 months (>669-760 days)	0 (0.0)	44 (9.3)	0 (0.0)	44 (9.3)	44 (9.1)
>25-28 months (>760-852 days)	0 (0.0)	121 (25.7)	0 (0.0)	121 (25.5)	121 (25.1)
>28-31 months (>852-943 days)	0 (0.0)	94 (20.0)	0 (0.0)	94 (19.8)	94 (19.5)
>31 months (>943 days)	0 (0.0)	66 (14.0)	0 (0.0)	66 (13.9)	66 (13.7)

Abbreviations: Max=maximum; Min=minimum; OLE=open-label extension; Q1=1st quartile; Q3=3rd quartile; Q3M=every 3 months; Q6M=every 6 months; SEM=standard error of the mean. %=100 x n/N. Note: The last dose level administered was used to categorize the subjects. For OLE portion, the plozasiran exposure during the OLE was determined as the last follow-up date minus the first dose date plus 1. For randomized period, the planned drug exposure is calculated as: for subjects taking 1 dose (Q3M or Q6M) only during the double-blinded studies, the planned exposure is 4 months (122 days); for subjects taking 2 doses (Q3M or Q6M) during the double-blinded studies, the planned exposure is 10 months (304 days); for subjects taking 3 or 4 doses during the double-blinded studies, the planned exposure is 12 months (365 days). Study duration was calculated by

study completion date minus randomization date +1 day per each individual subject. With both planned exposure and study duration available for individual subjects, their actual study drug exposure was determined as the shorter time of the planned drug exposure and study duration. For subjects with dose interruption or missing dose, actual exposure was determined based on medical review and documented. For OLE portion, the overall drug exposure during the OLE was determined as the last follow-up date minus the first dose date plus 1. For subjects taking plozasiran in both double-blinded studies and OLE studies, the overall drug exposure of plozasiran was calculated as the summation of exposures from these 2 portions. For subjects taking placebo in double-blinded studies, the overall plozasiran exposure was the same as OLE portion.

5.4.3. Adverse events

5.4.3.1. Common Adverse Events

Pool 1: Pivotal Phase 3 Study, Double-Blinded Period

An overview of TEAEs and EAIRs for Pool 1 is presented in Table 44.

Table 41: Pool 1: Overview of Adverse Events by Incidence and Exposure-Adjusted Incidence (Randomized Period, Safety Set)

						Risk Difference (%) (95% CI)	
Category		**Placebo (N=25)**	**Plozasiran 25 mg (N=26)**	**Plozasiran 50 mg (N=24)**	**Plozasiran (25 mg+ 50 mg) (N=50)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**
All TEAEs	n (%)	20 (80.0)	23 (88.5)	20 (83.3)	43 (86.0)	8.5 (-11.5, 28.4)	6.0 (-12.4, 24.4)
	(EAIR 100 PY)	242.0	240.0	259.1	248.5	-1.9 (-146.4, 142.5)	6.6 (-122.9, 136.1)
Treatment-related TEAEs	n (%)	6 (24.0)	7 (26.9)	8 (33.3)	15 (30.0)	2.9 (-21.0, 26.8)	6.0 (-15.0, 27.0)
	EAIR (100 PY)	32.7	36.0	40.0	37.9	3.3 (-34.0, 40.6)	5.2 (-27.6, 38.0)
Serious TEAEs	n (%)	7 (28.0)	5 (19.2)	2 (8.3)	7 (14.0)	-8.8 (-32.0, 14.5)	-14.0 (-34.1, 6.1)
	EAIR (100 PY)	37.6	22.5	9.5	16.2	-15.1 (-49.3, 19.0)	-21.4 (-51.8, 8.9)
Treatment-related Serious TEAEs	n (%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	-4.0 (-11.7, 3.7)	-4.0 (-11.7, 3.7)
	EAIR (100 PY)	4.6	0.0	0.0	0.0	-4.6 (-13.6, 4.4)	-4.6 (-13.6, 4.4)
Subjects with Any TEAEs by Maximum Severity							
Mild	n (%)	5 (20.0)	13 (50.0)	13 (54.2)	26 (52.0)	30.0 (5.2, 54.8)	32.0 (11.1, 52.9)
	EAIR (100 PY)	26.5	73.7	97.7	84.0	47.2 (0.9, 93.5)	57.6 (17.8, 97.3)
Moderate	n (%)	10 (40.0)	7 (26.9)	4 (16.7)	11 (22.0)	-13.1 (-38.8, 12.6)	-18.0 (-40.4, 4.4)
	EAIR (100 PY)	64.5	35.7	21.0	28.5	-28.7 (-76.7, 19.2)	-36.0 (-79.3, 7.4)
Severe	n (%)	5 (20.0)	2 (7.7)	3 (12.5)	5 (10.0)	-12.3 (-31.0, 6.4)	-10.0 (-27.7, 7.7)
	EAIR (100 PY)	25.7	8.5	14.8	11.4	-17.1 (-42.6, 8.3)	-14.2 (-38.9, 10.4)
Life Threatening	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5, 11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	4.1	0.0	2.2	4.1 (-3.9, 12.2)	2.2 (-2.1, 6.4)
TEAEs leading to study drug discontinuation	n (%)	0 (0.0)	2 (7.7)	1 (4.2)	3 (6.0)	7.7 (-2.6, 17.9)	6.0 (-0.6, 12.6)
	EAIR (100 PY)	0.0	8.6	4.6	6.6	8.6 (-3.3, 20.4)	6.6 (-0.9, 14.1)
TEAEs leading to study termination	n (%)	0 (0.0)	2 (7.7)	1 (4.2)	3 (6.0)	7.7 (-2.6, 17.9)	6.0 (-0.6, 12.6)
	EAIR (100 PY)	0.0	8.6	4.6	6.6	8.6 (-3.3, 20.4)	6.6 (-0.9, 14.1)
Deaths	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

Abbreviations: AE=adverse event; CI=confidence interval; EAIR=exposure-adjusted incidence rate; NA=not applicable; PY=person-year; TEAE=treatment emergent adverse event. %=100×n/N, where n was the number of subjects with specified adverse events. EAIR=100×n/PY, where n was the number of subjects with specified adverse events. Notes: A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. AE was considered treatment-related if the

relationship to the study drug was 'possibly related', 'probably related', or missing. Subjects with multiple events were counted only once within a category. Risk difference and 95% CI were calculated using Chi-square test. Risk difference and respective 95% CI for EAIR were calculated using Wald's method.

The overall incidence of subjects who reported a TEAE was modestly higher in the plozasiran groups (88.5% of subjects in the plozasiran 25 mg group and 83.3% of subjects in the plozasiran 50 mg group) compared to the placebo group (80.0% of subjects).

A summary of the most common TEAEs experienced in the long-term, DB Phase 3 study is shown in Table 45. The most common TEAEs (those occurring in at least 5 subjects in any treatment group) were abdominal pain (24.0% of subjects total), coronavirus disease-19 (COVID 19; 16.0%), headache (13.3%), and nasopharyngitis (13.3%). The incidence of COVID 19 was higher in the plozasiran groups compared to the placebo group which appears to be random since the Phase 2b plozasiran studies, also conducted during the pandemic, did not indicate an increased occurrence for COVID 19 in plozasiran treated subjects (refer to Table 45).

Table 42: Pool 1: Treatment-Emergent Adverse Events and Exposure-Adjusted Treatment-Emergent Adverse Events by Preferred Term Affecting ≥10% of Any Group (Randomized Period, Safety Set)

						Risk Difference and 95% CI	
Preferred Term		**Placebo (N=25)**	**Plozasiran 25 mg (N=26)**	**Plozasiran 50 mg (N=24)**	**Plozasiran (25 mg+ 50 mg) (N=50)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**
Subjects with Any TEAEs	n (%)	20 (80.0)	23 (88.5)	20 (83.3)	43 (86.0)	8.5 (-11.5, 28.4)	6.0 (-12.4, 24.4)
	EAIR (100 PY)	242.0	240.0	259.1	248.5	-1.9 (-146.4, 142.5)	6.6 (-122.9, 136.1)
Abdominal pain	n (%)	5 (20.0)	7 (26.9)	6 (25.0)	13 (26.0)	6.9 (-16.2, 30.1)	6.0 (-13.8, 25.8)
	EAIR (100 PY)	27.2	32.3	33.9	33.0	5.0 (-28.7, 38.8)	5.8 (-24.1, 35.6)
COVID-19	n (%)	0 (0.0)	5 (19.2)	7 (29.2)	12 (24.0)	19.2 (4.1, 34.4)	24.0 (12.2, 35.8)
	EAIR (100 PY)	0.0	21.1	37.0	28.2	21.1 (2.6, 39.7)	28.2 (12.2, 44.1)
Headache	n (%)	2 (8.0)	3 (11.5)	5 (20.8)	8 (16.0)	3.5 (-12.7, 19.8)	8.0 (-6.7, 22.7)
	EAIR (100 PY)	9.8	13.3	26.1	19.2	3.5 (-16.8, 23.9)	9.4 (-9.6, 28.4)
Nasopharyngitis	n (%)	3 (12.0)	5 (19.2)	2 (8.3)	7 (14.0)	7.2 (-12.6, 27.0)	2.0 (-14.0, 18.0)
	EAIR (100 PY)	14.6	22.2	4.7	13.7	7.6 (-17.9, 33.1)	-0.9 (-20.7, 18.9)
Nausea	n (%)	2 (8.0)	4 (15.4)	3 (12.5)	7 (14.0)	7.4 (-10.1, 24.9)	6.0 (-8.3, 20.3)
	EAIR (100 PY)	9.6	18.1	14.9	16.6	8.4 (-13.8, 30.6)	6.9 (-11.2, 25.1)
Glycosylated haemoglobin increased	n (%)	0 (0.0)	3 (11.5)	3 (12.5)	6 (12.0)	11.5 (-0.7, 23.8)	12.0 (3.0, 21.0)
	EAIR (100 PY)	0.0	12.9	14.6	13.7	12.9 (-1.7, 27.4)	13.7 (2.7, 24.7)
Diarrhoea	n (%)	2 (8.0)	1 (3.8)	4 (16.7)	5 (10.0)	-4.2 (-17.1, 8.8)	2.0 (-11.5, 15.5)
	EAIR (100 PY)	9.7	4.2	20.1	11.4	-5.6 (-21.3, 10.2)	1.7 (-15.1, 18.4)
Back pain	n (%)	2 (8.0)	3 (11.5)	2 (8.3)	5 (10.0)	3.5 (-12.7, 19.8)	2.0 (-11.5, 15.5)
	EAIR (100 PY)	9.7	8.5	9.6	9.0	-1.2 (-19.1, 16.7)	-0.7 (-16.8, 15.4)
Upper respiratory tract infection	n (%)	2 (8.0)	3 (11.5)	2 (8.3)	5 (10.0)	3.5 (-12.7, 19.8)	2.0 (-11.5, 15.5)
	EAIR (100 PY)	9.9	13.4	9.5	11.5	3.5 (-16.9, 23.9)	1.6 (-15.4, 18.6)
Abdominal discomfort	n (%)	0 (0.0)	0 (0.0)	3 (12.5)	3 (6.0)	NA	6.0 (-0.6, 12.6)
	EAIR (100 PY)	0.0	0.0	14.0	6.5	0.0 (0.0, 0.0)	6.5 (-0.9, 13.9)
Palpitations	n (%)	0 (0.0)	3 (11.5)	0 (0.0)	3 (6.0)	11.5 (-0.7, 23.8)	6.0 (-0.6, 12.6)
	EAIR (100 PY)	0.0	13.4	0.0	6.7	13.4 (-1.8, 28.5)	6.7 (-0.9, 14.4)
Pancreatitis acute	n (%)	3 (12.0)	2 (7.7)	0 (0.0)	2 (4.0)	-4.3 (-20.7, 12.0)	-8.0 (-21.8, 5.8)
	EAIR (100 PY)	14.7	8.5	0.0	4.4	-6.1 (-26.5, 14.3)	-10.3 (-27.9, 7.4)
Pancreatitis relapsing	n (%)	3 (12.0)	0 (0.0)	1 (4.2)	1 (2.0)	-12.0 (-24.7, 0.7)	-10.0 (-23.3, 3.3)
	EAIR (100 PY)	14.7	0.0	4.5	2.1	-14.7 (-31.2, 1.9)	-12.5 (-29.6, 4.6)

Abbreviations: AE=adverse event; CI=confidence interval; COVID-19=coronavirus disease-19; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; PY=person-year; TEAE=treatment-

emergent adverse event. %=100×n/N, where n is the number of subjects with specified AEs. EAIR=100×n/PY, where n is the number of subjects with specified AEs. Notes: AEs were coded using MedDRA dictionary version 26.1. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term or System Organ Class were counted once. Risk difference and 95% CI for incidence were calculated using Chi-square test. Risk difference and respective 95% CI for EAIR were calculated using Wald's method.

Pool 2: Phase 2/3 Blinded (Placebo-Controlled) Studies

An overview of TEAEs and EAIRs for Pool 2 is presented in Table 46.

Table 43: Pool 2: Overview of Adverse Events by Incidence and Exposure-Adjusted Incidence (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
Category		Placebo (N=173)	Plozasiran 10 mg (N=121)	Plozasiran 25 mg (N=148)	Plozasiran 50 mg Q12W (N=146)	Plozasiran 50 mg Q24W (N=66)	Plozasiran (25 mg+ 50 mg) (N=360)	Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)	Plozasiran 25 mg vs Placebo	Plozasiran (25 mg+ 50 mg) vs Placebo	Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo
All TEAEs	n (%)	118 (68.2)	89 (73.6)	104 (70.3)	116 (79.5)	49 (74.2)	269 (74.7)	358 (74.4)	1.4 (-8.6, 11.4)	6.9 (-1.3, 15.1)	6.9 (-1.0, 14.8)
	EAIR (100 PY)	160.5	195.7	169.0	211.2	188.7	188.7	190.4	4.5 (-39.8, 48.8)	29.0 (-8.4, 66.4)	32.9 (-2.8, 68.6)
Treatment-related TEAEs	n (%)	22 (12.7)	20 (16.5)	24 (16.2)	30 (20.5)	8 (12.1)	62 (17.2)	82 (17.0)	3.0 (-4.7, 10.7)	4.7 (-1.6, 10.9)	5.0 (-0.9, 11.0)
	EAIR (100 PY)	17.2	24.0	22.4	28.4	17.0	23.8	23.9	4.4 (-7.1, 16.0)	6.8 (-2.5, 16.1)	7.5 (-1.4, 16.4)
Serious TEAEs	n (%)	22 (12.7)	6 (5.0)	12 (8.1)	16 (11.0)	5 (7.6)	33 (9.2)	39 (8.1)	-5.2 (-11.8, 1.4)	-3.3 (-9.1, 2.4)	-4.1 (-9.6, 1.4)
	EAIR (100 PY)	13.5	5.3	10.2	12.2	7.9	10.6	9.3	-4.6 (-13.4, 4.1)	-2.9 (-10.2, 4.3)	-3.8 (-10.6, 3.1)
Treatment-related Serious TEAEs	n (%)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-1.2 (-2.8, 0.4)	-1.2 (-2.8, 0.4)	-1.1 (-2.7, 0.4)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.8 (-2.4, 0.8)	-0.7 (-2.1, 0.7)	-0.7 (-2.0, 0.6)
Subjects with Any TEAEs by Maximum Severity											
Mild	n (%)	45 (26.0)	42 (34.7)	48 (32.4)	57 (39.0)	24 (36.4)	129 (35.8)	171 (35.6)	6.5 (-3.5, 16.5)	9.7 (1.5, 18.0)	9.9 (2.0, 17.7)
	EAIR (100 PY)	37.6	57.2	49.5	60.0	59.2	55.3	55.8	12.2 (-5.7, 30.1)	17.8 (2.7, 32.8)	18.8 (4.5, 33.2)
Moderate	n (%)	58 (33.5)	44 (36.4)	48 (32.4)	47 (32.2)	21 (31.8)	116 (32.2)	160 (33.3)	-1.4 (-11.7, 8.9)	-0.9 (-9.4, 7.6)	-0.2 (-8.4, 8.0)
	EAIR (100 PY)	50.4	52.5	46.8	49.6	51.1	48.7	49.6	3.9 (-23.0, 15.3)	-0.4 (-16.5, 15.7)	-0.1 (-15.5, 15.2)
Severe	n (%)	14 (8.1)	3 (2.5)	6 (4.1)	10 (6.8)	3 (4.5)	19 (5.3)	2 (4.6)	-4.3 (-9.5, 0.8)	-2.8 (-7.4, 1.9)	-3.2 (-7.6, 1.3)
	EAIR (100 PY)	8.1	2.1	5.0	7.8	5.9	6.3	5.3	-3.8 (-10.4, 2.7)	-1.8 (-7.4, 3.7)	-2.5 (-7.7, 2.7)
Life Threatening	n (%)	1 (0.6)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.0 (-1.7, 1.7)	-0.3 (-1.5, 1.0)	-0.3 (-1.5, 0.9)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.7 (-0.7, 2.1)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)
TEAEs leading to study drug discontinuation	n (%)	2 (1.2)	1 (0.8)	2 (1.4)	2 (1.4)	0 (0.0)	4 (1.1)	5 (1.0)	0.1 (-2.2, 2.5)	-0.1 (-2.0, 1.9)	0.0 (-1.9, 1.9)
	EAIR (100 PY)	1.4	1.0	1.6	1.7	0.0	1.4	1.3	0.1 (-2.6, 2.9)	-0.1 (-2.6, 2.3)	0.0 (-2.4, 2.4)
TEAEs leading to study termination	n (%)	1 (0.6)	1 (0.8)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	4 (0.8)	0.7 (-1.4, 2.8)	0.3 (-1.2, 1.8)	0.4 (-1.1, 1.9)
	EAIR (100 PY)	0.7	1.0	1.6	0.8	0.0	1.0	1.0	0.8 (-1.6, 3.3)	0.3 (-1.6, 2.1)	0.5 (-1.4, 2.3)
Deaths	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.4)	1 (1.5)	4 (1.1)	4 (0.8)	0.7 (-0.6, 2.1)	1.0 (0.0, 2.1)	0.8 (0.0, 1.6)
	EAIR (100 PY)	0.0	0.0	0.8	1.7	1.9	1.4	1.0	0.9 (-0.8, 2.6)	1.3 (0.0, 2.5)	1.0 (0.0, 1.9)

In Pool 2, the overall incidence of TEAEs was similar between the placebo (68.2% of subjects) and plozasiran 25 mg group (70.3% of subjects), and slightly higher in the plozasiran 50 mg Q12W group and the plozasiran 25+50 mg group (79.5% and 74.7% of subjects, respectively). The majority of TEAEs were mild in the plozasiran groups and moderate in the placebo group.

A summary of the most common TEAEs that occurred in ≥13 subjects (≥2%) overall during the long-term, DB Phase 2/3 studies are shown in Table 47.

A comparison of the most common TEAEs showed that COVID-19 was the most common TEAE in both pools.

Exposure-Adjusted TEAEs

The EAIR of subjects who reported a TEAE was higher in the plozasiran 10+25+50 mg group (190.4 per 100 PYs) compared to placebo (160.5 per 100 PYs), although the EAIR for the plozasiran 25 mg group was again similar (169.0 per 100 PYs). All other EAIRs and risk differences showed a similar pattern to the crude incidence analysis. The EAIRs for SAEs was highest in the placebo group. EAIRs for TEAEs leading to study drug discontinuation showed a low risk and were similar across treatment groups.

Table 44: Pool 2: Incidence and Adjusted Incidence of Treatment-Emergent Adverse Events by Preferred Term Affecting ≥13 (2%) Subjects Overall (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
Preferred Term		**Placebo (N=173)**	**Plozasiran 10 mg (N=121)**	**Plozasiran 25 mg (N=148)**	**Plozasiran 50 mg Q12W (N=146)**	**Plozasiran 50 mg Q24W (N=66)**	**Plozasiran (25 mg+ 50 mg) (N=360)**	**Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**	**Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo**
Subjects with Any TEAEs	n (%)	118 (68.2)	89 (73.6)	104 (70.3)	116 (79.5)	49 (74.2)	269 (74.7)	358 (74.4)	1.4 (-8.6, 11.4)	6.9 (-1.3, 15.1)	6.9 (-1.0, 14.8)
	EAIR (100 PY)	160.5	195.7	169.0	211.2	188.7	188.7	190.4	4.5 (-39.8, 48.8)	29.0 (-8.4, 66.4)	32.9 (-2.8, 68.6)
COVID-19	n (%)	21 (12.1)	17 (14.0)	23 (15.5)	23 (15.8)	5 (7.6)	51 (14.2)	68 (14.1)	3.5 (-4.1, 11.1)	2.2 (-3.9, 8.3)	2.2 (-3.6, 8.1)
	EAIR (100 PY)	14.4	18.9	18.1	19.3	10.1	17.1	17.6	3.9 (-6.2, 13.9)	2.9 (-5.3, 11.0)	3.4 (-4.6, 11.4)
Upper respiratory tract infection	n (%)	13 (7.5)	8 (6.6)	14 (9.5)	10 (6.8)	9 (13.6)	33 (9.2)	41 (8.5)	2.0 (-4.2, 8.1)	1.7 (-3.3, 6.6)	1.1 (-3.6, 5.8)
	EAIR (100 PY)	9.8	7.5	11.2	6.9	14.4	10.0	9.4	1.5 (-6.6, 9.6)	0.2 (-6.3, 6.7)	-0.3 (-6.5, 5.9)
Type 2 diabetes mellitus	n (%)	7 (4.0)	6 (5.0)	8 (5.4)	14 (9.6)	11 (16.7)	33 (9.2)	39 (8.1)	1.5 (-3.2, 6.2)	5.0 (0.8, 9.2)	3.7 (-0.1, 7.5)
	EAIR (100 PY)	5.1	6.5	5.9	12.5	23.1	11.5	10.2	1.1 (-4.7, 6.9)	6.3 (0.9, 11.8)	4.7 (-0.3, 9.6)
Headache	n (%)	8 (4.6)	9 (7.4)	10 (6.8)	11 (7.5)	5 (7.6)	26 (7.2)	35 (7.3)	1.9 (-3.2, 6.9)	2.7 (-1.4, 6.8)	3.1 (-0.8, 7.0)
	EAIR (100 PY)	5.1	10.1	8.6	9.8	10.3	9.4	9.5	3.2 (-3.3, 9.7)	4.3 (-1.0, 9.5)	4.9 (-0.1, 9.9)
Abdominal pain	n (%)	7 (4.0)	3 (2.5)	7 (4.7)	13 (8.9)	1 (1.5)	21 (5.8)	24 (5.0)	-0.1 (-4.2, 4.0)	2.0 (-1.6, 5.5)	1.9 (-1.4, 5.2)
	EAIR (100 PY)	5.1	3.2	5.8	10.7	0.0	6.7	5.8	-0.7 (-6.4, 5.0)	1.5 (-3.3, 6.3)	1.6 (-2.9, 6.1)
Bronchitis	n (%)	5 (2.9)	8 (6.6)	2 (1.4)	7 (4.8)	5 (7.6)	14 (3.9)	22 (4.6)	-1.6 (-4.8, 1.6)	1.0 (-2.2, 4.2)	1.7 (-1.4, 4.8)
	EAIR (100 PY)	3.6	8.6	1.6	5.1	10.0	4.5	5.5	-2.0 (-6.2, 2.1)	0.9 (-3.0, 4.9)	1.9 (-1.9, 5.8)
Glycosylated haemoglobin increased	n (%)	4 (2.3)	6 (5.0)	6 (4.1)	7 (4.8)	2 (3.0)	15 (4.2)	21 (4.4)	1.6 (-2.3, 5.4)	1.9 (-1.1, 5.0)	2.3 (-0.7, 5.3)
	EAIR (100 PY)	2.9	6.4	5.0	6.1	3.9	5.2	5.5	1.9 (-2.8, 6.7)	2.4 (-1.5, 6.3)	2.9 (-0.9, 6.8)
Urinary tract infection	n (%)	13 (7.5)	7 (5.8)	5 (3.4)	8 (5.5)	0 (0.0)	13 (3.6)	20 (4.2)	-4.0 (-9.0, 0.9)	-3.9 (-8.3, 0.5)	-3.3 (-7.7, 1.0)
	EAIR (100 PY)	8.2	6.4	4.2	6.9	0.0	4.5	5.0	-3.9 (-10.1, 2.4)	-3.7 (-9.1, 1.7)	-3.2 (-8.5, 2.1)
Back pain	n (%)	5 (2.9)	5 (4.1)	6 (4.1)	6 (4.1)	0 (0.0)	12 (3.3)	17 (3.5)	1.0 (-3.0, 4.9)	0.4 (-2.7, 3.5)	0.9 (-2.1, 3.9)
	EAIR (100 PY)	3.6	4.2	4.1	5.1	0.0	3.8	3.9	0.3 (-4.6, 5.1)	0.0 (-3.8, 3.9)	0.4 (-3.3, 4.2)
Arthralgia	n (%)	8 (4.6)	2 (1.7)	3 (2.0)	7 (4.8)	4 (6.1)	14 (3.9)	16 (3.3)	-2.8 (-6.7, 1.1)	-0.6 (-4.3, 3.1)	-1.2 (-4.7, 2.3)
	EAIR (100 PY)	5.9	2.1	2.5	6.1	8.1	4.9	4.2	-3.6 (-8.7, 1.4)	-0.8 (-5.6, 3.9)	-1.5 (-6.0, 3.0)
Hypertension	n (%)	9 (5.2)	2 (1.7)	6 (4.1)	5 (3.4)	3 (4.5)	14 (3.9)	16 (3.3)	-1.3 (-5.9, 3.3)	-1.2 (-5.0, 2.7)	-1.8 (-5.4, 1.9)
	EAIR (100 PY)	5.8	2.1	5.0	4.3	6.0	4.9	4.2	-1.2 (-6.9, 4.6)	-0.8 (-5.6, 4.0)	-1.6 (-6.1, 2.9)
Lipase increased	n (%)	3 (1.7)	2 (1.7)	6 (4.1)	7 (4.8)	1 (1.5)	14 (3.9)	16 (3.3)	2.4 (-1.3, 6.1)	2.2 (-0.6, 5.0)	1.6 (-1.0, 4.1)
	EAIR (100 PY)	2.2	2.1	4.2	5.2	2.0	4.2	3.7	2.1 (-2.3, 6.5)	2.0 (-1.4, 5.4)	1.4 (-1.7, 4.6)
Nausea	n (%)	2 (1.2)	2 (1.7)	7 (4.7)	6 (4.1)	1 (1.5)	14 (3.9)	16 (3.3)	3.2 (-0.4, 6.9)	2.8 (0.3, 5.3)	2.6 (0.4, 4.8)

	EAIR (100 PY)	1.4	2.1	5.9	5.2	0.0	4.5	3.9	4.0 (-0.7, 8.7)	3.2 (0.0, 6.4)	3.0 (0.2, 5.9)
Sinusitis	n (%)	2 (1.2)	3 (2.5)	6 (4.1)	3 (2.1)	4 (6.1)	13 (3.6)	16 (3.3)	2.9 (-0.6, 6.5)	2.5 (-0.1, 5.0)	2.2 (-0.1, 4.5)
	EAIR (100 PY)	1.4	3.1	4.9	1.7	8.0	4.1	3.9	3.6 (-0.8, 8.0)	2.7 (-0.4, 5.9)	2.5 (-0.4, 5.3)
Nasopharyngitis	n (%)	6 (3.5)	3 (2.5)	6 (4.1)	6 (4.1)	0 (0.0)	12 (3.3)	15 (3.1)	0.2 (-3.8, 4.2)	-0.1 (-3.3, 3.2)	0.1 (-3.0, 3.2)
	EAIR (100 PY)	4.3	2.1	4.1	4.3	0.0	3.5	3.1	-0.8 (-5.7, 4.1)	-0.9 (-5.0, 3.2)	-0.8 (-4.7, 3.1)
Diarrhoea	n (%)	10 (5.8)	6 (5.0)	2 (1.4)	5 (3.4)	0 (0.0)	7 (1.9)	13 (2.7)	-4.6 (-8.6, -0.7)	-3.7 (-7.4, 0.1)	-2.8 (-6.5, 1.0)
	EAIR (100 PY)	6.6	6.5	1.6	4.3	0.0	2.4	3.4	-5.3 (-10.3, -0.4)	-4.0 (-8.7, 0.6)	-2.9 (-7.6, 1.9)
Fatigue	n (%)	4 (2.3)	3 (2.5)	5 (3.4)	3 (2.1)	2 (3.0)	10 (2.8)	13 (2.7)	0.9 (-2.8, 4.6)	0.5 (-2.3, 3.3)	0.6 (-2.0, 3.2)
	EAIR (100 PY)	2.9	3.2	4.1	2.6	3.9	3.5	3.4	1.1 (-3.7, 5.8)	0.6 (-3.0, 4.2)	0.7 (-2.6, 4.1)
Cystitis	n (%)	2 (1.2)	5 (4.1)	2 (1.4)	2 (1.4)	3 (4.5)	7 (1.9)	12 (2.5)	0.2 (-2.3, 2.7)	0.7 (-1.4, 2.8)	1.2 (-0.8, 3.3)
	EAIR (100 PY)	1.4	4.3	1.6	1.7	6.0	2.4	2.9	0.3 (-2.9, 3.4)	0.9 (-1.8, 3.5)	1.3 (-1.2, 3.8)
Diabetes mellitus	n (%)	2 (1.2)	3 (2.5)	2 (1.4)	6 (4.1)	1 (1.5)	9 (2.5)	12 (2.5)	0.1 (-2.3, 2.5)	1.5 (-0.8, 3.7)	1.4 (-0.7, 3.6)
	EAIR (100 PY)	1.4	3.2	1.6	5.2	1.9	3.1	3.1	0.1 (-2.9, 3.0)	1.8 (-1.0, 4.7)	1.8 (-0.9, 4.5)
	n (%)	3 (1.7)	1 (0.8)	5 (3.4)	4 (2.7)	1 (1.5)	10 (2.8)	11 (2.3)	1.8 (-1.7, 5.3)	1.0 (-1.6, 3.6)	0.5 (-1.9, 2.8)
Blood creatine phosphokinase increased	EAIR (100 PY)	2.2	1.0	3.3	3.4	0.0	2.8	2.3	1.3 (-2.8, 5.4)	0.6 (-2.5, 3.7)	0.1 (-2.8, 3.0)

Abbreviations: AE=adverse event; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; COVID-1=corona virus disease-19; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; MH=Mantel-Haenszel; NA=not applicable; PY=person-year; Q12W=every 12 weeks; Q24W=every 24 weeks; TEAE=treatment-emergent adverse event. % = 100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Notes: AEs were coded using MedDRA dictionary version 26.1. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using CMH test by stratifying with study. Risk difference and respective 95% CI for exposure-adjusted incidence were calculated using MH weights by stratifying with study.

Pool 3: Open-Label Extension Studies

An overview of TEAEs and EAIRs for Pool 3 is presented in Table 48.

Table 45: Pool 3: Overview of Adverse Events by Incidence and Adjusted Incidence (OLE Portion, Safety Set)

Category		Plozasiran 10 mg	Plozasiran 25 mg	Plozasiran 50 mg	Plozasiran (25 mg+ 50 mg)	Plozasiran (10 mg+ 25 mg+ 50 mg)
Total Number of Subjects Included in the Incidence analysis		N=114	N=472	N=52	N=476	N=483
Total Number of Subjects Included in EAIR analysis		N=8	N=471	N=4	N=475	N=483
All TEAEs	n (%)	61 (53.5)	304 (64.4)	32 (61.5)	322 (67.6)	338 (70.0)
	n (EAIR 100 PY)	4 (255.4)	332 (108.6)	2 (236.4)	ND	338 (109.7)
Treatment-related TEAEs	n (%)	16 (14.0)	60 (12.7)	8 (15.4)	66 (13.9)	78 (16.1)
	n (EAIR 100 PY)	1 (23.1)	76 (12.8)	1 (80.8)	ND	78 (13.0)
Serious TEAEs	n (%)	7 (6.1)	47 (10.0)	8 (15.4)	52 (10.9)	57 (11.8)
	n (EAIR 100 PY)	1 (21.8)	55 (8.8)	1 (78.5)	ND	57 (9.1)
Treatment-related Serious TEAEs	n (%)	0 (0.0)	2 (0.4)[a]	1 (1.9)	3 (0.6)	3 (0.6)
	n (EAIR 100 PY)	0 (0.0)	3 (0.5)	0 (0.0)	ND	3 (0.4)
Subjects with Any TEAEs by Maximum Severity						
Mild	n (%)	30 (26.3)	124 (26.3)	13 (25.0)	131 (27.5)	129 (26.7)
	n (EAIR 100 PY)	1 (30.7)	128 (23.5)	0 (0.0)	ND	129 (23.4)
Moderate	n (%)	29 (25.4)	145 (30.7)	10 (19.2)	149 (31.3)	165 (34.2)
	n (EAIR 100 PY)	2 (59.2)	162 (31.8)	1 (68.9)	ND	165 (32.0)
Severe	n (%)	2 (1.8)	31 (6.6)	8 (15.4)	37 (7.8)	39 (8.1)
	n (EAIR 100 PY)	1 (21.8)	37 (5.8)	1 (78.5)	ND	39 (6.1)
Life Threatening	n (%)	0 (0.0)	2 (0.4)	1 (1.9)	3 (0.6)	3 (0.6)
	n (EAIR 100 PY)	0 (0.0)	3 (0.5)	0 (0.0)	ND	3 (0.4)
Death	n (%)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.4)
	n (EAIR 100 PY)	0 (0.0)	2 (0.3)	0 (0.0)	ND	2 (0.3)
TEAEs leading to study drug discontinuation	n (%)	3 (2.6)	18 (3.8)	1 (1.9)	19 (4.0)	22 (4.6)
	n (EAIR 100 PY)	3 (82.4)	18 (2.7)	1 (80.8)	ND	22 (3.3)
TEAEs leading to study termination	n (%)	3 (2.6)	14 (3.0)	1 (1.9)	15 (3.2)	18 (3.7)
	n (EAIR 100 PY)	3 (82.4)	14 (2.1)	1 (80.8)	ND	18 (2.7)

Abbreviations: AE=adverse event; EAIR=exposure-adjusted incidence rate; ND=not determined; OLE=open-label extension; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. Notes: A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. For incidence, TEAEs were summarized according to the most recent treatment received prior to the TEAE onset. For exposure-adjusted, TEAEs were summarized according to the last treatment they received at the time of data cutoff. An AE was considered treatment-related if the relationship to the study drug was 'possibly related,', 'probably related,' or missing. Subjects with multiple events were counted only once within a category. a A possible SAE (PT: hospitalization) for a subject reported by the Investigator based on a conversation with the primary care provider that indicated that a hospitalization might have occurred. No admission or discharge details were provided, nor any information on a possible cause for the possible hospitalization. Although this event was documented on a CRF, the minimum reporting criteria was not met because the following information was not available: 1) date of the event 2) an adverse event term and 3) seriousness outcome. Reconciliation of this discrepancy is ongoing.

The overall incidences of TEAEs and EAIRs were somewhat lower in Pool 3 than in Pool 1 and Pool 2. Overall, TEAEs were reported in 64.4% of subjects in the plozasiran 25 mg group, and 61.5% of subjects in the plozasiran 50 mg group.

The most common TEAEs (those occurring in ≥9 [≥1.9%] subjects overall), are presented by PT in descending order of incidence in Table 49. The most frequently occurring TEAEs by PT were COVID-19 and Type 2 diabetes mellitus.

Table 46: Pool 3: Treatment-Emergent Adverse Events by Preferred Term Affecting ≥9 Subjects Overall (OLE Portion, Safety Set)

Preferred Term		Plozasiran 10 mg (N=114) n (%)	Plozasiran 25 mg (N=472) n (%)	Plozasiran 50 mg (N=52) n (%)	Plozasiran (25 mg+ 50 mg) (N=476) n (%)	Plozasiran (10 mg+ 25 mg+ 50 mg) (N=483) n (%)
Total Number of Subjects Included in the Incidence analysis		N=114	N=472	N=52	N=476	N=483
Total Number of Subjects Included in EAIR analysis		N=8	N=471	N=4	ND	N=483
Subjects with any TEAEs	n (%)	61 (53.5)	304 (64.4)	32 (61.5)	322 (67.6)	338 (70.0)
	n (EAIR 100 PY)	4 (255.4)	332 (108.6)	2 (236.4)	ND	338 (109.7)
COVID-19	n (%)	6 (5.3)	28 (5.9)	2 (3.8)	30 (6.3)	35 (7.2)
	n (EAIR 100 PY)	1 (21.9)	34 (5.4)	0 (0.0)	ND	35 (5.5)
Type 2 diabetes mellitus	n (%)	7 (6.1)	28 (5.9)	1 (1.9)	29 (6.1)	35 (7.2)
	n (EAIR 100 PY)	1 (23.3)	34 (5.3)	0 (0.0)	ND	35 (5.4)
Upper respiratory tract infection	n (%)	6 (5.3)	17 (3.6)	4 (7.7)	21 (4.4)	27 (5.6)
	n (EAIR 100 PY)	1 (23.5)	26 (4.0)	0 (0.0)	ND	27 (4.1)
Back pain	n (%)	4 (3.5)	15 (3.2)	5 (9.6)	20 (4.2)	24 (5.0)
	n (EAIR 100 PY)	0 (0.0)	24 (3.7)	0 (0.0)	ND	24 (3.7)
Diabetes mellitus	n (%)	1 (0.9)	17 (3.6)	1 (1.9)	18 (3.8)	19 (3.9)
	n (EAIR 100 PY)	0 (0.0)	18 (2.7)	1 (80.8)	ND	19 (2.9)
Headache	n (%)	2 (1.8)	18 (3.8)	0 (0.0)	18 (3.8)	19 (3.9)
	n (EAIR 100 PY)	0 (0.0)	19 (2.9)	0 (0.0)	ND	19 (2.9)
Influenza	n (%)	5 (4.4)	11 (2.3)	1 (1.9)	12 (2.5)	17 (3.5)
	n (EAIR 100 PY)	0 (0.0)	16 (2.5)	1 (80.1)	ND	17 (2.6)
Urinary tract infection	n (%)	3 (2.6)	14 (3.0)	1 (1.9)	15 (3.2)	17 (3.5)
	n (EAIR 100 PY)	0 (0.0)	17 (2.6)	0 (0.0)	ND	15 (2.6)
Arthralgia	n (%)	4 (3.5)	10 (2.1)	1 (1.9)	11 (2.3)	15 (3.1)
	n (EAIR 100 PY)	0 (0.0)	15 (2.3)	0 (0.0)	ND	17 (2.3
Hypertension	n (%)	3 (2.6)	11 (2.3)	1 (1.9)	12 (2.5)	15 (3.1)
	n (EAIR 100 PY)	0 (0.0)	15 (2.3)	0 (0.0)	ND	17 (2.3
Glycosylated haemoglobin increased	n (%)	3 (2.6)	11 (2.3)	0 (0.0)	11 (2.3)	14 (2.9)
	n (EAIR 100 PY)	1 (23.1)	13 (2.0)	0 (0.0)	ND	14 (2.1)
Pain in extremity	n (%)	3 (2.6)	10 (2.1)	1 (1.9)	11 (2.3)	14 (2.9)
	n (EAIR 100 PY)	0 (0.0)	14 (2.1)	0 (0.0)	ND	14 (2.1
Abdominal pain	n (%)	1 (0.9)	7 (1.5)	5 (9.6)	12 (2.5)	13 (2.7)
	n (EAIR 100 PY)	1 (21.8)	12 (1.8)	0 (0.0)	ND	13 (2.0)
Diarrhoea	n (%)	2 (1.8)	9 (1.9)	0 (0.0)	9 (1.9)	11 (2.3)
	n (EAIR 100 PY)	0 (0.0)	11 (1.7)	0 (0.0)	ND	11 (1.7)
Lipase increased	n (%)	0 (0.0)	9 (1.9)	2 (3.8)	11 (2.3)	11 (2.3)
	n (EAIR 100 PY)	0 (0.0)	11 (1.7)	0 (0.0)	ND	11 (1.7)
Sinusitis	n (%)	1 (0.9)	9 (1.9)	1 (1.9)	10 (2.1)	11 (2.3)
	n (EAIR 100 PY)	0 (0.0)	11 (1.7)	0 (0.0)	ND	11 (1.7)
Bronchitis	n (%)	2 (1.8)	8 (1.7)	0 (0.0)	8 (1.7)	10 (2.1)
	n (EAIR 100 PY)	0 (0.0)	10 (1.5)	0 (0.0)	ND	10 (1.5)
Constipation	n (%)	2 (1.8)	8 (1.7)	0 (0.0)	8 (1.7)	10 (2.1)
	n (EAIR 100 PY)	0 (0.0)	10 (1.5)	0 (0.0)	ND	10 (1.5)
Contusion	n (%)	3 (2.6)	5 (1.1)	1 (1.9)	6 (1.3)	9 (1.9)
	n (EAIR 100 PY)	0 (0.0)	9 (1.4)	0 (0.0)	ND	9 (1.4)
Gastroenteritis	n (%)	2 (1.8)	5 (1.1)	3 (5.8)	7 (1.5)	9 (1.9)
	n (EAIR 100 PY)	0 (0.0)	9 (1.4)	0 (0.0)	ND	9 (1.4)

Abbreviations: COVID-19=coronavirus disease-19; ND=not determined; OLE=open-label extension; TEAE=treatment-emergent adverse event. % = 100×n/N, where n is the number of subjects with specified AEs.
Notes: AEs are coded using MedDRA dictionary version 26.1. A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. TEAEs

are summarized according to the most recent treatment received prior to the TEAE onset. Subjects with multiple events for a given Preferred Term are counted once. For exposure-adjusted, TEAEs were summarized according to the last treatment they received at the time of data cutoff.

5.4.3.2. Adverse drug reactions (identified by the applicant)

The TEAEs that occurred in ≥10% in the plozasiran 25 mg group and at least 5% more frequently in the plozasiran-treated subjects than placebo-treated subjects were abdominal pain, COVID-19, nasopharyngitis, nausea, and palpitations. After analysis of plausibility, abdominal pain and COVID-19 were removed from the list.

None of the ADRs summarized in Table 50 met the criteria of serious.

Table 47: Adverse Drug Reactions – Pool 1: Phase 3 Pivotal Study

Adverse Reactions	Placebo (N=25)	Plozasiran 25 mg (N=26)
Worsening of glycemic control[a]	2 (8.0)	6 (23.1)
Nasopharyngitis	3 (12.0)	5 (19.2)
Nausea	2 (8.0)	4 (15.4)
Local Injection Site Reaction[b]	1 (4.0)	4 (15.4)
Palpitations	0 (0.0)	3 (11.5)

a Worsening of glycemic control included observed preferred terms: blood glucose increased, diabetes mellitus, gestational diabetes, glucose tolerance impaired, glycosylated haemoglobin increased, and hyperglycaemia. b Local Injection Site Reaction included observed preferred terms: injection site pain and injection site reaction.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

5.4.4.1. Deaths

Treatment-Emergent Adverse Events Leading to Death

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

No deaths occurred during the Phase 3 Study AROAPOC3-3001.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

Four deaths occurred in Pool 2; all were in Study ARO-APOC3-2002. None of the 4 deaths were considered treatment related.

Pool 3: Open-Label Extension Studies

Two deaths occurred in the OLE studies; neither death was considered treatment related.

5.4.4.2. Serious Adverse Events

Pool 1: Phase 3 Pivotal Study, Double-Blinded Period

The overall incidence of SAEs was higher in the placebo group (28.0% subjects) compared to the plozasiran 25 mg (19.2% of subjects) and the plozasiran 50 mg group (8.3% of subjects). Overall, no

dose relationship was observed. The difference in incidence of SAEs between the treatment groups was mostly driven by the Gastrointestinal Disorders SOC (20.0%, 7.7.%, and 4.2% subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively). The majority of SAEs in the Gastrointestinal Disorders SOC were PTs related to pancreatitis as follows:

- Pancreatitis acute: 12.0%, 7.7%, and 0.0% of subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively
- Pancreatitis relapsing: 12.0%, 0.0%, and 4.2% of subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively
- Pancreatitis: 4.0%, 0.0%, and 0.0% of subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively.

No other SAEs were reported in >1 subject in any dose group.

Pool 2: Phase 2/3 Blinded (Placebo-Controlled) Studies

Consistent with Pool 1, the overall incidence of SAEs was higher in the placebo group (12.7% of subjects) compared to the plozasiran 25 mg (8.1% subjects) and plozasiran 10+25+50 mg group (8.1% of subjects). The only PTs reported in more than 1 subject treated with plozasiran were pancreatitis acute (2 subjects in the 25 mg group and 2 subjects in the 50 mg groups), COVID-19 (2 subjects in the 25 mg group and 1 subject in the 50 mg Q12W group), osteoarthritis (1 subject in the plozasiran 10 mg group and 1 subject in the 50 mg Q12W group) and acute kidney injury (AKI; 1 subject in the plozasiran 25 mg group and 1 subject in the 50 mg Q12W group). None of the SAEs were considered treatment-related in the plozasiran group.

The SOCs with the highest incidence of SAEs were Gastrointestinal Disorders, Infections and Infestations, and Cardiac Disorders (occurring in <5%, ≤2.7%, and ≤2.3% of subjects across all treatment groups, respectively), and lower in the treatment group.

Overall results for EAIRs and risk differences showed a similar pattern to the crude incidence TEAE analysis.

Pool 3: Open-Label Extension Studies

At the time of the database cutoff of 08 November 2024 (AROAPOC3-2003) and 01 November 2024 (AROAPOC3-3001), 57 (11.8%) subjects had experienced an SAE, including 6.1%, 10.0%, and 15.4% of subjects in the plozasiran 10, 25 (other), and 50 mg groups, respectively.

Only 3 subjects had an SAE that were considered to be treatment-related (abdominal pain; hospitalization; clear cell renal cell carcinoma). One of these 3 events was a possible SAE (PT: hospitalization) No admission or discharge details were provided, nor any information on a possible cause for the possible hospitalization. Although this event was documented on a CRF, the minimum reporting criteria was not met because the following information was not available: 1) date of the event 2) an adverse event term and 3) seriousness outcome. Reconciliation of this discrepancy is ongoing.

The SOCs with the highest incidence of SAEs across all treatment groups were Neoplasms (2.5%), Cardiac disorders (2.3%), Nervous system disorder (1.9%), Gastrointestinal disorders (1.7%), and Injury, poisoning and procedural complications (1.7%), with no clear pattern or trend.

In comparison to Pool 2, the overall EAIR for any subject in Pool 3 experiencing an SAE was similar (9.1 per 100 PYs) compared to 9.3 per 100 PYs in the plozasiran 25 mg dose in Pool 2. Overall, no SAE by PT had an overall EAIR >0.4 per 100 PYs.

Potential for Renal Injury

siRNA drugs are partially cleared by glomerular filtration. It is known that the proximal tubules reabsorb some of the filtered siRNA and accumulated drug is evident in toxicological studies, described as basophilic stippling; these effects are generally considered non-adverse (Janas 2018). Four cases of AKI from clinical trials were assessment as not related cases to the treatment with plozasiran.

5.4.4.3. Adverse Events of Clinical Interest

Adverse events of special interest (AESI) included:

- SMQs: Hyperglycaemia/New Onset Diabetes Mellitus SMQ and Acute Pancreatitis
- AMQs: Worsening of Glycemic Control, Local Injection Site Reaction (LISR), and Acute Pancreatitis
- FMQs: Dysglycemia-Related (Hyperglycemia, Hypoglycemia, and Diabetic Ketoacidosis), Liver Safety (Hepatic Injury and Hepatic Failure), and Hypersensitivity (Hypersensitivity, Algorithmic Hypersensitivity, and Anaphylactic Reaction)

Each SMQ and AMQ category includes numerous predefined PTs. The SMQ and AMQ categories aim for high sensitivity at the expense of low specificity and, as such, help with hypothesis generation but require substantiation for confidence in interpretation. The SMQ and AMQ assessments evaluated potential plozasiran-related risks that would not, a priori, be expected to differ between placebo-treated subjects and plozasiran-treated subjects, with the exception of injection-related adverse events. The EAIRs with corresponding risk differences between plozasiran-treated and placebo-treated subjects with corresponding 95% CIs were used to identify any risks that may be higher for the plozasiran groups compared to placebo. A summary of risk differences and 95% CIs for the SMQ and AMQs is presented in the Table 51. In Pool 2, EAIRs were reported to account for differences between exposures across subjects and studies for analysis.

Overall, no increased risk was found for Acute Pancreatitis (Narrow).

Table 48: Summary of Risk Differences with 95% Confidence Intervals for AMQ and SMQ TEAEs – Safety Set.

Preferred Term		Pool 1 (Phase 3 Pivotal Study)		Pool 2 (Phase 2/3 Studies)		
		Risk Difference (95% CI)		Risk Difference (95% CI)		
		Plozasiran 25 mg vs Placebo	Plozasiran (25 mg+ 50 mg) vs Placebo	Plozasiran 25 mg vs Placebo	Plozasiran (25 mg+ 50 mg) vs Placebo	Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo
SMQs						
Hyperglycaemia/New Onset Diabetes Mellitus (Narrow)	Incidence	15.1 (-4.3,34.5)	14.0 (-1.7,29.7)	4.0 (-3.1,11.2	8.4 (2.4,14.4)	8.1 (2.5,13.7)
	EAIR (100 PY)	13.3 (-10.9, 37.5)	14.6 (-5.6, 34.8)	3.8 (-5.9, 13.5)	11.4 (2.8, 19.9)	11.2 (3.1, 19.2)
Hyperglycaemia/New Onset Diabetes Mellitus (Broad)	Incidence	18.9 (-1.2, 39.0)	18.0 (1.8, 34.2)	2.5 (-5.1, 10.2)	6.9 (0.4, 13.3)	6.2 (0.1, 12.4)
	EAIR (100 PY)	18.2 (-7.9, 44.3)	20.2(-1.4, 41.8)	2.5 (-8.1, 13.0)	10.2 (0.8, 19.5)	9.5 (0.7,18.4)
Acute Pancreatitis (Narrow)	Incidence	-16.3 (-35.9, 3.3)	-16.0 (-34.4,2.4)	-4.4 (-8.1, -0.6)	-3.4 (-6.9, 0.0)	-3.4 (-6.8, -0.1)
	EAIR (100 PY)	-23.7 (-52.2, 4.7)	-23.5 (-50.7, 3.8)	-6.0 (-11.2, -0.8)	-5.1 (-9.7, -0.5)	-5.0 (-9.4, -0.6)
Acute Pancreatitis (Broad)	Incidence	10.2 (-16.7, 37.0)	6.0 (-17.3, 29.3)	1.3 (-5.3, 8.0)	3.8 (-1.7, 9.4)	2.7 (-2.5, 7.9)
	EAIR (100 PY)	9.3 (-43.6, 62.3)	5.1 (-40.7, 50.9)	0.1 (-10.0, 10.1)	3.7 (-4.7, 12.0)	2.5 (-5.2, 10.3)
AMQs						
Worsening of Glycemic Control	Incidence	11.2 (-7.3, 29.7)	12.0 (-3.4, 27.4)	2.2 (-4.8, 9.2)	7.2 (1.2, 13.2)	7.0 (1.3, 12.7)
	EAIR (100 PY)	13.3 (-10.9, 37.5)	14.6 (-5.6, 34.8)	2.0 (-7.6, 11.7)	10.0 (1.4, 18.7)	10.0 (1.8, 18.2)
Local Injection Site Reaction	Incidence	11.4 (-4.5, 27.2)	6.0 (-5.3, 17.3)	3.2 (-0.5, 6.9)	3.2 (0.6, 5.8)	2.9 (0.6, 5.2)
	EAIR (100 PY)	13.7 (-6.7, 34.1)	6.9 (-7.0, 20.8)	4.1 (-0.6, 8.7)	4.1 (0.7, 7.4)	3.7 (0.7, 6.7)
Acute Pancreatitis	Incidence	-1.4 (-27.6, 24.9)	0.0 (-23.0, 23.0)	-0.7 (-6.8, 5.5)	2.2 (-3.0, 7.4)	1.3 (-3.6, 6.1)
	EAIR (100 PY)	-11.4 (-58.4, 35.5)	-7.4 (-50.5, 35.7)	-3.2 (-12.2, 5.8)	0.9 (-6.7, 8.5)	0.1 (-7.0, 7.2)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable; PY=person-year; TEAE=treatment-emergent adverse event. % = 100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using Chi-square test. Risk difference and respective 95% CI for exposure-adjusted incidence were calculated using Wald's method.

5.4.4.3.1. Hyperglycaemia/New Onset Diabetes Mellitus SMQ

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow)

The incidence and exposure-adjusted incidence of Hyperglycaemia/New Onset Diabetes Mellitus (Narrow) SMQ by PT are summarized in table 52.

The overall incidence of Hyperglycaemia/New Onset Diabetes Mellitus SMQ Narrow events was 8.0%, 23.1%, and 20.8% of subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. Glycosylated hemoglobin increased was the most frequent PT, which occurred in 0%, 11.5%, and 12.5% in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. All other PTs occurred in only 1 subject in any dose group.

Similar trends were observed for the exposure-adjusted analysis. None of the Hyperglycaemia/New Onset Diabetes Mellitus SMQ Narrow PTs had 95% CIs of the risk difference that excluded zero, with the exception of Glycosylated hemoglobin increased.

Table 49: Pool 1: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of SMQ for Hyperglycaemia/New Onset Diabetes Mellitus (Narrow) by Preferred Term (Randomized Period, Safety Set)

						Risk Difference (%) (95% CI)	
Preferred Term		**Placebo (N=25)**	**Plozasiran 25 mg (N=26)**	**Plozasiran 50 mg (N=24)**	**Plozasiran (25 mg+ 50 mg) (N=50)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**
Subjects with Any SMQ TEAEs for Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow)	n (%)	2 (8.0)	6 (23.1)	5 (20.8)	11 (22.0)	15.1 (-4.3, 34.5)	14.0 (-1.7, 29.7)
	EAIR (100 PY)	9.7	23.0	25.8	24.3	13.3 (-10.9, 37.5)	14.6 (-5.6, 34.8)
Blood glucose increased	n (%)	1 (4.0)	1 (3.8)	1 (4.2)	2 (4.0)	-0.2 (-10.8, 10.5)	0.0 (-9.4, 9.4)
	EAIR (100 PY)	4.7	4.2	0.0	2.2	-0.5 (-12.8, 11.8)	-2.5 (-12.6, 7.6)
Diabetes mellitus	n (%)	0 (0.0)	1 (3.8)	1 (4.2)	2 (4.0)	3.8 (-3.5, 11.2)	4.0 (-1.4, 9.4)
	EAIR (100 PY)	0.0	4.2	4.6	4.4	4.2 (-4.0, 12.4)	4.4 (-1.7, 10.5)
Diabetes mellitus inadequate control	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	4.7	2.2	0.0 (0.0, 0.0)	2.2 (-2.1, 6.4)
Gestational diabetes	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5, 11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glucose tolerance impaired	n (%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	-4.0 (-11.7, 3.7)	-4.0 (-11.7, 3.7)
	EAIR (100 PY)	4.7	0.0	0.0	0.0	-4.7 (-14.0, 4.6)	-4.7 (-14.0, 4.6)
Glucose urine present	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glycosylated haemoglobin increased	n (%)	0 (0.0)	3 (11.5)	3 (12.5)	6 (12.0)	11.5 (-0.7, 23.8)	12.0 (3.0, 21.0)
	EAIR (100 PY)	0.0	12.9	14.6	13.7	12.9 (-1.7, 27.4)	13.7 (2.7, 24.7)
Hyperglycaemia	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5, 11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	4.2	0.0	2.2	4.2 (-4.0, 12.5)	2.2 (-2.1, 6.5)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable; PY=patient-year; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using Chi-square test. Risk difference and respective 95% CI for EAIR were calculated using Wald's method.

Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad)

The incidence and exposure-adjusted incidence of Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad) by PT are summarized in Table 53.

The overall incidence of Hyperglycaemia/New Onset Diabetes Mellitus SMQ Broad events was 8.0%, 26.9%, and 25.0% of subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. Glycosylated hemoglobin increased was the most frequent PT, which occurred in 0%, 11.5%, and 12.5% in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. All other PTs occurred in only 1 subject in any dose group.

Similar trends were observed for the exposure-adjusted analysis. Glycosylated hemoglobin increased occurred with a risk difference compared to placebo of 12.9 (95% CI -1.7, 27.4) in the plozasiran 25 mg group and 12.0% (95% CI 3.0, 21.0) in the plozasiran 25+50 mg group. The 95% CIs of the risk difference excluded zero for all other Hyperglycaemia/New Onset Diabetes Mellitus SMQ Broad PTs for both plozasiran dose groups.

Table 50: Pool 1: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of SMQ for Hyperglycaemia/New Onset Diabetes Mellitus (Broad) by Preferred Term (Randomized Period, Safety Set)

						Risk Difference (%) (95% CI)	
Preferred Term		**Placebo (N=25)**	**Plozasiran 25 mg (N=26)**	**Plozasiran 50 mg (N=24)**	**Plozasiran (25 mg+ 50 mg) (N=50)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for Worsening of Glycemic Control	n (%)	2 (8.0)	7 (26.9)	6 (25.0)	13 (26.0)	18.9 (-1.2, 39.0)	18.0 (1.8, 34.2)
	EAIR (100 PY)	9.7	27.9	32.1	29.9	18.2 (-7.9, 44.3)	20.2(-1.4, 41.8)
Blood glucose increased	n (%)	1 (4.0)	1 (3.8)	1 (4.2)	2 (4.0)	-0.2 (-10.8,10.5)	0.0 (-9.4, 9.4)
	EAIR (100 PY)	4.7	4.2	0.0	2.2	-0.5 (-12.8, 11.8)	-2.5 (-12.6, 7.6)
Blood triglycerides increased	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5,11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	4.1	0.0	2.2	4.1 (-3.9, 12.1)	2.2 (-2.1, 6.4)
Dehydration	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	4.7	2.2	0.0 (0.0, 0.0)	2.2 (-2.1, 6.4)
Diabetes mellitus	n (%)	0 (0.0)	1 (3.8)	1 (4.2)	2 (4.0)	3.8 (-3.5,11.2)	4.0 (-1.4, 9.4)
	EAIR (100 PY)	0.0	4.2	4.6	4.4	4.2 (-4.0, 12.4)	4.4 (-1.7, 10.5)
Diabetes mellitus inadequate control	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	4.7	2.2	0.0 (0.0, 0.0)	2.2 (-2.1, 6.4)
Gestational diabetes	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5,11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glucose tolerance impaired	n (%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	-4.0 (-11.7, 3.7)	-4.0 (-11.7, 3.7)
	EAIR (100 PY)	4.7	0.0	0.0	0.0	-4.7 (-14.0, 4.6)	-4.7 (-14.0, 4.6)
Glucose urine present	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glycosylated haemoglobin increased	n (%)	0 (0.0)	3 (11.5)	3 (12.5)	6 (12.0)	11.5 (-0.7, 23.8)	12.0 (3.0, 21.0)
	EAIR (100 PY)	0.0	12.9	14.6	13.7	12.9 (-1.7, 27.4)	13.7 (2.7, 24.7)
Hyperglycaemia	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5,11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	4.2	0.0	2.2	4.2 (-4.0, 12.5)	2.2 (-2.1, 6.5)
Increased appetite	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	4.5	2.1	0.0 (0.0, 0.0)	2.1 (-2.1, 6.3)
Weight increased	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	4.7	2.2	0.0 (0.0, 0.0)	2.2 (-2.1, 6.4)

Abbreviations: CI=Confidence interval; EAIR=Exposure adjusted incidence rate; SMQ=Standardised MedDRA query; PY=Person-Year. EAIR=100*n/PY, where n is the number of subjects with specified adverse events. Note: Adverse events are coded using MedDRA dictionary version 26.1. Note: A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. Note: Subjects with multiple events for a given Preferred Term are counted once. Note: Risk difference and respective 95% CI are calculated using Wald's method. Note: Broad SMQ Analysis incorporates SMQ (Narrow) preferred terms to maximize.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow)

The incidence and exposure-adjusted incidence of Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow) by PT are summarized in Table 54.

In Pool 2, EAIRs were reported to account for differences between exposures across subjects and studies for analysis.

Similar to Pool 1, EAIRs for the Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow) were 12.9, 16.9, 29.0, and 30.4 per 100 PYs in the placebo, plozasiran 25 mg, plozasiran 50 mg Q12W, and plozasiran 50 mg Q24W groups, respectively. The plozasiran 25 mg group and placebo performed similarly as shown by the low risk difference of 3.8% (95% CI -5.9, 13.5). The most common PTs were Type 2 diabetes mellitus and glycosylated hemoglobin increased. The risk difference was low for Type 2 diabetes mellitus for the plozasiran 25 mg (1.1% [95% CI -4.7, 6.9]); however, the 95% CI of the risk differences excluded zero in the plozasiran 25+50 mg group driven by the plozasiran 50 mg dose. No other PTs, including glycosylated hemoglobin increased, had 95% CIs of the risk difference excluding zero.

Table 51: Pool 2: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of SMQ for Hyperglycaemia/New Onset Diabetes Mellitus (Narrow) by Preferred Term (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
Preferred Term		Placebo (N=173)	Plozasiran 10 mg (N=121)	Plozasiran 25 mg (N=148)	Plozasiran 50 mg Q12W (N=146)	Plozasiran 50 mg Q24W (N=66)	Plozasiran (25 mg+ 50 mg) (N=360)	Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)	Plozasiran 25 mg vs Placebo	Plozasiran (25 mg+ 50 mg) vs Placebo	Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo
Subjects with Any AMQ TEAEs for Hyperglycaemia/ New Onset Diabetes Mellitus SMQ (Narrow)	n (%)	17 (9.8)	20 (16.5)	21 (14.2)	30 (20.5)	14 (21.2)	65 (18.1)	85 (17.7)	4.0 (-3.1, 11.2	8.4 (2.4, 14.4)	8.1 (2.5, 13.7)
	EAIR (100 PY)	12.9	23.5	16.9	29.0	30.4	24.1	23.9	3.8 (-5.9, 13.5)	11.4 (2.8, 19.9)	11.2 (3.1, 19.2)
Blood glucose increased	n (%)	2 (1.2)	3 (2.5)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	6 (1.2)	0.1 (-2.3, 2.5)	-0.3 (-2.2, 1.6)	0.2 (-1.6, 2.1)
	EAIR (100 PY)	1.4	3.2	1.6	0.0	0.0	0.7	1.3	0.1 (-2.9, 3.0)	-0.7 (-3.0, 1.5)	0.0 (-2.3, 2.2)
Diabetes mellitus	n (%)	2 (1.2)	3 (2.5)	2 (1.4)	6 (4.1)	1 (1.5)	9 (2.5)	12 (2.5)	0.1 (-2.3,2.5)	1.5 (-0.8,3.7)	1.4 (-0.7,3.6)
	EAIR (100 PY)	1.4	3.2	1.6	5.2	1.9	3.1	3.1	0.1 (-2.9, 3.0)	1.8 (-1.0, 4.7)	1.8 (-0.9, 4.5)
Diabetes mellitus inadequate control	n (%)	0 (0.0)	2 (1.7)	0 (0.0)	1 (0.7)	1 (1.5)	2 (0.6)	4 (0.8)	N/A	0.5 (-0.2,1.3)	0.9 (0.0,1.7)
	EAIR (100 PY)	0.0	2.1	0.0	0.8	1.9	0.7	1.0	0.0	0.7 (-0.3, 1.6)	1.1 (0.0, 2.2)
Gestational diabetes	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.6 (-0.6, 1.9)	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Glucose tolerance impaired	n (%)	1 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	-0.6 (-1.8, 0.5)	-0.6 (-1.7, 0.6)	-0.3 (-1.5, 0.8)
	EAIR (100 PY)	0.7	1.0	0.0	0.0	0.0	0.0	0.3	-0.8 (-2.4, 0.8)	-0.7 (-2.2, 0.7)	-0.4 (-1.8, 1.0)
Glucose urine present	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	N/A	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.)	0 (0.0)	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glycosylated Haemoglobin increased	n (%)	4 (2.3)	6 (5.0)	6 (4.1)	7 (4.8)	2 (3.0)	15 (4.2)	21 (4.4)	1.6 (-2.3, 5.4)	1.9 (-1.1, 5.0)	2.3 (-0.7, 5.3)
	EAIR (100 PY)	2.9	6.4	5.0	6.1	3.9	5.2	5.5	1.9 (-2.8, 6.7)	2.4 (-1.5, 6.3)	2.9 (-0.9, 6.8)
Hyperglycaemia	n (%)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	3 (0.6)	1.3 (-0.5,3.1)	0.9 (-0.1, 1.8)	0.7 (-0.1, 1.4)
	EAIR (100 PY)	0.0	0.0	1.6	0.8	0.0	1.0	0.8	1.6 (-0.6, 3.7)	1.0 (-0.1, 2.2)	0.8 (-0.1, 1.8)
Impaired fasting glucose	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	-0.5 (-1.6, 0.6)	-0.3 (-1.6, 1.0)	-0.4 (-1.6, 0.8)
	EAIR (100 PY)	0.7	0.0	0.0	0.8	0.0	0.3	0.3	0.7 (-2.0, 0.6)	-0.4 (-2.0, 1.3)	-0.5 (-2.0, 1.1)
Latent autoimmune diabetes in adults	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.7 (-0.6, 2.0)	0.3 (-0.3, 0.9)	0.2 (-0.2, 0.6)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.8 (-0.8, 2.4)	1.0 (-0.1, 2.2)	0.8 (-0.1, 1.8)
Type 2 diabetes mellitus	n (%)	7 (4.0)	6 (5.0)	8 (5.4)	14 (9.6)	11 (16.7)	33 (9.2)	39 (8.1)	1.5 (-3.2, 6.2)	5.0 (0.8, 9.2)	3.7 (-0.1, 7.5)
	EAIR (100 PY	5.1	6.5	5.9	12.5	23.1	11.5	10.2	1.1 (-4.7, 6.9)	6.3 (0.9, 11.8)	4.7 (-0.3, 9.6)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; MH=Mantel-Haenszel; NA=not applicable; PY=person-year; Q12W=every 12 weeks; Q24W=every 24 weeks; TEAE=treatment-emergent adverse event. % = 100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using MedDRA dictionary version 26.1. A TEAE was defined as any event which is not present before exposure to study drug or any

event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using CMH test by stratifying with study. Risk difference and respective 95% CI for EAIR were calculated using MH weights by stratifying with study.

Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad)

The incidence and exposure-adjusted incidence of Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad) by PT are summarized in Table 55.

In Pool 2, EAIRs were reported to account for differences between exposures across subjects and studies for analysis.

Similar to Pool 1, EAIRs for the Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad) were 16.2, 23.5, 18.9, 31.2, 32.9 per 100 PYs in the placebo, plozasiran 10 mg, plozasiran 25 mg, plozasiran 50 mg Q12W, and plozasiran 50 mg Q24W groups, respectively. The plozasiran 25 mg group and placebo performed similarly as shown by the low risk difference of 2.5% (95% CI -8.1, 13.0). The most common PTs were Type 2 diabetes mellitus and glycosylated haemoglobin increased. The risk difference was low for Type 2 diabetes mellitus; however, the 95% CI of the risk differences excluded zero in the plozasiran 25+50 mg group driven by the plozasiran 50 mg dose. No other PTs, including glycosylated haemoglobin increased, had 95% CIs of the risk difference excluding zero.

Table 52: Pool 2: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of SMQ for Hyperglycaemia/New Onset Diabetes Mellitus (Broad) by Preferred Term (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
Preferred Term		**Placebo (N=173)**	**Plozasiran 10 mg (N=121)**	**Plozasiran 25 mg (N=148)**	**Plozasiran 50 mg Q12W (N=146)**	**Plozasiran 50 mg Q24W (N=66)**	**Plozasiran (25 mg+ 50 mg) (N=360)**	**Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**	**Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for New Onset Diabetes Mellitus SMQ (Broad)	n (%)	22 (12.7)	20 (16.5)	23 (15.5)	32 (21.9)	15 (22.7)	70 (19.4)	90 (18.7)	2.5 (-5.1,10.2)	6.9 (0.4, 13.3)	6.2 (0.1, 12.4)
	EAIR (100 PY)	16.2	23.5	18.9	31.2	32.9	26.2	25.5	2.5 (-8.1, 13.0)	10.2 (0.8, 19.5)	9.5 (0.7, 18.4)
Acidosis	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
Blood glucose increased	n (%)	2 (1.2)	3 (2.5)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	6 (1.2)	0.1 (-2.3, 2.5)	-0.3 (-2.2, 1.6)	0.2 (-1.6, 2.1)
	EAIR (100 PY)	1.4	3.2	1.6	0.0	0.0	0.7	1.3	0.1 (-2.9, 3.0)	-0.7 (-3.0, 1.5)	0.0 (-2.3, 2.2)
Blood triglycerides increased	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.6 (-0.6, 1.9)	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.7 (-0.7, 2.1)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)
Dehydration	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	-0.5 (-1.6, 0.6)	-0.3 (-1.6, 1.0)	-0.3 (-1.6, 0.9)
	EAIR (100 PY)	0.0	0.0	0.0	0.8	0.0	0.3	0.3	0.0 (0.0, 0.0)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)
Diabetes mellitus	n (%)	2 (1.2)	3 (2.5)	2 (1.4)	6 (4.1)	1 (1.5)	9 (2.5)	12 (2.5)	0.1 (-2.3, 2.5)	1.5 (-0.8, 3.7)	1.4 (-0.7, 3.6)
	EAIR (100 PY)	1.4	3.2	1.6	5.2	1.9	3.1	3.1	0.1 (-2.9, 3.0)	1.8 (-1.0, 4.7)	1.8 (-0.9, 4.5)
Diabetes mellitus inadequate control	n (%)	0 (0.0)	2 (1.7)	0 (0.0)	1 (0.7)	1 (1.5)	2 (0.6)	4 (0.8)	NA	0.5 (-0.2, 1.3)	0.9 (0.0, 1.7)
	EAIR (100 PY)	0.0	2.1	0.0	0.8	1.9	0.7	1.0	0.0 (0.0, 0.0)	0.7 (-0.3, 1.6)	1.1 (0.0, 2.2)
Gestational diabetes	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.6 (-0.6, 1.9)	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glucose tolerance impaired	n (%)	1 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	-0.6 (-1.8, 0.5)	-0.6 (-1.7, 0.6)	-0.3 (-1.5, 0.8)
	EAIR (100 PY)	0.7	1.0	0.0	0.0	0.0	0.0	0.3	-0.8 (-2.4, 0.8)	-0.7 (-2.2, 0.7)	-0.4 (-1.8, 1.0)
Glucose urine present	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	NA	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glycosylated haemoglobin increased	n (%)	4 (2.3)	6 (5.0)	6 (4.1)	7 (4.8)	2 (3.0)	15 (4.2)	21 (4.4)	1.6 (-2.3, 5.4)	1.9 (-1.1, 5.0)	2.3 (-0.7, 5.3)
	EAIR (100 PY)	2.9	6.4	5.0	6.1	3.9	5.2	5.5	1.9 (-2.8, 6.7)	2.4 (-1.5, 6.3)	2.9 (-0.9, 6.8)
Hyperglycaemia	n (%)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	3 (0.6)	1.3 (-0.5, 3.1)	0.9 (-0.1, 1.8)	0.7 (-0.1, 1.4)
	EAIR (100 PY)	0.0	0.0	1.6	0.8	0.0	1.0	0.8	1.6 (-0.6, 3.7)	1.0 (-0.1, 2.2)	0.8 (-0.1, 1.8)
Hyperlipidaemia	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.3)	1 (0.2)	NA	0.3 (-0.3, 0.8)	0.2 (-0.2, 0.6)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	1.9	0.3	0.3	0.0 (0.0, 0.0)	0.3 (-0.3, 0.9)	0.2 (-0.2, 0.7)

Hypoglycaemia	n (%)	1 (0.6)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.6)	2 (0.4)	0.1 (-1.7, 1.8)	0.0 (-1.3, 1.4)	-0.2 (-1.4, 1.1)
	EAIR (100 PY)	0.7	0.0	0.8	0.8	0.0	0.7	0.5	0.1 (-2.0, 2.2)	0.0 (-1.6, 1.7)	-0.2 (-1.8, 1.4)
Impaired fasting glucose	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	-0.5 (-1.6, 0.6)	-0.3 (-1.6, 1.0)	-0.4 (-1.6, 0.8)
	EAIR (100 PY)	0.7	0.0	0.0	0.8	0.0	0.3	0.3	-0.7 (-2.0, 0.6)	-0.4 (-2.0, 1.3)	-0.5 (-2.0, 1.1)
Increased appetite	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	NA	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.0	0.8	0.0	0.3	0.3	0.0 (0.0, 0.0)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)
Latest autoimmune diabetes in adults	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.7 (-0.6, 2.0)	0.3 (-0.3, 0.9)	0.2 (-0.2, 0.6)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.8 (-0.8, 2.4)	0.4 (-0.4, 1.1)	0.3 (-0.3, 0.8)
Loss of consciousness	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
Metabolic acidosis	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
Type 2 diabetes mellitus	n (%)	7 (4.0)	6 (5.0)	8 (5.4)	14 (9.6)	11 (16.7)	33 (9.2)	39 (8.1)	1.5 (-3.2, 6.2)	5.0 (0.8, 9.2)	3.7 (-0.1, 7.5)
	EAIR (100 PY)	5.1	6.5	5.9	12.5	23.1	11.5	10.2	1.1 (-4.7, 6.9)	6.3 (0.9, 11.8)	4.7 (-0.3, 9.6)
Weight decreased	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.3)	1 (0.2)	-0.5 (-1.6, 0.6)	-0.3 (-1.6, 0.9)	-0.4 (-1.6, 0.8)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	1.9	0.3	0.3	0.0 (0.0, 0.0)	0.3 (-0.3, 0.9)	0.2 (-0.2, 0.7)
Weight increased	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	NA	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.0	0.8	0.0	0.3	0.3	0.0 (0.0, 0.0)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; MH=Mantel-Haenszel; NA=not applicable; PY=person-year; Q12W=every 12 weeks; Q24W=every 24 weeks; TEAE=treatment-emergent adverse event. % = 100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using MedDRA dictionary version 26.1. A TEAE was defined as any event which is not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using CMH test by stratifying with study. Risk difference and respective 95% CI for EAIR were calculated using MH weights by stratifying with study. Broad SMQ Analysis incorporates SMQ (Narrow) preferred terms to maximize sensitivity.

Pool 3: Open-Label Extension Studies

Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow)

The exposure-adjusted incidence and incidence of the Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow) by PT are summarized in Table 56.

In the OLE period, the EAIR for the Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow) was 12.7 per 100 PYs in the plozasiran 25 mg group, which was lower than Pool 2 (16.9 per 100 PYs) and similar to placebo (12.9 per 100 PY) in Pool 2. This indicates that variations in glycemic control were mitigatable in real-world practice outside of the confines of the blinded period of the Phase 2/3 studies. The most commonly reported PTs in the plozasiran 25 mg group were Type 2 diabetes mellitus (5.3 per 100 PYs) and diabetes mellitus (2.7 per 100 PYs). The EAIR for glycosylated hemoglobin increased was low (2.0 per 100 PYs).

Table 53: Pool 3: Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of by Preferred Term (OLE Portion, Safety Set) Treatment-Emergent Adverse Events of Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow)

Preferred Term	Plozasiran 25 mg[a] (N=471) EAIR (100 PY)	Plozasiran (10mg+50mg+Other[a]) (N=483) EAIR (100 PY)
Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow)	12.7	13.1
Blood glucose increased	0.3	0.3
Diabetes mellitus	2.7	2.9
Diabetes mellitus inadequate control	0.9	0.9
Glucose tolerance impaired	0.9	0.9
Glycosuria	0.2	0.1
Glycosylated haemoglobin increased	2.0	2.1
Impaired fasting glucose	0.2	0.1
Insulin resistance	0.2	0.1
Type 2 diabetes mellitus	5.3	5.4

Abbreviations: SMQ=Standardised MedDRA query; EAIR=Exposure adjusted incidence rate; PY=Person-Year; OLE=Open-label extension. EAIR=100*n/PY, where n is the number of subjects with specified adverse events. Note: Adverse events are coded using MedDRA dictionary version 26.1. Note: A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. Note: Subjects with multiple events for a given Preferred Term are counted once. a Subjects who take Plozasiran 25mg through the OLE period or switch doses during the OLE period are summarized under Plozasiran Other.

Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad)

In the OLE period, the EAIR for the Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad) was 15.0 per 100 PYs in the plozasiran 25 mg group, which was lower than Pool 2 (18.9 per 100 PYs for the plozasiran 25 mg group and 16.2 per 100 PYs for the placebo group). The most commonly reported PTs in the plozasiran 25 mg group were Type 2 diabetes mellitus (5.3 per 100 PYs) and diabetes mellitus (2.7 per 100 PYs). The EAIR for glycosylated hemoglobin increased was low (2.0 per 100 PYs).

Table 54: Pool 3: Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of by Preferred Term (OLE Portion, Safety Set) Treatment-Emergent Adverse Events of Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Broad)

Preferred Term	Plozasiran 25 mg[a] (N=471) EAIR (100 PY)	Plozasiran (10mg+50mg+Other[a]) (N=483) EAIR (100 PY)
Hyperglycaemia/New Onset Diabetes Mellitus SMQ (Narrow)	15.0	15.4
Blood glucose increased	0.3	0.3
Blood triglyceride increased	0.5	0.4
Dehydration	0.2	0.1
Diabetes mellitus	2.7	2.9
Diabetes mellitus inadequate control	0.9	0.9
Glucose tolerance impaired	0.9	0.9
Glycosuria	0.2	0.1
Glycosylated haemoglobin increased	2.0	2.1
Hyperlipidaemia	0.3	0.3
Hypertriglyceridaemia	0.5	0.4
Hypoglycaemia	0.3	0.3
Impaired fasting glucose	0.2	0.1
Insulin resistance	0.2	0.1
Loss of consciousness	0.2	0.1
Type 2 diabetes mellitus	5.3	5.4
Weight decreased	0.2	0.1
Weight increased	0.3	0.3

Abbreviations: SMQ=Standardised MedDRA query; EAIR=Exposure adjusted incidence rate; PY=Person-Year; OLE=Open-label extension. EAIR=100*n/PY, where n is the number of subjects with specified adverse events.
Note: Adverse events are coded using MedDRA dictionary version 26.1. A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term are counted once. a Subjects who take Plozasiran 25mg through the OLE period or switch doses during the OLE period are summarized under Plozasiran Other. Broad SMQ Analysis incorporates SMQ (Narrow) preferred terms to maximize sensitivity.

5.4.4.3.2. Acute Pancreatitis SMQ

Severe hypertriglyceridemia can result in a range of abdominal symptomatology (Fortson 1995). Those with severe forms of chylomicronemia are at risk for acute pancreatitis, which is the most serious complication associated with sustained hypertriglyceridemia (Baass 2020; Murphy 2013). This condition can be recurrent and may lead to complications such as diabetes due to islet cell destruction in the pancreas and exocrine pancreatic insufficiency (Whitcomb 2006). Severe episodes of pancreatitis often require hospitalization, frequently with admission to the intensive care unit, and these can be fatal (Nawaz 2015; Wang 2017). Accordingly, the incidence of possible pancreatitis and related abdominal events were outcomes of clinical interest to the Sponsor. However, it is important to note that the symptoms are nonspecific and, as such, the Sponsor used blinded, expert adjudication to identify cases of definitive acute pancreatitis, which was used as an efficacy endpoint in the pivotal Phase 3 study AROAPOC3-3001.

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

Acute Pancreatitis SMQ (Narrow)

The incidence and exposure-adjusted incidence of Acute Pancreatitis SMQ (Narrow) by PT are summarized for Pool 1 in Table 58.

Overall, the incidence of Acute Pancreatitis SMQ (Narrow) was low in the plozasiran groups (2 subjects in each the 25 mg [7.7%] and 50 mg [8.3%] groups) compared to the placebo group (6 subjects, 24%). Pancreatitis acute was the most frequent PT, which was reported in 12%, 7.7%, and 0% in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively.

Similar trends were observed for the exposure-adjusted analysis. Overall, the lower incidence and EAIRs in the plozasiran groups is consistent with the statistically significant reduction observed with blinded adjudication in the pivotal study.

Table 55: Pool 1: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events by Preferred Term of SMQ for Acute Pancreatitis (Narrow) (Randomized Period, Safety Set)

						Risk Difference (%)(95% CI)	
Preferred Term		Placebo (N=25) n (%)	Plozasiran 25mg (N=26) n (%)	Plozasiran 50mg (N=24) n (%)	Plozasiran (25mg+50mg) (N=50) n (%)	Plozasiran 25mg vs Placebo	Plozasiran (25mg+50mg) vs Placebo
Acute Pancreatitis SMQ (Narrow)	n (%)	6 (24.0)	2 (7.7)	2 (8.3)	4 (8.0)	-16.3 (-35.9, 3.3)	-16.0 (-34.4, 2.4)
	EAIR (100 PY)	32.3	8.5	9.1	8.8	-23.7 (-52.2, 4.7)	-23.5 (-50.7, 3.8)
Pancreatitis	n (%)	2 (8.0)	0 (0.0)	1 (4.2)	1 (2.0)	-8.0 (-18.6, 2.6)	-6.0 (-17.3, 5.3)
	EAIR (100 PY)	9.8	0.0	4.5	2.1	-9.8 (-23.4, 3.8)	-7.7 (-21.9, 6.6)
Pancreatitis acute	n (%)	3 (12.0)	2 (7.7)	0 (0.0)	2 (4.0)	-4.3 (-20.7, 12.0)	-8.0 (-21.8, 5.8)
	EAIR (100 PY)	14.7	8.5	0.0	4.4	-6.1 (-26.5, 14.3)	-10.3 (-27.9, 7.4)
Pancreatitis relapsing	n (%)	3 (12.0)	0 (0.0)	1 (4.2)	1 (2.0)	-12.0 (-24.7, 0.7)	-10.0 (-23.3, 3.3)
	EAIR (100 PY)	14.7	0.0	4.5	2.1	-14.7 (-31.2, 1.9)	-12.5 (-29.6, 4.6)

Abbreviations: CI=Confidence interval; EAIR=Exposure adjusted incidence rate; PY=Person-Year; SMQ=Standardised MedDRA query. EAIR=100*n/PY, where n is the number of subjects with specified adverse events. % = 100 x n/N, where n is the number of subjects with specified adverse events. Note: Adverse events are coded using MedDRA dictionary version 26.1. A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term are counted once. Risk difference and 95% CI are calculated using Chi-square test and Wald's method.

Acute Pancreatitis SMQ (Broad)

The overall incidence of Acute Pancreatitis SMQ (Broad) events was 36.0%, 46.2%, and 37.5% of subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively, demonstrating the lack of specificity in this SMQ. Abdominal pain was the most frequent PT, which occurred in 20%, 26.9%, and 25.0% in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. Similar trends were observed for the exposure-adjusted analysis.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

Acute Pancreatitis SMQ (Narrow)

In Pool 2, EAIRs were reported to account for differences between exposures across subjects and studies for analysis.

Similar to Pool 1, EAIR risk differences for plozasiran dose groups versus placebo were low and none of the 95% CIs of the risk difference excluded zero. Pancreatitis acute was the most frequent PT, which occurred with a risk difference compared to placebo of -1.8 % (95% CI -5.5, 2.0) in the plozasiran 25 mg group and -1.9 % (95% CI -4.9, 1.1) in the plozasiran 25+50 mg group.

Acute Pancreatitis SMQ (Broad)

In Pool 2, EAIRs were reported to account for differences between exposures across subjects and studies for analysis.

Similar to Pool 1, EAIR risk differences for plozasiran dose groups versus placebo were low. Abdominal pain, nausea, and lipase increased were the most frequent PTs, which occurred with a risk difference for the plozasiran 25 mg group compared to placebo of -0.7% (95% CI -6.4, 5.0), 4.0 (95% CI -0.7, 8.7), and 2.1 (95% CI -2.3, 6.5), respectively. Risk differences for the plozasiran 25+50 mg groups for abdominal pain, nausea and lipase were similar to the plozasiran 25 mg group.

Pool 3: Phase 2/3 Placebo-Controlled, Double-Blind Studies

Acute Pancreatitis SMQ (Narrow)

In the OLE period, the EAIR for the Acute Pancreatitis (Narrow) SMQ events was 0.3 per 100 PYs in the plozasiran 25 mg group, which was lower than Pool 2 (1.6 per 100 PYs).

Acute Pancreatitis SMQ (Broad)

In the OLE period, EAIR for the Acute Pancreatitis (Broad) SMQ was 5.6 per 100 PYs in the plozasiran 25 mg group, which was lower than Pool 2 (17 per 100 PYs). The most frequently reported PTs were abdominal pain (1.8 per 100 PYs), lipase increase (1.7 per 100 PYs) nausea (1.2 per 100 PYs), and vomiting (1.1 per 100 PYs).

5.4.4.3.3. Worsening of Glycemic Control AMQ

Previous studies suggested that therapies that reduce TGs may lead to worsening of glycemic control in vulnerable patients with preexisting diabetes, or at risk of diabetes, such as subjects with metabolic syndrome (Goldie 2016; Gouni-Berthold 2021; Ooba 2017; Sabatine 2004). This could plausibly be caused by the sustained increase in delivery of dietary free fatty acids and glycerol following improved hydrolysis of circulating TG-containing particles, especially postprandially. Patients with FCS can also become diabetic due to loss of islet cell mass caused by recurrent or severe pancreatitis. Accordingly, worsening of glycemic control was an outcome of special interest.

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

The incidence and exposure-adjusted incidence of Worsening of Glycemic Control AMQ by PT are summarized in table 59.

Overall, the incidence of Worsening of Glycemic Control AMQ PTs occurred in 8.0% of subjects in the placebo group, 19.2% of subjects in the plozasiran 25 mg group, and 20.8% of subjects in the plozasiran 50 mg group. Glycosylated hemoglobin increased was the most frequent PT, which occurred in 0% of subjects in the placebo group, 11.5% of subjects in the plozasiran 25 mg group, and 12.5% of subjects in the plozasiran 50 mg group. All other PTs occurred in only 1 subject in any dose group.

Similar trends were observed for the exposure-adjusted analysis. Glycosylated hemoglobin increased occurred with a risk difference compared to placebo of 12.9% (95% CI -1.7, 27.4) in the plozasiran 25 mg group and 13.7% (95% CI 2.7, 24.7) in the plozasiran 25+50 mg group.

Overall, the effects of plozasiran on glycemic control were most apparent in subjects with already compromised glucose tolerance (those with pre-diabetes or diabetes). Among 43 subjects with normoglycemia at baseline (HbA1c <5.7%) and 14 subjects with prediabetes at baseline (HbA1c ≥ 5.7% and <6.5%), incidences of TEAEs indicating worsening of diabetes and other evidence of worsening glycemic control (excursions to HbA1c ≥6.5% and new onset diabetes) were generally similar for placebo and plozasiran treatment groups. Clinically confirmed new onset diabetes mellitus at baseline in subjects with normoglycemia occurred in 1 subject (placebo-treated) and in 3 subjects with prediabetes (2 subjects in the plozasiran 25 mg group and 1 subject in the plozasiran 50 mg group. Of

the 27 subjects with diabetes at baseline (HbA1c ≥6.5%) incidences of TEAEs indicating worsening of diabetes was higher in the plozasiran-treated subjects (60% in the plozasiran 25 mg and 75% in the plozasiran 50 mg group) compared to placebo (11.1%).

Table 56: Pool 1: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of AMQ for Worsening of Glycemic Control by Preferred Term (Randomized Period, Safety Set).

						Risk Difference (%) (95% CI)	
Preferred Term		**Placebo (N=25)**	**Plozasiran 25 mg (N=26)**	**Plozasiran 50 mg (N=24)**	**Plozasiran (25 mg+ 50 mg) (N=50)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for Worsening of Glycemic Control	n (%)	2 (8.0)	5 (19.2)	5 (20.8)	10 (20.0)	11.2 (-7.3, 29.7)	12.0 (-3.4, 27.4)
	EAIR (100 PY)	9.7	23.0	25.8	24.3	13.3 (-10.9, 37.5)	14.6 (-5.6, 34.8)
Blood glucose increased	n (%)	1 (4.0)	1 (3.8)	1 (4.2)	2 (4.0)	-0.2 (-10.8, 10.5)	0.0 (-9.4, 9.4)
	EAIR (100 PY)	4.7	4.2	0.0	2.2	-0.5 (-12.8, 11.8)	-2.5 (-12.6, 7.6)
Diabetes mellitus	n (%)	0 (0.0)	1 (3.8)	1 (4.2)	2 (4.0)	3.8 (-3.5, 11.2)	4.0 (-1.4, 9.4)
	EAIR (100 PY)	0.0	4.2	4.6	4.4	4.2 (-4.0, 12.4)	4.4 (-1.7, 10.5)
Diabetes mellitus inadequate control	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	4.7	2.2	0.0 (0.0, 0.0)	2.2 (-2.1, 6.4)
Glucose tolerance impaired	n (%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	-4.0 (-11.7, 3.7)	-4.0 (-11.7, 3.7)
	EAIR (100 PY)	4.7	0.0	0.0	0.0	-4.7 (-14.0, 4.6)	-4.7 (-14.0, 4.6)
Glucose urine present	n (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (2.0)	NA	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glycosylated haemoglobin increased	n (%)	0 (0.0)	3 (11.5)	3 (12.5)	6 (12.0)	11.5 (-0.7, 23.8)	12.0 (3.0, 21.0)
	EAIR (100 PY)	0.0	12.9	14.6	13.7	12.9 (-1.7, 27.4)	13.7 (2.7, 24.7)
Hyperglycaemia	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5, 11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	4.2	0.0	2.2	4.2 (-4.0, 12.5)	2.2 (-2.1, 6.5)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable; PY=patient-year; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using Chi-square test. Risk difference and respective 95% CI for EAIR were calculated using Wald's method.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

The incidence and exposure-adjusted incidence of Worsening of Glycemic Control AMQ by PT are summarized in Table 60.

Similar to Pool 1, EAIRs for the Worsening of Glycemic Control AMQ were 13.7 per 100 PYs in the placebo group, 16.0 per 100 PYs in the plozasiran 25 mg group, and 29.0 per 100 PYs in the plozasiran 50 mg Q12W group. The most common PTs were Type 2 diabetes mellitus and glycosylated hemoglobin increased. The risk difference was low for Type 2 diabetes mellitus; however, the 95% CI of the risk differences excluded zero in the plozasiran 25+50 mg group driven by the plozasiran 50 mg dose. No other PTs, including glycosylated hemoglobin increased, had 95% CIs of the risk difference excluding zero.

An additional analysis was completed to assess the effects of baseline glycemic status (i.e., baseline HbA1c levels) on excursion of HbA1c levels, TEAEs of indicative of worsening of diabetes, new diabetes medications added during study and new onset diabetes. Overall, the effects of plozasiran on glycemic control were most apparent in subjects with already compromised glucose tolerance (those with pre-diabetes or diabetes). Among 176 subjects with normoglycemia at baseline (HbA1c <5.7%), incidences of TEAEs indicating worsening of diabetes and other evidence of worsening glycemic control (excursions to HbA1c ≥6.5% and new onset diabetes) were generally similar in the plozasiran groups compared to placebo. Of the 176 subjects with normoglycemia at baseline, clinically confirmed new

onset diabetes mellitus occurred in 2 (4.2%) placebo-treated subjects and 0.0% in plozasiran-treated subjects. Of the 198 subjects with prediabetes at baseline (HbA1c ≥5.7% to <6.5%, clinically confirmed new onset diabetes mellitus occurred in 0.0% of placebo-treated subjects and 13 subjects with prediabetes (2.5%, 9.3%, 15.4%, and 9.1% in the plozasiran 10 mg, 25 mg, 50 mg Q12W and 50 mg Q24W groups, respectively). Of the 280 subjects with diabetes at baseline (HbA1c ≥6.5%) incidences of TEAEs indicating worsening of diabetes was higher in the plozasiran-treated subjects (31.6% in the plozasiran 10+25+50 mg group) compared to placebo (16.9%). The number of subjects with new diabetic medications added was generally similar across the treatment groups in diabetic subjects at baseline.

Table 57: Pool 2: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of AMQ for Worsening of Glycemic Control by Preferred Term (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
Preferred Term		**Placebo (N=173)**	**Plozasiran 10 mg (N=121)**	**Plozasiran 25 mg (N=148)**	**Plozasiran 50 mg Q12W (N=146)**	**Plozasiran 50 mg Q24W (N=66)**	**Plozasiran (25 mg+ 50 mg) (N=360)**	**Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**	**Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for Worsening of Glycemic Control	n (%)	18 (10.4)	20 (16.5)	19 (12.8)	30 (20.5)	14 (21.2)	63 (17.5)	83 (17.3)	2.2(-4.8, 9.2)	7.2 (1.2, 13.2)	7.0 (1.3, 12.7)
	EAIR (100 PY)	13.7	23.5	16.0	29.0	30.4	23.7	23.6	2.0 (-7.6, 11.7)	10.0 (1.4, 18.7)	10.0 (1.8, 18.2)
Blood glucose increased	n (%)	2 (1.2)	3 (2.5)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	6 (1.2)	0.1 (-2.3, 2.5)	-0.3 (-2.2, 1.6)	0.2 (-1.6, 2.1)
	EAIR (100 PY)	1.4	3.2	1.6	0.0	0.0	0.7	1.3	0.1 (-2.9, 3.0)	-0.7 (-3.0, 1.5)	0.0 (-2.3, 2.2)
Diabetes mellitus	n (%)	2 (1.2)	3 (2.5)	2 (1.4)	6 (4.1)	1 (1.5)	9 (2.5)	12 (2.5)	0.1 (-2.3, 2.5)	1.5 (-0.8, 3.7)	1.4 (-0.7, 3.6)
	EAIR (100 PY)	1.4	3.2	1.6	5.2	1.9	3.1	3.1	0.1 (-2.9, 3.0)	1.8 (-1.0, 4.7)	1.8 (-0.9, 4.5)
Diabetes mellitus inadequate control	n (%)	0 (0.0)	2 (1.7)	0 (0.0)	1 (0.7)	1 (1.5)	2 (0.6)	4 (0.8)	NA	0.5 (-0.2, 1.3)	0.9 (0.0, 1.7)
	EAIR (100 PY)	0.0	2.1	0.0	0.8	1.9	0.7	1.0	0.0 (0.0, 0.0)	0.7 (-0.3, 1.6)	1.1 (0.0, 2.2)
Glucose tolerance impaired	n (%)	1 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	-0.6 (-1.8, 0.5)	-0.6 (-1.7, 0.6)	-0.3 (-1.5, 0.8)
	EAIR (100 PY)	0.7	1.0	0.0	0.0	0.0	0.0	0.3	-0.8 (-2.4, 0.8)	-0.7 (-2.2, 0.7)	-0.4 (-1.8, 1.0)
Glucose urine present	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	NA	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Glycosylated haemoglobin increased	n (%)	4 (2.3)	6 (5.0)	6 (4.1)	7 (4.8)	2 (3.0)	15 (4.2)	21 (4.4)	1.6 (-2.3, 5.4)	1.9 (-1.1, 5.0)	2.3 (-0.7, 5.3)
	EAIR (100 PY)	2.9	6.4	5.0	6.1	3.9	5.2	5.5	1.9 (-2.8, 6.7)	2.4 (-1.5, 6.3)	2.9 (-0.9, 6.8)
Hyperglycaemia	n (%)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	3 (0.6)	1.3 (-0.5, 3.1)	0.9 (-0.1, 1.8)	0.7 (-0.1, 1.4)
	EAIR (100 PY)	0.0	0.0	1.6	0.8	0.0	1.0	0.8	1.6 (-0.6, 3.7)	1.0 (-0.1, 2.2)	0.8 (-0.1, 1.8)
Impaired fasting glucose	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	-0.5 (-1.6, 0.6)	-0.3 (-1.6, 1.0)	-0.4 (-1.6, 0.8)
	EAIR (100 PY)	0.7	0.0	0.0	0.8	0.0	0.3	0.3	-0.7 (-2.0, 0.6)	-0.4 (-2.0, 1.3)	-0.5 (-2.0, 1.1)
Metabolic acidosis	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
Type 2 diabetes mellitus	n (%)	7 (4.0)	6 (5.0)	8 (5.4)	14 (9.6)	11 (16.7)	33 (9.2)	39 (8.1)	1.5 (-3.2, 6.2)	5.0 (0.8, 9.2)	3.7 (-0.1, 7.5)
	EAIR (100 PY)	5.1	6.5	5.9	12.5	23.1	11.5	10.2	1.1 (-4.7, 6.9)	6.3 (0.9, 11.8)	4.7 (-0.3, 9.6)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; MH=Mantel-Haenszel; NA=not applicable; PY=person-year; Q12W=every 12 weeks; Q24W=every 24 weeks; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event which is not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using CMH test

by stratifying with study. Risk difference and respective 95% CI for EAIR were calculated using MH weights by stratifying with study.

Pool 3: Open-Label Extension Studies

The exposure-adjusted incidence and incidence of the Worsening of Glycemic Control AMQ by PT are summarized in Table 61.

In the OLE period, EAIR for the Worsening of Glycemic Control AMQ was 12.7 per 100 PYs in the plozasiran 25 mg group, which was lower than Pool 2 (16.0 per 100 PYs). The most commonly reported PTs were Type 2 diabetes mellitus (5.4 per 100 PYs) and diabetes mellitus (2.9 per 100 PYs). The EAIR for glycosylated hemoglobin increased was low (2.1 per 100 PYs).

Table 58: Pool 3: Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events of AMQ for Worsening of Glycemic Control by Preferred Term (OLE Portion, Safety Set)

Preferred Term	Plozasiran 25 mg[a] (N=471) EAIR (100 PY)	Plozasiran (10 mg+ 50 mg+ Other[a]) (N=483) EAIR (100 PY)
Subjects with any AMQ TEAEs for Worsening of Glycemic Control	12.7	13.1
Blood glucose increased	0.3	0.3
Diabetes mellitus	2.7	2.9
Diabetes mellitus inadequate control	0.9	0.9
Glucose tolerance impaired	0.9	0.9
Glycosuria	0.2	0.1
Glycosylated haemoglobin increased	2.0	2.1
Impaired fasting glucose	0.2	0.1
Insulin resistance	0.2	0.1
Type 2 diabetes mellitus	5.3	5.4

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PY=person-year; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event which was not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. TEAEs were summarized according to the most recent treatment received prior to the TEAE onset. Subjects with multiple events for a given Preferred Term were counted once.

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

The incidence and exposure-adjusted incidence of LISR AMQs by PT are summarized in Table 62.

Overall, the incidence of LISR AMQ PTs occurred in 4.0% of subjects in the placebo group, 15.4% of subjects in the plozasiran 25 mg group, and 4.2% of subjects in the plozasiran 50 mg group. Injection site pain was the most frequent PT and occurred at a higher incidence in the plozasiran 25 mg group (7.7% of subjects) compared to placebo (4.0% of subjects). The only other PT reported (injection site reaction) occurred in 2 (7.7%) subjects in the plozasiran 25 mg group.

Table 59: Pool 1: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events by Preferred Term of AMQ for Local Injection Site Reaction (Randomized Period, Safety Set)

						Risk Difference (%) (95% CI)	
Preferred Term		**Placebo (N=25)**	**Plozasiran 25 mg (N=26) n (%)**	**Plozasiran 50 mg (N=24) n (%)**	**Plozasiran (25 mg+ 50 mg) (N=50) n (%)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for Local Injection Site Reaction	n (%)	1 (4.0)	4 (15.4)	1 (4.2)	5 (10.0)	11.4 (-4.5, 27.2)	6.0 (-5.3, 17.3)
	EAIR (100 PY)	4.8	18.5	4.7	11.7	13.7 (-6.7, 34.1)	6.9 (-7.0, 20.8)
Injection site pain	n (%)	1 (4.0)	2 (7.7)	1 (4.2)	3 (6.0)	3.7 (-9.1, 16.5)	2.0 (-8.1, 12.1)
	EAIR (100 PY)	4.8	8.8	4.7	6.9	4.0 (-11.4, 19.5)	2.1 (-10.1, 14.2)
Injection site reaction	n (%)	0 (0.0)	2 (7.7)	0 (0.0)	2 (4.0)	7.7 (-2.6, 17.9)	4.0 (-1.4, 9.4)
	EAIR (100 PY)	0.0	8.5	0.0	4.4	8.5 (-3.3, 20.2)	4.4 (-1.7, 10.4)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; PY=person-year; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event which is not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using Chi-square test. Risk difference and respective 95% CI for exposure-adjusted incidence were calculated using Wald's method.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

The incidence and exposure-adjusted incidence of the LISR AMQ by PT for Pool 2 are summarized in Table 63.

Similar to Pool 1 (Section 5.9.5.1), the EAIRs for LISR were higher across the plozasiran groups (5.9 per 100 PYs in the plozasiran 25 mg group and 5.2 per 100 PYs in the 50 mg Q12W plozasiran group) compared to 1.4 per 100 PYs in the placebo group. Similar to Pool 1, the most common PT was injection site pain. The risk difference was low for injection site pain and the 95% CI did not exclude zero (1.9% [95% CI -0.9, 4.7]) in the plozasiran 25 mg group. Injection site erythema occurred in 1 subject in the plozasiran 25 mg group and 2 subjects in each of the plozasiran 50 mg groups. Risk differences of injection site erythema did not exclude zero in the plozasiran 25 mg group but did exclude zero in the plozasiran 25+50 mg group. Too few subjects experienced erythema to determine a clinically meaningful difference between plozasiran and placebo.

Table 60: Pool 2: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events by Preferred Term of AMQ for Local Injection Site Reaction (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
Preferred Term		**Placebo (N=173)**	**Plozasiran 10 mg (N=121)**	**Plozasiran 25 mg (N=148)**	**Plozasiran 50 mg Q12W (N=146)**	**Plozasiran 50 mg Q24W (N=66)**	**Plozasiran (25 mg+ 50 mg) (N=360)**	**Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**	**Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for LISR	n (%)	2 (1.2)	3 (2.5)	7 (4.7)	6 (4.1)	2 (3.0)	15 (4.2)	18 (3.7)	3.2 (-0.5, 6.9)	3.2 (0.6, 5.8)	2.9 (0.6, 5.2)
	EAIR (100 PY)	1.4	3.2	5.9	5.2	4.0	5.3	4.8	4.1 (-0.6, 8.7)	4.1 (0.7, 7.4)	3.7 (0.7, 6.7)
Injection site erythema	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.4)	2 (3.0)	5 (1.4)	5 (1.0)	0.7 (-0.6, 2.0)	1.4 (0.2, 2.6)	1.0 (0.1, 1.9)
	EAIR (100 PY)	0.0	0.0	0.8	1.7	4.0	1.7	1.3	0.8 (-0.8, 2.4)	1.7 (0.2, 3.3)	1.3 (0.2, 2.4)
Injection site pain	n (%)	1 (0.6)	3 (2.5)	4 (2.7)	3 (2.1)	0 (0.0)	7 (1.9)	10 (2.1)	1.9 (-0.9, 4.7)	1.5 (-0.4, 3.3)	1.7 (0.0, 3.4)
	EAIR (100 PY)	0.7	3.2	3.3	2.6	0.0	2.4	2.6	2.4 (-1.1, 5.8)	1.8 (-0.5, 4.1)	2.1 (0.0, 4.3)
Injection site pruritus	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	-0.6 (-1.7, 0.6)	-0.2 (-1.5, 1.0)	-0.4 (-1.6, 0.8)
	EAIR (100 PY)	0.7	0.0	0.0	0.8	0.0	0.3	0.3	-0.7 (-2.2, 0.7)	-0.3 (-1.8, 1.2)	-0.4 (-1.9, 1.0)
Injection site reaction	n (%)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.7)	0 (0.0)	3 (0.8)	3 (0.6)	1.2 (-0.5, 3.0)	0.8 (-0.1, 1.8)	0.7 (0.0, 1.5)
	EAIR (100 PY)	0.0	0.0	1.6	0.8	0.0	1.0	0.8	1.5 (-0.6, 3.5)	1.0 (-0.1, 2.1)	0.9 (-0.1, 1.9)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; EAIR=exposure-adjusted incidence rate; LISR=local injection site reaction; MedDRA=Medical Dictionary for Regulatory Activities; MH=Mantel-Haenszel; PY=person-year; Q12W=every 12 weeks; Q24W=every 24 weeks; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using Cochran-Mantel-Haenszel (CMH) test by stratifying with study. Risk difference and respective 95% CI for exposure-adjusted incidence were calculated using MH weights by stratifying with study.

Pool 3: Open-Label Extension Studies

In the OLE period, EAIR for the LISR AMQ was 2.1 per 100 PYs in the plozasiran 25 mg group, which was lower than Pool 2 (5.9 per 100 PYs). The most commonly reported PT was injection site pain (1.1 per 100 PYs).

Table 61: Pool 3: Overview of Treatment-Emergent-Adverse Events by Exposure-Adjusted Incidence for Local Injection Site Reaction (OLE Portion, Safety Set)

Preferred Term	**Plozasiran 25 mg[a] (N=471) EAIR (100 PY)**	**Plozasiran 10 mg+ 50 mg Other[a] (N=483) EAIR (100 PY)**
Subjects with any AMQ TEAEs for LISR	2.1	2.1
Injection site bruising	0.5	0.4
Injection site discolouration	0.3	0.3
Injection site erythema	0.2	0.1
Injection site pain	1.1	1.1
Injection site pruritus	0.2	0.1
Injection site rash	0.2	0.1
Injection site reaction	0.2	0.1

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; EAIR=exposure adjusted incidence rate; LISR=local injection site reactions MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PY=person-year; TEAE=treatment-emergent adverse event. %=100×n/N, where n when the number of subjects

with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. TEAEs were summarized according to the most recent treatment received prior to the TEAE onset. Subjects with multiple events for a given Preferred Term were counted once.

5.4.4.3.4. Acute Pancreatitis AMQ

Severe hypertriglyceridemia can result in a range of abdominal symptomatology (Fortson 1995). Those with severe forms of chylomicronemia are at risk for acute pancreatitis, which is the most serious complication associated with sustained hypertriglyceridemia (Baass 2020; Murphy 2013). This condition can be recurrent and may lead to complications such as diabetes due to islet cell destruction in the pancreas and exocrine pancreatic insufficiency (Whitcomb 2006). Severe episodes of pancreatitis often require hospitalization, frequently with admission to the intensive care unit, and these can be fatal (Nawaz 2015; Wang 2017). Accordingly, the incidence of possible pancreatitis and related abdominal events were outcomes of special interest. However, it is important to note that the symptoms are nonspecific and, as such, blinded, expert adjudication to identify cases of definitive acute pancreatitis were used, which was used as an efficacy endpoint in the pivotal Phase 3 study AROAPOC3-3001.

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

The incidence and exposure-adjusted incidence of Acute Pancreatitis AMQ by PT are summarized for Pool 1 in Table 65.

Overall, the incidence of the AMQ TEAEs for Acute Pancreatitis was similar across the treatment groups: 36.0% of subjects in the placebo group, 34.6% of subjects in the plozasiran 25 mg group, and 37.5% of subjects for the plozasiran 50 mg group. The EAIRs of the Acute Pancreatitis AMQ were similar in the plozasiran groups (44.8 per 100 PYs in the plozasiran 25 mg group and 53.6 per 100 PYs in the 50 mg Q12W plozasiran group) compared to placebo (56.2 per 100 PYs). Abdominal pain was the most frequent PT, which occurred in 20.0%, 26.9%, and 25.0% of subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. Notably, all pancreatitis PTs occurred to a lesser extent in the plozasiran groups compared to the placebo group.

Similar trends were observed for the EAIR of abdominal pain (27.2, 32.3, and 33.9 per 100 PYs in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively). Abdominal pain occurred with a risk difference compared to placebo of 5.0% (95% CI -28.7, 38.8) in the plozasiran 25 mg group and 5.8% (95% CI 24.1, 35.6) in the plozasiran 25+50 mg group.

Table 62: Pool 1: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events by Preferred Term of AMQ for Acute Pancreatitis (Randomized Period, Safety Set)

						Risk Difference (%) (95% CI)	
Preferred Term		**Placebo (N=25)**	**Plozasiran 25 mg (N=26) n (%)**	**Plozasiran 50 mg (N=24) n (%)**	**Plozasiran (25 mg+ 50 mg) (N=50) n (%)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for Acute Pancreatitis	n (%)	9 (36.0)	9 (34.6)	9 (37.5)	18 (36.0)	-1.4 (-27.6, 24.9)	0.0 (-23.0, 23.0)
	EAIR (100 PY)	56.2	44.8	53.6	48.8	-11.4 (-58.4, 35.5)	-7.4 (-50.5, 35.7)
Abdominal pain	n (%)	5 (20.0)	7 (26.9)	6 (25.0)	13 (26.0)	6.9 (-16.2, 30.1)	6.0 (-13.8, 25.8)
	EAIR (100 PY)	27.2	32.3	33.9	33.0	5.0 (-28.7, 38.8)	5.8 (-24.1, 35.6)
Abdominal pain upper	n (%)	1 (4.0)	0 (0.0)	2 (8.3)	2 (4.0)	-4.0 (-11.7, 3.7)	0.0 (-9.4, 9.4)
	EAIR (100 PY)	4.7	0.0	9.5	4.4	-4.7 (-13.9, 4.5)	-0.3 (-11.3, 10.7)
Lipase increased	n (%)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.0)	3.8 (-3.5, 11.2)	2.0 (-1.9, 5.9)
	EAIR (100 PY)	0.0	4.1	0.0	2.2	4.1 (-4.0, 12.3)	2.2 (-2.1, 6.4)
Pancreatitis	n (%)	2 (8.0)	0 (0.0)	1 (4.2)	1 (2.0)	-8.0 (-18.6, 2.6)	-6.0 (-17.3, 5.3)
	EAIR (100 PY)	9.8	0.0	4.5	2.1	-9.8 (-23.4, 3.8)	-7.7 (-21.9, 6.6)
Pancreatitis acute	n (%)	3 (12.0)	2 (7.7)	0 (0.0)	2 (4.0)	-4.3 (-20.7, 12.0)	-8.0 (-21.8, 5.8)
	EAIR (100 PY)	14.7	8.5	0.0	4.4	-6.1 (-26.5, 14.3)	-10.3 (-27.9, 7.4)
Pancreatitis relapsing	n (%)	3 (12.0)	0 (0.0)	1 (4.2)	1 (2.0)	-12.0 (-24.7, 0.7)	-10.0 (-23.3, 3.3)
	EAIR (100 PY)	14.7	0.0	4.5	2.1	-14.7 (-31.2, 1.9)	-12.5 (-29.6, 4.6)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; PY=person-year; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event that is not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using Chi-square test. Risk difference and respective 95% CI for exposure-adjusted incidence were calculated using Wald's method.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

The incidence and exposure-adjusted incidence of Acute Pancreatitis AMQ by PT are summarized for Pool 2 in Table 66.

In Pool 2, EAIRs were reported to account for differences between exposures across subjects and studies for analysis.

Similar to Pool 1, the EAIRs of the Acute Pancreatitis AMQ were 13.0 per 100 PYs in the placebo group, 12.1 per 100 PYs in the plozasiran 25 mg group, and 21.5 per 100 PYs in the plozasiran 50 mg Q12W group. Similar to Pool 1, abdominal pain was the most common PT. None of the Acute Pancreatitis AMQ PTs had 95% CIs of the risk differences that excluded zero in Pool 2.

Although the overall occurrence of the AMQ TEAEs for Acute Pancreatitis was similar to placebo in the plozasiran 25 mg group, all pancreatitis-related PTs were lower in the plozasiran 25 mg group compared to the placebo group. An explanation for this observation is the dilution of the effect on pancreatitis from the other PTs in the AMQ, for example, abdominal pain and lipase increased.

Table 63: Pool 2: Incidence and Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events by Preferred Term of AMQ for Acute Pancreatitis (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
Preferred Term		**Placebo (N=173)**	**Plozasiran 10 mg (N=121)**	**Plozasiran 25 mg (N=148)**	**Plozasiran 50 mg Q12W (N=146)**	**Plozasiran 50 mg Q24W (N=66)**	**Plozasiran (25 mg+ 50 mg) (N=360)**	**Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)**	**Plozasiran 25 mg vs Placebo**	**Plozasiran (25 mg+ 50 mg) vs Placebo**	**Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo**
Subjects with Any AMQ TEAEs for Acute Pancreatitis	n (%)	17 (9.8)	5 (4.1)	15 (10.1)	25 (17.1)	2 (3.0)	42 (11.7)	47 (9.8)	-0.7 (-6.8, 5.5)	2.2 (-3.0, 7.4)	1.3 (-3.6, 6.1)
	EAIR (100 PY)	13.0	5.3	12.1	21.5	4.0	14.3	12.0	-3.2 (-12.2, 5.8)	0.9 (-6.7, 8.5)	0.1 (-7.0, 7.2)
Abdominal pain	n (%)	7 (4.0)	3 (2.5)	7 (4.7)	13 (8.9)	1 (1.5)	21 (5.8)	24 (5.0)	-0.1 (-4.2, 4.0)	2.0 (-1.6, 5.5)	1.9 (-1.4, 5.2)
	EAIR (100 PY)	5.1	3.2	5.8	10.7	0.0	6.7	5.8	-0.7 (-6.4, 5.0)	1.5 (-3.3, 6.3)	1.6 (-2.9, 6.1)
Abdominal pain upper	n (%)	3 (1.7)	1 (0.8)	1 (0.7)	4 (2.7)	0 (0.0)	5 (1.4)	6 (1.2)	-1.1 (-3.6, 1.3)	-0.2 (-2.5, 2.0)	-0.3 (-2.5, 1.8)
	EAIR (100 PY)	2.2	1.0	0.8	3.4	0.0	1.7	1.5	-1.4 (-4.5, 1.7)	-0.3 (-3.2, 2.5)	-0.4 (-3.1, 2.3)
Abdominal tenderness	n (%)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	NA	NA	0.2 (-0.2, 0.6)
	EAIR (100 PY)	0.0	1.0	0.0	0.0	0.0	0.0	0.3	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.3 (-0.3, 0.8)
Amylase increased	n (%)	2 (1.2)	0 (0.0)	1 (0.7)	1 (0.7)	1 (1.5)	3 (0.8)	3 (0.6)	-0.4 (-2.5, 1.7)	-0.4 (-2.2, 1.5)	-0.6 (-2.3, 1.2)
	EAIR (100 PY)	1.4	0.0	0.8	0.8	2.0	1.0	0.8	-0.5 (-3.1, 2.1)	-0.5 (-2.7, 1.8)	-0.7 (-2.9, 1.4)
Gastrointestinal pain	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.7 (-0.6, 2.1)	0.3 (-0.3, 0.8)	0.2 (-0.2, 0.6)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.9 (-0.8, 2.6)	0.3 (-0.3, 0.9)	0.2 (-0.2, 0.7)
Lipase increased	n (%)	3 (1.7)	2 (1.7)	6 (4.1)	7 (4.8)	1 (1.5)	14 (3.9)	16 (3.3)	2.4 (-1.3, 6.1)	2.2 (-0.6, 5.0)	1.6 (-1.0, 4.1)
	EAIR (100 PY)	2.2	2.1	4.2	5.2	2.0	4.2	3.7	2.1 (-2.3, 6.5)	2.0 (-1.4, 5.4)	1.4 (-1.7, 4.6)
Pancreatic enzymes increased	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.3)	1 (0.2)	-0.5 (-1.6, 0.6)	-0.3 (-1.6, 0.9)	-0.4 (-1.6, 0.8)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	2.0	0.3	0.3	-0.7 (-2.0, 0.6)	-0.4 (-2.0, 1.2)	-0.5 (-2.0, 1.0)
Pancreatic pseudocyst	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Pancreatitis	n (%)	3 (1.7)	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.5)	2 (0.6)	2 (0.4)	-1.8 (-3.8, 0.2)	-1.2 (-3.3, 0.9)	-1.2 (-3.2, 0.8)
	EAIR (100 PY)	2.2	0.0	0.0	0.8	1.9	0.7	0.5	-2.4 (-5.1, 0.3)	-1.6 (-4.2, 1.1)	-1.6 (-4.1, 0.9)
Pancreatitis acute	n (%)	4 (2.3)	0 (0.0)	2 (1.4)	1 (0.7)	1 (1.5)	4 (1.1)	4 (0.8)	-1.3 (-4.1, 1.6)	-1.1 (-3.6, 1.3)	-1.2 (-3.5, 1.1)
	EAIR (100 PY)	2.9	0.0	1.6	0.0	1.9	1.0	0.8	-1.8 (-5.5, 2.0)	-1.9 (-4.9, 1.1)	-1.9 (-4.7, 1.0)
Pancreatitis necrotising	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Pancreatitis relapsing	n (%)	4 (2.3)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	-2.5 (-4.9, -0.2)	-2.0 (-4.3, 0.3)	-1.9 (-4.1, 0.3)
	EAIR (100 PY)	2.9	0.0	0.0	0.8	0.0	0.3	0.3	-3.3 (-6.4, -0.1)	-2.6 (-5.5, 0.3)	-2.4 (-5.2, 0.3)

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; MH=Mantel-Haenszel; PY=person-year; Q12W=every 12 weeks; Q24W=every 24 weeks; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event that was not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term were counted once. Risk difference and 95% CI for incidence were calculated using CMH test by stratifying with study. Risk difference and respective 95% CI for exposure adjusted incidence were calculated using MH weights by stratifying with study.

Pool 3: Open-Label Extension Studies

The exposure-adjusted incidence and incidence of TEAEs of the AMQ for Acute Pancreatitis by PT are presented inTable 67.

In the OLE period, the EAIR for the Acute Pancreatitis AMQ was 4.0 per 100 PYs in the plozasiran 25 mg group, which was lower than Pool 2 (12.1 per 100 PYs). The most commonly reported PTs were abdominal pain (2.0 per 100 PYs) and lipase increase (1.7 per 100 PYs).

Table 64: Pool 3: Exposure-Adjusted Incidence of Treatment-Emergent Adverse Events by Preferred Term of AMQ for Acute Pancreatitis (OLE Portion, Safety Set)

Preferred Term	Plozasiran 25 mg[a] (N=471) EAIR (100 PY)	Plozasiran (10 mg+ 50 mg Other[a]) (N=483) EAIR (100 PY)
Subjects with any AMQ TEAEs for Acute Pancreatitis	4.0	4.1
Abdominal pain	1.8	2.0
Abdominal pain upper	0.5	0.4
Amylase increased	0.2	0.1
Hyperlipasaemia	0.2	0.1
Lipase increased	1.7	1.7
Obstructive pancreatitis	0.2	0.1
Pancreatitis	0.2	0.1
Pancreatitis relapsing	0.2	0.1

Abbreviations: AE=adverse event; AMQ=Arrowhead MedDRA Query; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PY=person-year; TEAE=treatment-emergent adverse event. %=100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the number of subjects with specified AEs. Note: AEs were coded using AMQ by Program Safety Team. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. TEAEs were summarized according to the most recent treatment received prior to the TEAE onset. Subjects with multiple events for a given Preferred Term were counted once.

5.4.4.3.5. Medical Device Adverse Events

During the randomized period of the 3 Phase 2/3 studies (Studies AROAPOC3-3001 AROAPOC3-2001, and AROAPOC3-2002) plozasiran was supplied to sites in vials, hence no medical device AEs were reported during the randomized period of the 3 Phase 2/3 studies.

In the OLE period of Study AROAPOC3-3001, of the 11 subjects treated with the plozasiran PFS 6 subjects (54.5%) reported TEAEs. One of these subjects experienced 2 SAEs that were deemed not related to study drug by the Investigator (PTs: syncopy and back pain). No life-threatening events or events leading to study drug or study discontinuation were reported in these subjects. None of these TEAEs appeared related to the device.

In the OLE period of Study AROAPOC3-2003, no TEAEs were reported in the 7 subjects that were administered the plozasiran 25 mg PFS

5.4.5. Discontinuation due to adverse events

Pool 1: Pivotal Phase 3 Study, Randomized Double-Blind Period

Three subjects discontinued study drug due to TEAEs including:

- Plozasiran 25 mg group: 2 subjects (diabetes mellitus and urticaria in 1 subject each)
- Plozasiran 50 mg group: glycosylated haemoglobin increased (1 subject)

In addition, 3 subjects in the placebo group were discontinued from blinded study drug due to acute pancreatitis (per the Investigator's assessment) who subsequently enrolled into the OLE period of the study. No other subjects in the placebo group had TEAEs that led to study drug discontinuation.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

In Pool 2, 7 subjects had TEAEs leading to study drug discontinuation due to TEAEs, 3 of which were in the phase 3 study (Table 68). The incidence of subjects who discontinued due to a TEAE in the Phase 2/3 studies was low and similar for the placebo group (1.2% subjects) and plozasiran treatment groups (1.0% subjects in the plozasiran 10+25+50 mg group). Three of the 7 subjects discontinued study drug due to a laboratory abnormality and included glycosylated hemoglobin increased (1 subject in the plozasiran 10 mg group and 1 subject in the plozasiran 50 mg Q12W group), insulin C-peptide increased (1 placebo subject), and blood insulin increased (1 placebo subject). One subject discontinued due to diabetes mellitus in the plozasiran 25 mg group.

Overall results for EAIRs and risk differences showed a similar pattern to the crude incidence TEAE analysis.

Table 65: Pool 2: Treatment-Emergent Adverse Events and Exposure-Adjusted Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Randomized Period, Safety Set)

									Risk Difference (%) (95% CI)		
System Organ Class Preferred Term		Placebo (N=173)	Plozasiran 10 mg (N=121)	Plozasiran 25 mg (N=148)	Plozasiran 50 mg Q12W (N=146)	Plozasiran 50 mg Q24W (N=66)	Plozasiran (25 mg+ 50 mg) (N=360)	Plozasiran (10 mg+ 25 mg+ 50 mg) (N=481)	Plozasiran 25 mg vs Placebo	Plozasiran (25 mg+ 50 mg) vs Placebo	Plozasiran (10 mg+ 25 mg+ 50 mg) vs Placebo
Subjects with Any TEAEs Leading to Study Drug Discontinuation	n (%)	2 (1.2)	1 (0.8)	2 (1.4)	2 (1.4)	0 (0.0)	4 (1.1)	5 (1.0)	0.1 (-2.2, 2.5)	-0.1 (-2.0, 1.9)	0.0 (-1.9, 1.9)
	EAIR (100 PY)	1.4	1.0	1.6	1.7	0.0	1.4	1.3	0.1 (-2.6, 2.9)	-0.1 (-2.6, 2.3)	0.0 (-2.4, 2.4)
Cardiac disorders	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	NA	0.3 (-0.3, 0.8)	0.2 (-0.2, 0.6)
	EAIR (100 PY)	0.0	0.0	0.0	0.8	0.0	0.3	0.3	0.0 (0.0, 0.0)	0.3 (-0.3, 0.9)	0.2 (-0.2, 0.7)
Myocardial infarction	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)	NA	0.3 (-0.3, 0.8)	0.2 (-0.2, 0.6)
	EAIR (100 PY)	0.0	0.0	0.0	0.8	0.0	0.3	0.3	0.0 (0.0, 0.0)	0.3 (-0.3, 0.9)	0.2 (-0.2, 0.7)
Infections and infestations	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Lower respiratory tract infection	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Investigations	n (%)	1 (0.6)	1 (0.8)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.4)	-0.5 (-1.6, 0.6)	-0.3 (-1.6, 1.0)	-0.1 (-1.4, 1.2)
	EAIR (100 PY)	0.7	1.0	0.0	0.8	0.0	0.3	0.5	-0.7 (-2.0, 0.6)	-0.4 (-2.0, 1.2)	-0.2 (-1.8, 1.5)
Blood insulin increased	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
Glycosylated haemoglobin increased	n (%)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.4)	NA	0.3 (-0.3, 0.8)	0.5 (-0.1, 1.1)
	EAIR (100 PY)	0.0	1.0	0.0	0.8	0.0	0.3	0.5	0.0 (0.0, 0.0)	0.3 (-0.3, 1.0)	0.6 (-0.2, 1.4)
Insulin C-peptide increased	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.6 (-0.6, 1.9)	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
Metabolism and nutrition disorders	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.7 (-0.7, 2.2)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)
Diabetes mellitus	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.6 (-0.6, 1.9)	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.7 (-0.7, 2.2)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)
Respiratory, thoracic and mediastinal disorders	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
Dyspnoea	n (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.5 (-1.6, 0.6)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
	EAIR (100 PY)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	-0.7 (-2.0, 0.6)	-0.7 (-2.2, 0.7)	-0.7 (-2.2, 0.7)
Skin and subcutaneous tissue disorders	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.6 (-0.6, 1.9)	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.7 (-0.7, 2.2)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)
Urticaria	n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0.6 (-0.6, 1.9)	0.3 (-0.3, 0.8)	0.3 (-0.2, 0.7)
	EAIR (100 PY)	0.0	0.0	0.8	0.0	0.0	0.3	0.3	0.7 (-0.7, 2.2)	0.3 (-0.3, 1.0)	0.3 (-0.3, 0.9)

Abbreviations: AE=adverse event; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; MH=Mantel-Haenszel; NA=not applicable; PY=person-year; Q12W=every 12 weeks; Q24W=every 24 weeks; TEAE=treatment-emergent adverse event. % = 100×n/N, where n was the number of subjects with specified AEs. EAIR=100×n/PY, where n was the

number of subjects with specified AEs. Note: AEs were coded using MedDRA dictionary version 26.1. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. Subjects with multiple events for a given Preferred Term or System Organ Class were counted once. Risk difference and 95% CI for incidence were calculated using CMH test by stratifying with study. Risk difference and respective 95% CI for EAIR were calculated using MH weights by stratifying with study.

Pool 3: Open-Label Extension Studies

Consistent with Pool 1 and Pool 2, the incidence of TEAEs leading to discontinuation was low and occurred at similar frequencies across the plozasiran 10, 25, and 50 mg treatment groups (2.6%, 3.8%, and 1.9%, respectively).

TEAEs leading to discontinuation that occurred in >3 subjects overall included:

- Glycosylated haemoglobin increased: 0.9%, 0.6%, and 0% of subjects in the 10, 25, and 50 mg plozasiran groups, respectively
- Diabetes mellitus: 0%, 1.3%, and 1.9% subjects in the 10, 25, and 50 mg plozasiran groups, respectively
- Type 2 diabetes mellitus: 0.9%, 0.6%, and 0% subjects in the 10, 25, and 50 mg plozasiran groups, respectively

5.4.6. Safety in special populations

Subgroup analyses were performed in the following intrinsic factors, i.e. age, BMI, sex, race, ethnicity, baseline diabetes disease state, baseline liver disease state, and confirmation of FCS, and in the extrinsic factor region.

Intrinsic factors

Age

Of the 75 subjects in Pool 1, only 9 subjects were ≥65 years of age (≤4 subjects in each dose group). Given the small number of subjects who were ≥65 years of age, it is difficult to assess differences in rates of occurrence for specific PTs.

Of the 654 subjects in Pool 2, 456 subjects were <65 years of age and 198 subjects were ≥65 years of age. The EAIRs for all TEAEs were slightly lower in the older age group and in both groups EAIRs for all TEAEs were slightly higher in the plozasiran groups compared to placebo although 95% CIs included zero. The EAIR differences were smallest for the plozasiran 25 mg group. TEAEs demonstrated a similar pattern between the BMI groups as the overall population.

In both age groups, the majority of TEAEs were mild or moderate. In subjects <65 years of age, EAIRs for severe TEAEs were lower in the plozasiran groups compared to placebo, but in the older age group there was a trend toward higher EAIRs in the plozasiran 25 mg group and 25+50 mg groups compared to placebo with risk differences of 2.6% [95% CI –6.9, 12.1] in the plozasiran 25 mg group and 7.4% [95% CI 1.9, 12.9] in the plozasiran 25+50 mg group. Overall, no clinically meaningful differences in safety were observed between the age subgroups in the plozasiran 25 mg group; however, trends for higher SAEs and severe TEAEs for plozasiran 50 mg were observed in >65 years of age group.

Body Mass Index

Of the 75 subjects in Pool 1, only 13 subjects were ≥30 kg/m2 (3 to 6 subjects in any treatment group). Overall, the incidence of all TEAEs was similar between the BMI subgroups in all treatment groups.

Of the 654 subjects in Pool 2, 298 subjects were <30 kg/m2 and 356 subjects were ≥30 kg/m2. EAIRs for all TEAEs were similar between the BMI subgroups. There did not appear to be an important BMI-related difference in the incidence of TEAE PTs across subgroups. TEAE PTs demonstrated a similar pattern between the BMI groups as the overall population.

In both BMI groups, the majority of TEAEs were mild or moderate. In subjects <30 kg/m2, EAIRs for severe TEAEs were lower in the plozasiran groups compared to placebo but in the ≥30 kg/m2 group there was a trend toward higher EAIRs in the plozasiran 25 mg and plozasiran 50 mg groups compared to placebo with risk differences of 4.1% [95% CI -4.8, 12.9] in the plozasiran 25 mg group and 7.1% [95% CI 2.9, 11.9] in the plozasiran 25+50 mg group), respectively. Overall, no clinically meaningful differences were observed in the BMI subgroups for the plozasiran 25 mg group; however, trends for higher SAEs and severe TEAEs in the plozasiran 50 mg group were observed in subjects ≥30 kg/m2.

Sex

Of the 75 subjects in Pool 1, 37 subjects were male, and 38 subjects were female. Overall, there were no clinically meaningful differences between female and male subjects for the plozasiran 25 mg group.

Of the 654 subjects in Pool 2, 242 subjects were female, and 412 subjects were male. The EAIRs for all TEAEs were slightly higher in the male subjects and in both genders the EAIRs for TEAEs tended to be modestly higher in the plozasiran groups than placebo, although 95% CIs of the risk differences included zero. The EAIR differences from placebo were small for the plozasiran 25 mg group in both sexes. Overall, there were no clinically meaningful differences between females and males for the plozasiran 25 mg group.

Race

Of the 75 subjects in Pool 1, all subjects were White, therefore differences based on race could not be determined.

Of the 654 subjects in Pool 2, 639 subjects were White and only 15 subjects were Black or African American; therefore, it is difficult to interpret differences based on race.

Ethnicity

Of the 75 subjects in Pool 1, all but one subject was Not Hispanic/Latino, therefore differences based on ethnicity could not be determined.

Of the 651 subjects in Pool 2, 108 subjects were Hispanic/Latino, and 543 subjects were Not Hispanic/Latino. Due to the low number of subjects in the Hispanic/Latino group (ranging from 15 to 30 subjects per group) the effect of ethnicity should be interpreted with caution. It does not seem that ethnicity drives any major changes in risk relative to the overall population.

Baseline Diabetes Disease State

Of the 75 subjects in Pool 1, 28 subjects had diabetes, 8 subjects had prediabetes, and 39 subjects had normoglycemia. Due to the low number of subjects in the prediabetic group (2 to 3 subjects in any group) the effect of prediabetes was not interpreted. In summary, other than a few TEAE PTs related to dysglycemia, there were no clinically meaningful differences between subgroups in the plozasiran 25 mg group.

Of the 654 subjects in Pool 2, 386 subjects had diabetes, 103 were prediabetic, and 165 subjects were normoglycemic at baseline. Due to the low number of subjects in the prediabetic group (ranging from 15 to 25 subjects per group) the effect of prediabetes should be interpreted with caution.

TEAE PTs demonstrated a similar pattern across the subgroups. Notably, glycosylated hemoglobin increased and diabetes mellitus were only experienced in the diabetes and prediabetes subgroups, and not in the normoglycemia group. In the prediabetes and normoglycemic groups, EAIRs for severe TEAEs were either similar or lower in the plozasiran group compared to placebo but in the diabetes group severe TEAEs were increased in the 50 mg group; the risk difference was low but the 95% CI excluded zero (6.7 [2.8, 10.7] in the 25+50 mg group). Similarly, in all subgroups, the EAIRs for SAEs were similar in the plozasiran 25 mg group compared to placebo, and slightly higher in the diabetic subgroup for plozasiran 50 mg Q12W group but none of the 95% CIs excluded zero. In summary, subjects with diabetes at baseline experienced more TEAEs and had higher mortality than their nondiabetic counterparts; they also were at a modestly greater risk for SAEs in the plozasiran 50 mg group.

Baseline Liver Disease State

In pool 1, there were no enrolled subjects with abnormal liver function at baseline.

Of the 654 subjects in Pool 2, 615 subjects had normal ALT levels at baseline and 39 subjects had ALT levels >ULN at baseline (3 to 11 subjects per dose group). As would be expected, EAIRs for all TEAEs varied widely (26.5 to 462.9 per 100 PYs) in subjects with ALT >ULN; the same was true for treatment-related TEAEs (0 to 64.0 per 100 PYs). Overall, the impression is that the subjects with abnormal baseline liver function tolerated plozasiran similarly to subjects with normal baseline function.

Confirmation of FCS

This analysis for confirmation of FCS was only done for Pool 1. Genetic FCS was confirmed at the time of database lock in 41 of the 75 subjects in the Phase 3 study. Looking across these subgroups, EAIRs for all TEAEs were similar as were EAIRs for SAEs. Both subgroups shared the tendency for TEAEs to be milder in plozasiran-treated subjects and moderate in placebo subjects. Three subjects discontinued study drug and study due to TEAEs which were all plozasiran-treated subjects in the Clinical FCS subgroup.

This analysis for confirmation of FCS was not planned or performed for Pool 2.

Extrinsic factors

Geographic Region

In pool 1, 9 subjects were from the United States, 23 subjects were from Europe, and 43 subjects in the ROW. In all geographic subgroups, EAIRs of all TEAEs were either lower or generally similar in the plozasiran 25 mg group compared to placebo. No region-specific difference was observed in severe TEAEs or SAEs.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

Of the 654 subjects in Pool 2, 267 subjects were from the US, 61 subjects from Europe, and 326 subjects from the ROW. The EAIRs for all TEAEs were slightly higher in the plozasiran groups than placebo in the ROW subgroup. In the US and Europe, EAIRs of all TEAEs were similar in the plozasiran and placebo groups.

In the US, Europe, and ROW, the majority of TEAEs were mild or moderate. In all geographic regions, few subjects had severe TEAEs in any dose group (1 to 6 subjects). No region-specific differences between plozasiran and placebo were observed in severe TEAEs or SAEs.

Use in Pregnancy and Lactation

Overall, 2 subjects became pregnant during the studies.

Overdose

There are no clinical data on signs or symptoms of ARO-APOC3 overdose.

There were 4 overdose cases (dosing errors of active study drug) reported in the clinical studies. No significant safety signals have been observed in the overdose cases.

Drug Abuse

Not applicable. Plozasiran is not controlled under the Controlled Substances Act. Therefore, there is no applicable important information to convey to health care practitioners related to abuse and dependence.

Withdrawal and Rebound

There are no clinical data on signs or symptoms of plozasiran withdrawal or rebound. Plozasiran has a very long duration of action and the intended pharmacologic effects taper over a period of several months after stopping the drug administration.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There are no applicable data, but plozasiran does not cross the blood/brain barrier. Thus, it is unlikely that plozasiran affects the ability to drive or operate machinery, or that it impairs mental ability.

5.4.7. Immunological events

Please be referred to immunology sections of clinical pharmacology and efficacy.

5.4.8. Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction (DDI) studies have been performed for plozasiran. In vitro metabolism studies suggest that plozasiran is not a substrate, inhibitor or inducer of a set of cytochrome P450 (CYP) enzymes or transporters typically encountered in clinical DDI. Plozasiran is not expected to cause or be affected by DDIs via mechanisms involving CYP or drug transporters.

5.4.9. Vital signs and laboratory findings

5.4.9.1. Vital signs and other observations related to safety

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

Vital Signs

There were no notable trends in vital signs except for weight. At 6 and 12 months there were weight changes of -0.36 and +0.07 kg in the placebo group, compared with increases of +0.50 kg and +0.59 kg in the plozasiran 25 mg group, and +0.12 kg and +1.19 kg in the plozasiran 50 mg group.

Electrocardiogram

Measured electrocardiographic intervals were generally unremarkable (Table 69 and Table 70).

Table 66: Incidence of Abnormality of Electrocardiogram (ECG) Parameters Based on Any Post-baseline Result Pool 1 - Randomized Period

Parameter Level	Placebo (N=25) n (%)	Plozasiran 25mg (N=26) n (%)	Plozasiran 50mg (N=24) n (%)	Plozasiran (25mg+50mg) (N=50) n (%)	Risk Difference (%) (95% CI) Plozasiran 25mg vs Placebo	Risk Difference (%) (95% CI) Plozasiran (25mg+50mg) vs Placebo
QTcF Interval (ms)						
> 450 ms	1 (4.0)	2 (7.7)	2 (8.3)	4 (8.0)	3.7(-9.1, 16.5)	4.0(-6.7, 14.7)
> 480 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
> 500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
increases from baseline > 30 ms	2 (8.0)	2 (7.7)	1 (4.2)	3 (6.0)	-0.3(-15.1, 14.5)	-2.0(-14.5, 10.5)
increases from baseline > 60 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
QTcB Interval (ms)						
> 450 ms	7 (28.0)	8 (30.8)	5 (20.8)	13 (26.0)	2.8(-22.2, 27.8)	-2.0(-23.4, 19.4)
> 480 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
> 500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
increases from baseline > 30 ms	5 (20.0)	4 (15.4)	7 (29.2)	11 (22.0)	-4.6(-25.5, 16.3)	2.0(-17.4, 21.4)
increases from baseline > 60 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA

Abbreviations: CI=Confidence interval; NA=Not applicable. % = 100 x n/N, where n is the number of subjects with specified events. Note: Risk difference and 95% CI are calculated using Chi-square test.

Table 67: Exposure Adjusted Incidence of Abnormality of Electrocardiogram (ECG) Parameters Based on Any Post-baseline Result Pool 1 - Randomized Period Safety Set

Parameter Level	Placebo (N=25)	Plozasiran 25mg (N=26)	Plozasiran 50mg (N=24)	Plozasiran (25mg+50mg) (N=50)	Risk Difference and 95% CI Plozasiran 25mg vs Placebo	Risk Difference and 95% CI Plozasiran (25mg+50mg) vs Placebo
QTcF Interval (ms)						
>450 ms						
n, PY of exposure	1, 21.83	2, 24.04	2, 20.38	4, 44.42		
EAIR (100 PY)	4.6	8.3	9.8	9.0	3.7	4.4
95% CI of EAIR (100 PY)	(-4.4, 13.6)	(-3.2, 19.8)	(-3.8, 23.4)	(0.2, 17.8)	(-10.9, 18.4)	(-8.2, 17.0)
>480 ms						
n, PY of exposure	0, 21.83	0, 24.64	0, 22.10	0, 46.73		
EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0
95% CI of EAIR (100 PY)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
>500 ms						
n, PY of exposure	0, 21.83	0, 24.64	0, 22.10	0, 46.73		
EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0
95% CI of EAIR (100 PY)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
increases from baseline >30 ms						
n, PY of exposure	2, 21.09	2, 24.64	1, 21.37	3, 46.00		
EAIR (100 PY)	9.5	8.1	4.7	6.5	-1.4	-3.0
95% CI of EAIR (100 PY)	(-3.7, 22.6)	(-3.1, 19.4)	(-4.5, 13.9)	(-0.9, 13.9)	(-18.7, 15.9)	(-18.0, 12.1)
increases from baseline >60 ms						
n, PY of exposure	0, 21.83	0, 24.64	0, 22.10	0, 46.73		
EAIR (100 PY)	0.0	0.0	0.0	0.0	0.0	0.0
95% CI of EAIR (100 PY)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)

Abbreviations: CI=Confidence interval; EAIR=Exposure adjusted incidence rate; PY=Person-Year. EAIR=100*n/PY, where n is the number of subjects with specified events. Note: Risk difference and respective 95% CI are calculated using Wald's method.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

Vital Signs

As in Pool 1, plozasiran was not shown to impact any vital sign of interest in Pool 2. Specifically, plozasiran did not appear to induce changes in blood pressure or pulse, and the modest increases in body weight noted in Pool 1 were not observed in Pool 2.

Electrocardiogram

As in Pool 1, plozasiran did not appear to have any clinically relevant effect on measured electrocardiographic intervals.

Table 68: Incidence of Abnormality of Electrocardiogram (ECG) Parameters based on Any Post-baseline Result Pool 2 – Randomized

Parameter Level	Placebo (N=173) n (%)	Plozasiran 10mg (N=121) n (%)	Plozasiran 25mg (N=148) n (%)	Plozasiran 50mg Q12W (N=146) n (%)	Plozasiran 50mg Q24W (N=66) n (%)	Risk Difference(%) (95% CI) Plozasiran 25mg vs Placebo
QTcF Interval (ms)						
> 450 ms	26 (15.0)	17 (14.0)	28 (18.9)	23 (15.8)	7 (10.6)	4.5(-3.7, 12.6)
> 480 ms	5 (2.9)	5 (4.1)	7 (4.7)	4 (2.7)	0 (0.0)	2.1(-2.2, 6.4)
> 500 ms	1 (0.6)	1 (0.8)	4 (2.7)	1 (0.7)	0 (0.0)	2.2(-0.7, 5.1)
increases from baseline > 30 ms	24 (13.9)	16 (13.2)	30 (20.3)	20 (13.7)	8 (12.1)	6.8(-1.5, 15.1)
increases from baseline > 60 ms	7 (4.0)	5 (4.1)	6 (4.1)	3 (2.1)	1 (1.5)	0.1(-4.2, 4.5)
QTcB Interval (ms)						
> 450 ms	63 (36.4)	36 (29.8)	46 (31.1)	55 (37.7)	18 (27.3)	-5.3(-15.7, 5.1)
> 480 ms	14 (8.1)	8 (6.6)	8 (5.4)	10 (6.8)	0 (0.0)	-2.5(-7.9, 3.0)
> 500 ms	3 (1.7)	3 (2.5)	4 (2.7)	2 (1.4)	0 (0.0)	1.1(-2.2, 4.4)
increases from baseline > 30 ms	34 (19.7)	18 (14.9)	34 (23.0)	26 (17.8)	12 (18.2)	3.2(-5.8, 12.2)
increases from baseline > 60 ms	7 (4.0)	5 (4.1)	8 (5.4)	3 (2.1)	1 (1.5)	1.5(-3.2, 6.1)

Abbreviations: Q12W=Every 12 weeks; Q24W=Every 24 weeks; CI=Confidence interval. % = 100 x n/N, where n is the number of subjects with specified events. Note: Risk difference and 95% CI are calculated using Cochran-Mantel-Haenszel (CMH) test by stratifying with study.

Table 69: Exposure Adjusted Incidence of Abnormality of Electrocardiogram (ECG) Parameters based on Any Post-baseline Result Pool 2 – Randomized Period Safety Set

Parameter Level	Placebo (N=173)	Plozasiran 10mg (N=121)	Plozasiran 25mg (N=148)	Plozasiran 50mg Q12W (N=146)	Plozasiran 50mg Q24W (N=66)	Risk Difference and 95% CI Plozasiran 25mg vs Placebo
QTcF Interval (ms)						
>450 ms						
n, PY of exposure	25, 126.06	16, 87.72	26, 106.58	20, 107.98	7, 47.74	
EAIR (100 PY)	19.8	18.2	24.4	18.5	14.7	5.7
95% CI of EAIR (100 PY)	(12.1, 27.6)	(9.3, 27.2)	(15.0, 33.8)	(10.4, 26.6)	(3.8, 25.5)	(-6.5, 17.9)
>480 ms						
n, PY of exposure	5, 137.83	4, 94.82	5, 120.36	4, 117.50	0, 51.86	
EAIR (100 PY)	3.6	4.2	4.2	3.4	0.0	0.8
95% CI of EAIR (100 PY)	(0.4, 6.8)	(0.1, 8.4)	(0.5, 7.8)	(0.1, 6.7)	(0.0, 0.0)	(-4.1, 5.7)
>500 ms						
n, PY of exposure	1, 140.34	1, 96.05	4, 120.50	1, 118.78	0, 51.86	
EAIR (100 PY)	0.7	1.0	3.3	0.8	0.0	2.7
95% CI of EAIR (100 PY)	(-0.7, 2.1)	(-1.0, 3.1)	(0.1, 6.6)	(-0.8, 2.5)	(0.0, 0.0)	(-0.9, 6.4)
increases from baseline >30 ms						
n, PY of exposure	24, 129.19	16, 88.31	26, 109.65	19, 108.39	8, 48.02	
EAIR (100 PY)	18.6	18.1	23.7	17.5	16.7	6.1
95% CI of EAIR (100 PY)	(11.1, 26.0)	(9.2, 27.0)	(14.6, 32.8)	(9.6, 25.4)	(5.1, 28.2)	(-5.9, 18.2)
increases from baseline >60 ms						
n, PY of exposure	7, 137.43	5, 93.77	4, 121.18	3, 117.36	1, 51.49	
EAIR (100 PY)	5.1	5.3	3.3	2.6	1.9	-1.6
95% CI of EAIR (100 PY)	(1.3, 8.9)	(0.7, 10.0)	(0.1, 6.5)	(-0.3, 5.4)	(-1.9, 5.7)	(-6.6, 3.4)

Abbreviations: CI=Confidence interval; EAIR=Exposure adjusted incidence rate; PY=Person-Year; Q12W=Every 12 weeks; Q24W=Every 24 weeks. EAIR=100*n/PY, where n is the number of subjects with specified events. Note: Risk difference and respective 95% CI are calculated using Mantel-Haenszel (MH) weights by stratifying with study.

Pool 3: Open-Label Extension Studies

Vital Signs

As in Pool 1 and Pool 2, plozasiran was not shown to impact any vital sign of interest in Pool 3. Specifically, plozasiran did not appear to induce changes in blood pressure or pulse, and the modest increases in body weight noted in Pool 1 were not observed in Pool 3.

Electrocardiogram

No new electrocardiographic safety signal was identified in Pool 3. For subjects receiving plozasiran 25+50 mg, approximately 14% of subjects experienced a >30 msec increase in QTcF above baseline, and 1.5% of subjects had a >60 msec increase.

5.4.9.2. Clinical laboratory evaluations

Pool 1: Pivotal Phase 3 Study, Double-Blind Period

Chemistry

Clinical laboratory values were within normal limits for most subjects and generally unremarkable throughout the study, except for measures of glycemia and LFTs discussed below. Creatine kinase (CK) showed mean elevations at Months 3 and 9 in the plozasiran 50 mg group, driven by outliers, but mean changes in the placebo and plozasiran 25 mg groups were unremarkable.

There were no Grade 3 clinical laboratory abnormalities postbaseline. A Grade 4 clinical laboratory abnormality of CK elevation was observed postbaseline for 1 subject in the plozasiran 50 mg group.

Hyperglycemic Parameters

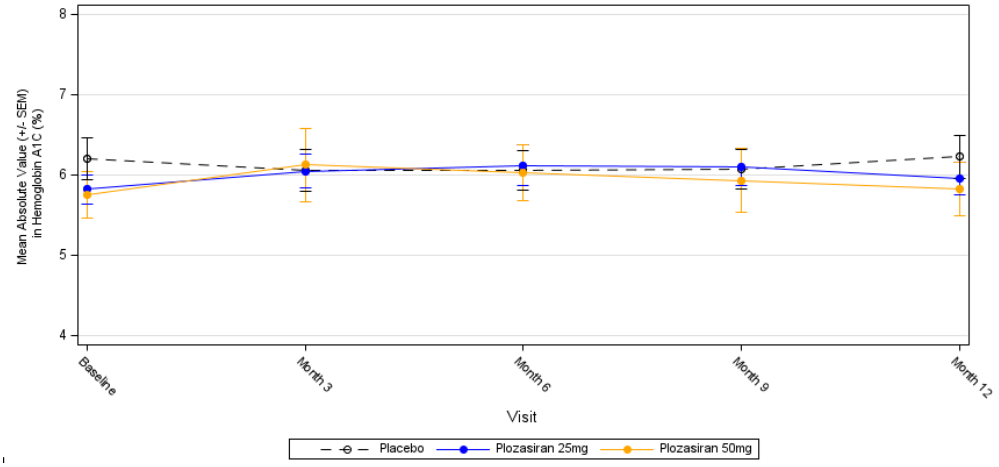
Glycemic Status at Baseline

Diabetes or prediabetes were common in this study and present at baseline in 12 (48%) subjects, 11 (42%) subjects, and 9 (38%) subjects randomized to placebo, plozasiran 25 mg, and plozasiran 50 mg, respectively.

Worsening of Glycemic Control by HbA1c, Fasting Blood Glucose, and HOMA IR

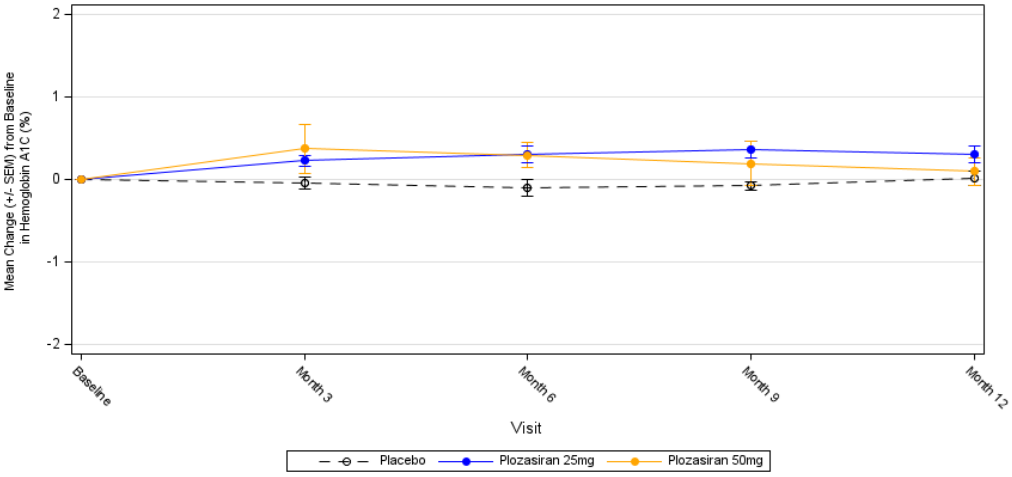
Mean HbA1c values at baseline were in the prediabetic range for all 3 treatment groups but higher in the placebo group. The benefit of participation in a controlled study with emphasis on dietary compliance was shown in the placebo group with a decline in mean HbA1c through the first 9 months. Mean absolute values in HbA1c over time are shown in Figure 33. Mean increases from baseline in HbA1c Figure 34 were observed for plozasiran-treated subjects in this study, without clear differentiation between the plozasiran 25 mg and 50 mg groups. However, these changes were modest. Subgroup analyses also suggest that these changes were most pronounced in subjects with prediabetes or diabetes at baseline.

Figure 36: Pool 1: Plot of Mean Absolute Value (±SEM) in HbA1c (Randomized Period, Safety Set)



Abbreviations: HbA1c=hemoglobin A1c; SEM = Standard error of the mean.

Figure 37: Pool 1: Plot of Mean Change (±SEM) from Baseline in HbA1c: –(Randomized Period, Safety Set)



Abbreviation: HbA1c=hemoglobin A1c; SEM=standard error of the mean.

The interpretation of fasting serum blood glucose was limited by the unknown reliability of self-reported fasting status. However, the changes from baseline were small, especially in the plozasiran 25 mg group.

A minor increase in mean Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was also observed in plozasiran groups, though these changes appeared to be driven by individuals with diabetes at baseline and may have been confounded by outliers (median changes were smaller than mean changes).

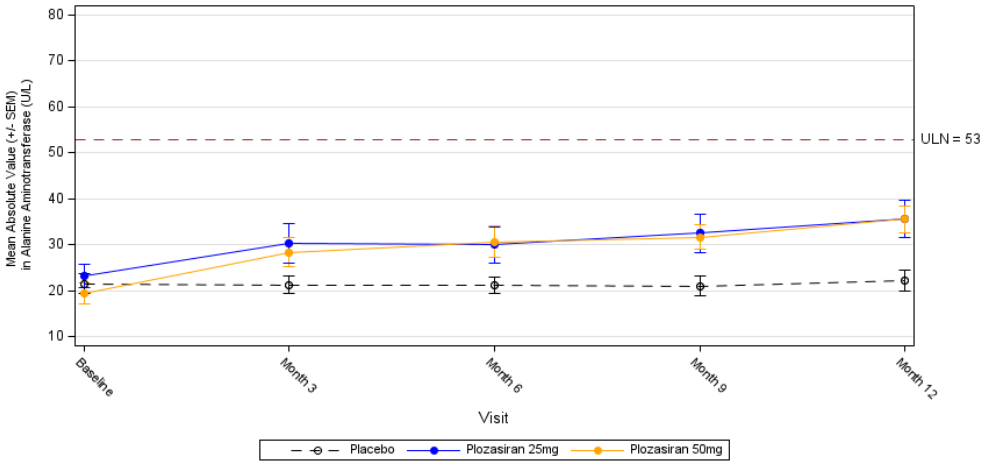
C peptide levels and insulin levels did not demonstrate a consistent, dose-dependent change in relationship to study drug in Pool 1.

Liver Function Tests

Modest increases in transaminases were observed for subjects in the plozasiran groups. No subject had a peak liver function value >3×ULN and no cases of Hy's Law criteria (maximum ALT or AST >3x ULN and maximum corresponding bilirubin >2x ULN) were observed. The subject incidence of any postbaseline ALT level >ULN was 1 (4.0%), 8 (30.8%), and 11 (45.8%) subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. The number of subjects who had a postbaseline AST level >ULN was 2 (8.0%), 5 (19.2%), and 9 (37.5%) subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively.

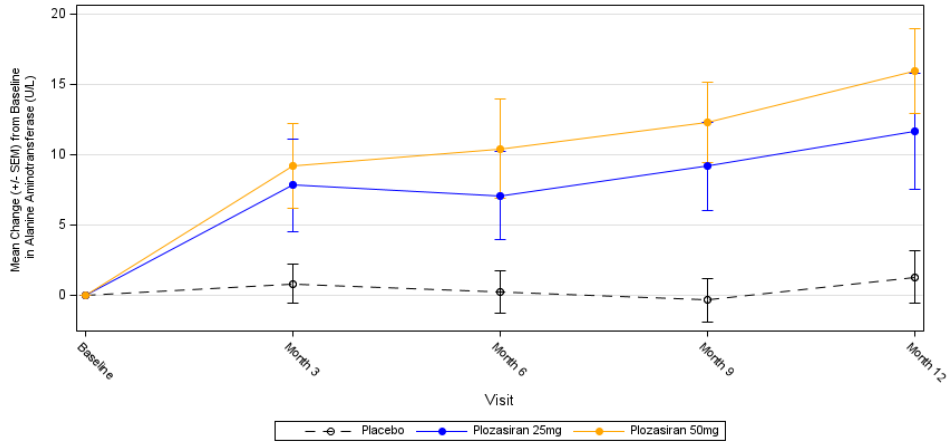
Mean changes in ALT level at any quarterly assessment reached a high of 11.8 U/L and 16.0 U/L for the plozasiran 25 and 50 mg doses, respectively, whereas values showed minimal changes in the placebo group. Mean changes in AST level were less notable, with mean elevations as high of 6.1 U/L and 9.0 U/L for the plozasiran 25 and 50 mg doses, respectively, at Month 12. Mean changes in GGT level were minor, variable, and not dose related. Any changes in ALP and bilirubin levels were minimal. The overall impression is that plozasiran modestly increases transaminases, ALT more so than AST, in a dose-dependent manner.

Figure 38: Pool 1: Plot of Mean Absolute Value (±SEM) in ALT (Randomized Period, Safety Set)



Abbreviations: ALT=Alanine aminotransferase; SEM = Standard error of the mean.

Figure 39: Pool 1: Plot of Mean Change (±SEM) in ALT (Randomized Period, Safety Set)



Abbreviations: ALT=Alanine aminotransferase; SEM=Standard error of the mean.

One ALT increase (1.6×ULN) was noted as a TEAE for a subject in the plozasiran 50 mg group, but no cases of DILI were identified. No subject experienced a transaminase increase >3 × ULN during the study. No postbaseline shift in either transaminase was greater than grade 1 in severity.

Renal Function Tests

Mean eGFR and shift tables cannot be used for this parameter. Median values for eGFR were 60 mL/min/m2 and remained at this value throughout the quarterly testing for Pool 1, 2, and 3. This is only useful in showing that more than 50% of subjects had eGFRs at baseline and all subsequent time points above the LLN.

Mean and median creatinine values at baseline in Pool 1 were not well balanced, as they were substantially higher in the plozasiran 25 mg group (70.2 µmol/L [0.794 mg/dL] and 72.5 µmol/L [0.820 mg/dL], respectively) relative to placebo (62.0 µmol/L [0.701 mg/dL] and 60.0 µmol/L [0.680 mg/dL], respectively) and the plozasiran 50 mg dose (56.6 µmol/L [0.641 mg/dL] and 55.0 µmol/L [0.625 mg/dL], respectively). Mean and median change from baseline of creatinine values increased modestly in the 3 treatment groups, in the following rank order beginning at Month 3: plozasiran 50 mg (9.2 µmol/L [0.104 mg/dL] and 5.0 µmol/L [0.060 mg/dL], respectively); placebo (8.3 µmol/L [0.094 mg/dL] and 6.5 µmol/L [0.075 mg/dL], respectively); and plozasiran 25 mg (3.5 µmol/L [0.041 mg/dL] and 1.0 µmol/L [0.010 mg/dL], respectively). Mean and median change from baseline of creatinine values at Month 12: placebo (5.8 µmol/L [0.065 mg/dL] and 4.0 µmol/L [0.050 mg/dL], respectively), plozasiran 25 mg (8.4 µmol/L [0.094 mg/dL] and 10.0 µmol/L [0.110 mg/dL], respectively), and plozasiran 50 mg (10.5 µmol/L [0.119 mg/dL and 7.0 µmol/L [0.080 mg/dL], respectively).

Regarding BUN, as expected from the plasma creatinine values at baseline in Pool 1, BUN mean and median baseline values were not well balanced, as they were higher in the plozasiran 25 mg group (6.39 mmol/L [17.9 mg/dL] and 6.07 mmol/L [17.0 mg/dL], respectively) relative to placebo (5.60 mmol/L [15.7 mg/dL] and 5.36 mmol/L [15.0 mg/dL], respectively) and the plozasiran 50 mg dose (5.30 mmol/L [14.8 mg/dL] and 5.71 mmol/L [16.0 mg/dL], respectively). Mean and median change from baseline of BUN values changed modestly in the 3 treatment groups, in the following rank order beginning at Month 3: plozasiran 50 mg (0.40 mmol/L [1.1 mg/dL] and -0.18 mmol/L [-0.5 mg/dL], respectively); placebo (0.06 mmol/L [0.2 mg/dL] and 0.18 mmol/L [0.5 mg/dL], respectively) and plozasiran 25 mg (0.01 mmol/L [0.0 mg/dL] and 0.00 mmol/L [0.0 mg/dL], respectively). Mean and median change from baseline of BUN values at Month 12: placebo (0.24 mmol/L [0.7 mg/dL] and 0.36

mmol/L [1.0 mg/dL], respectively), plozasiran 25 mg (0.33 mmol/L [0.9 mg/dL] and 0.72 mmol/L [2.0 mg/dL], respectively), and plozasiran 50 mg (0.18 mmol/L [0.5 mg/dL] and 0.00 mmol/L [0.0 mg/dL], respectively).

Shifts for serum creatinine from normal baseline to Grade 1 occurred in 7 plozasiran-treated subjects (4/22 treated with 25 mg plozasiran and 3/24 treated with 50 mg); 1 subject treated with placebo shifted from normal to Grade 2.
Four subjects in the plozasiran 25 mg group had abnormal creatinine at baseline; none of these values shifted to a higher-grade abnormality during treatment. No subjects in the placebo group and plozasiran 50 mg group had an abnormal creatinine value at baseline. BUN shifts did not show a different pattern than for creatinine shifts, for subjects with normal BUN at baseline and subjects with abnormal BUN at baseline. Overall, potential effects on renal function were hard to assess in Pool 1 due to the relatively small size of the treatment groups and the imbalances at baseline. Nonetheless, the results indicate that any deterioration in renal function was mild, not progressive over the course of 12 months, and not related to dose.

Hematology

Hematology and coagulation laboratory values were within normal limits for most subjects throughout the study and the observed changes from baseline were not clinically meaningful.

Platelets

Changes in mean and median platelet counts were minimal. In Pool 1, a nonserious TEAE of thrombocytopenia was reported in 1 subject randomized to plozasiran (50 mg group).

Urinalysis

No meaningful changes or trends on urinalysis parameters were noted. Renal and urinary TEAEs were rare and generally mild.

Pool 2: Phase 2/3 Placebo-Controlled, Double-Blind Studies

Chemistry

Although some rare and sporadic chemistry lab shifts were observed in both Pool 1 and Pool 2, most chemistry laboratory values demonstrated no discernable pattern, with the exception of certain renal and LFT abnormalities, which are discussed below. Specifically, no consistent perturbations in amylase, LDH, thyroid function testing, or other routine laboratories were observed. Creatine kinase showed variability in Pool 2, with numerous subjects experiencing postbaseline excursions above normal in both the placebo and plozasiran groups. For example, in the placebo group, 36.3% of subjects had a Grade 1 excursion, 3.5% of subjects had a Grade 2 excursion, and 0.6% of subjects had a Grade 3 excursion. In contrast, the combined plozasiran (10+25+50 mg) group had slightly fewer Grade 1 excursions (29.0% of subjects), and slightly more higher-grade excursions (5.2% subjects with Grade 2, 1.7% of subjects with Grade 3, and 1.0% of subjects with Grade 4). There was variability in mean hsCRP across all groups including placebo, with no apparent difference due to treatment assignment and no sustained increase over time. Mean change from baseline of lipase levels were slightly lower at most timepoints in the plozasiran groups relative to placebo, including a 3.0 U/L increase in the placebo group versus a -3.6 U/L reduction in the plozasiran 25+50 mg group at Month 12.

Hyperglycemic Parameters

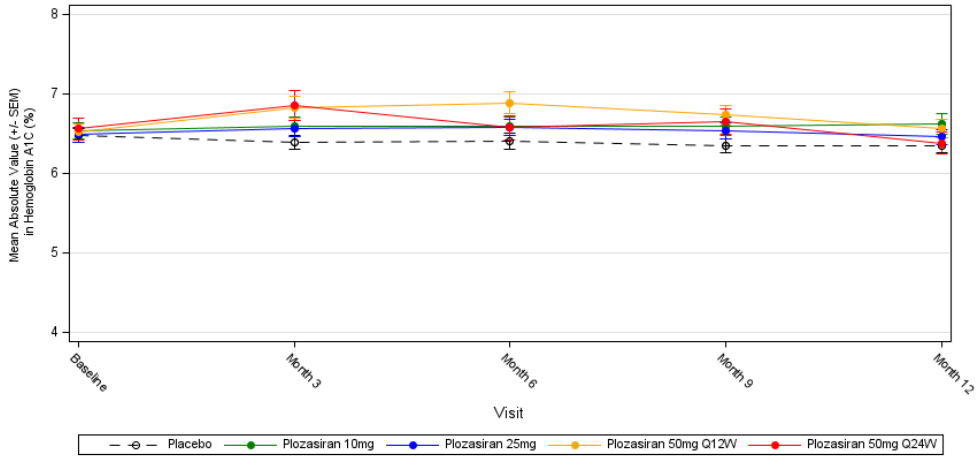
Glycemic Status at Baseline

Amongst all plozasiran-treated subjects included in Pool 2, 26.6% of subjects were normoglycemic, 29.9% of subjects were prediabetic, and 43.5% of subjects had diabetes at baseline. Amongst all placebo-treated subjects included in Pool 2, 27.7% of subjects were normoglycemic, 31.2% of subjects were prediabetic, and 41.0% of subjects had diabetes at baseline. Approximately half of all subjects were taking an antidiabetic medication at baseline. These co-morbidities were generally well balanced across the pooled placebo and pooled plozasiran groups.

Worsening of Glycemic Control by HbA1c, Fasting Blood Glucose, and HOMA IR

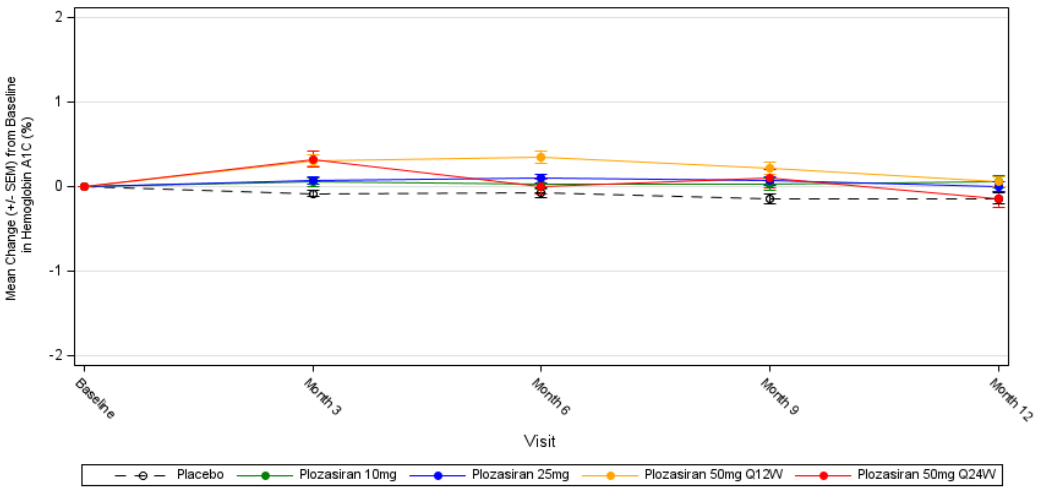
Overall, plozasiran-treated subjects experienced a modest, early increase in HbA1c, which was minimal for the plozasiran 10 and 25 mg doses and most pronounced in the plozasiran 50 mg groups. This change peaked around Month 3 for the plozasiran 25 and 50 mg groups. There was a general tendency for HbA1c values to gradually decline between Month 6 to Month 12, demonstrating reversibility during plozasiran washout. The modest overall increase in HbA1c was largely driven by subjects with diabetes at baseline, as minimal or no change was observed for those in the plozasiran 25+50 mg group amongst prediabetic subjects and normoglycemic subjects.

Figure 40: Pool 2: Plot of Mean Absolute Value (±SEM) in HbA1c (Randomized Period, Safety Set)



Abbreviations: HbA1c=hemoglobin A1c; Q12W=every 12 weeks; Q24W=every 24 weeks; SEM=standard error of the mean. Note: For subjects in AROAPOC3-2001 and AROAPOC3-2002 studies, the last measurements between Month 6 and Month 9 are carried forward to Month 9, and the last measurements after Month 9 are carried forward to Month 12.

Figure 41: Pool 2: Plot of Mean Change (±SEM) in HbA1c (Randomized Period, Safety Set)



Abbreviations: HbA1c=hemoglobin A1c; Q12W=every 12 weeks; Q24W=every 24 weeks; SEM=standard error of the mean. Note: For subjects in AROAPOC3-2001 and AROAPOC3-2002 studies, the last measurements between Month 6 and Month 9 are carried forward to Month 9, and the last measurements after Month 9 are carried forward to Month 12.

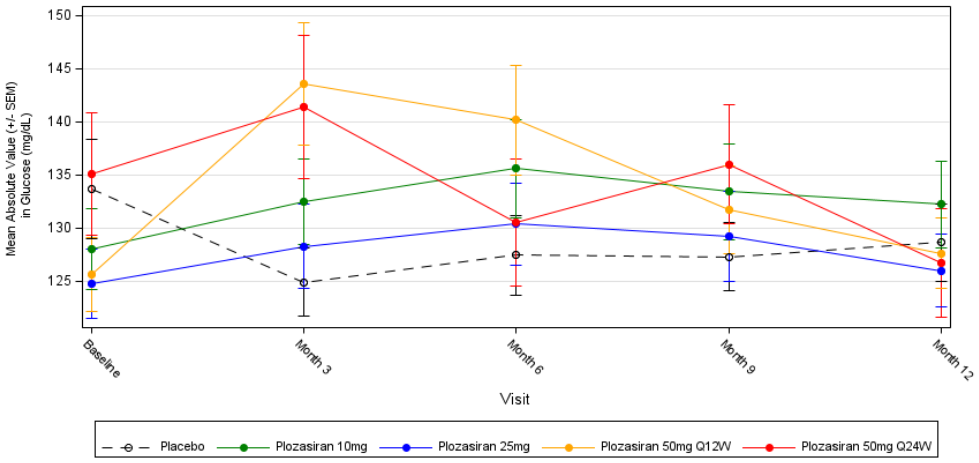
Table 70: Summary of HbA1c (%) by Visit - Pool 2 – Randomized Period Safety Set

Visit Statistics	Placebo (N=173)	Plozasiran 10mg (N=121)	Plozasiran 25mg (N=148)	Plozasiran 50mg Q12W (N=146)	Plozasiran 50mg Q24W (N=66)	Plozasiran (25mg+50mg) (N=360)	Plozasiran (10mg+25mg+50mg) (N=481)
Baseline							
n	173	121	148	146	66	360	481
Mean (SEM)	6.47 (0.087)	6.53 (0.101)	6.49 (0.093)	6.52 (0.101)	6.56 (0.135)	6.52 (0.061)	6.52 (0.052)
SD	1.141	1.113	1.126	1.223	1.100	1.159	1.147
Median	6.20	6.30	6.25	6.30	6.10	6.20	6.20
Min, Max	4.5, 10.3	4.5, 9.6	4.6, 9.5	4.3, 10.2	5.2, 8.9	4.3, 10.2	4.3, 10.2
Baseline at Month 3							
n [1]	171	121	148	146	65	359	480
Mean (SEM)	6.47 (0.087)	6.53 (0.101)	6.49 (0.093)	6.52 (0.101)	6.53 (0.134)	6.51 (0.061)	6.52 (0.052)
SD	1.132	1.113	1.126	1.223	1.082	1.156	1.144
Median	6.20	6.30	6.25	6.30	6.10	6.20	6.20
Min, Max	4.5, 10.3	4.5, 9.6	4.6, 9.5	4.3, 10.2	5.2, 8.9	4.3, 10.2	4.3, 10.2
Month 3							
n	171	121	148	146	65	359	480
Mean (SEM)	6.39 (0.088)	6.59 (0.122)	6.56 (0.100)	6.83 (0.135)	6.85 (0.189)	6.72 (0.077)	6.69 (0.065)
SD	1.149	1.345	1.223	1.626	1.520	1.455	1.428
Median	6.10	6.20	6.20	6.35	6.20	6.30	6.30
Min, Max	4.3, 10.1	4.2, 12.4	4.5, 11.9	4.6, 15.2	5.1, 11.7	4.5, 15.2	4.2, 15.2
Change from baseline to Month 3							
n [1]	171	121	148	146	65	359	480
Mean (SEM)	-0.08 (0.039)	0.06 (0.052)	0.07 (0.047)	0.31 (0.065)	0.32 (0.096)	0.21 (0.038)	0.17 (0.031)
SD	0.513	0.577	0.569	0.791	0.770	0.712	0.683
Median	-0.10	0.00	0.10	0.10	0.20	0.10	0.10
Min, Max	-1.7, 2.3	-1.8, 3.4	-2.2, 2.9	-1.5, 6.7	-1.1, 3.6	-2.2, 6.7	-2.2, 6.7
Baseline at Month 6							
n [1]	167	116	145	141	65	351	467
Mean (SEM)	6.48 (0.088)	6.56 (0.103)	6.48 (0.093)	6.54 (0.104)	6.57 (0.137)	6.52 (0.062)	6.53 (0.053)
SD	1.137	1.114	1.115	1.240	1.105	1.162	1.149
Median	6.20	6.30	6.30	6.30	6.10	6.20	6.30
Min, Max	4.5, 10.3	4.6, 9.6	4.6, 9.5	4.3, 10.2	5.2, 8.9	4.3, 10.2	4.3, 10.2
Month 6							
n	167	116	145	141	65	351	467
Mean (SEM)	6.41 (0.097)	6.59 (0.113)	6.58 (0.104)	6.89 (0.138)	6.58 (0.154)	6.70 (0.076)	6.68 (0.064)
SD	1.257	1.222	1.253	1.642	1.241	1.425	1.377
Median	6.10	6.20	6.20	6.50	6.10	6.20	6.20
Min, Max	4.4, 12.5	4.6, 10.5	4.7, 12.3	4.6, 10.9	4.9, 10.0	4.6, 12.3	4.6, 12.3
Change from baseline to Month 6							
n [1]	167	116	145	141	65	351	467
Mean (SEM)	-0.07 (0.057)	0.03 (0.056)	0.10 (0.052)	0.35 (0.073)	0.00 (0.089)	0.18 (0.041)	0.14 (0.034)
SD	0.737	0.606	0.621	0.873	0.718	0.760	0.727
Median	-0.10	0.00	0.10	0.20	0.00	0.10	0.10
Min, Max	-2.1, 4.1	-1.7, 2.2	-2.1, 3.3	-2.8, 3.4	-2.7, 1.9	-2.8, 3.4	-2.8, 3.4

Baseline at Month 9							
n [1]	164	111	142	139	62	343	454
Mean (SEM)	6.49 (0.089)	6.57 (0.105)	6.47 (0.093)	6.52 (0.103)	6.55 (0.138)	6.50 (0.062)	6.52 (0.053)
SD	1.144	1.108	1.112	1.214	1.087	1.147	1.137
Median	6.20	6.30	6.25	6.30	6.15	6.20	6.30
Min, Max	4.5, 10.3	4.6, 9.6	4.6, 9.5	4.3, 10.2	5.2, 8.6	4.3, 10.2	4.3, 10.2
Month 9							
n	164	111	142	139	62	343	454
Mean (SEM)	6.35 (0.091)	6.60 (0.116)	6.54 (0.100)	6.73 (0.128)	6.65 (0.157)	6.64 (0.072)	6.63 (0.061)
SD	1.159	1.219	1.186	1.507	1.234	1.332	1.304
Median	6.10	6.30	6.15	6.40	6.10	6.30	6.30
Min, Max	4.5, 12.1	4.6, 10.4	4.2, 11.8	4.4, 13.3	5.1, 9.8	4.2, 13.3	4.2, 13.3
Change from baseline to Month 9							
n [1]	164	111	142	139	62	343	454
Mean (SEM)	-0.14 (0.064)	0.03 (0.069)	0.07 (0.051)	0.22 (0.071)	0.10 (0.113)	0.14 (0.041)	0.11 (0.035)
SD	0.823	0.725	0.609	0.833	0.894	0.761	0.753
Median	-0.10	0.00	0.00	0.10	0.10	0.10	0.10
Min, Max	-2.9, 3.7	-2.1, 3.1	-1.8, 2.8	-3.2, 4.8	-2.7, 3.1	-3.2, 4.8	-3.2, 4.8
Baseline at Month 12							
n [1]	152	110	138	135	61	334	444
Mean (SEM)	6.49 (0.093)	6.57 (0.106)	6.46 (0.094)	6.51 (0.105)	6.53 (0.138)	6.49 (0.063)	6.51 (0.054)
SD	1.143	1.113	1.110	1.226	1.078	1.150	1.140
Median	6.20	6.30	6.25	6.30	6.10	6.20	6.30
Min, Max	4.5, 10.3	4.6, 9.6	4.6, 9.5	4.3, 10.2	5.2, 8.6	4.3, 10.2	4.3, 10.2
Month 12							
n	152	110	138	135	61	334	444
Mean (SEM)	6.36 (0.092)	6.62 (0.125)	6.46 (0.095)	6.57 (0.115)	6.38 (0.138)	6.49 (0.066)	6.52 (0.058)
SD	1.133	1.316	1.111	1.341	1.081	1.203	1.232
Median	6.10	6.25	6.15	6.30	6.00	6.20	6.20
Min, Max	4.4, 11.2	4.5, 11.1	4.8, 10.4	4.5, 10.2	4.9, 10.0	4.5, 10.4	4.5, 11.1
Change from baseline to Month 12							
n [1]	152	110	138	135	61	334	444
Mean (SEM)	-0.14 (0.064)	0.05 (0.071)	0.00 (0.054)	0.06 (0.056)	-0.15 (0.094)	0.00 (0.036)	0.01 (0.032)
SD	0.793	0.749	0.630	0.652	0.732	0.661	0.683
Median	-0.10	0.00	0.00	0.10	0.00	0.00	0.00
Min, Max	-3.7, 2.4	-2.5, 2.5	-1.7, 2.4	-2.2, 1.9	-2.7, 1.8	-2.7, 2.4	-2.7, 2.5

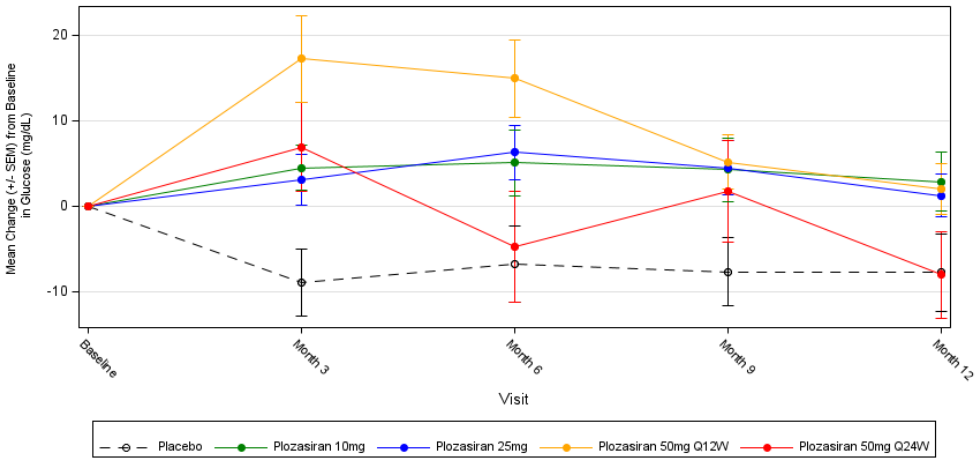
Fasting glucose similarly fluctuated throughout the study with minimal increases in mean fasting serum blood glucose for doses of plozasiran <50 mg (see Figure 39 and Figure 40). No changes from baseline were observed in mean fasting serum blood glucose at Month 12 in the plozasiran 25+50 mg group.

Figure 42: Pool 2: Plot of Mean Absolute Value (+/-SEM) in Fasting Serum Blood Glucose (Randomized Period, Safety Set)



Abbreviations: Q12W=every 12 weeks; Q24W=every 24 weeks; SEM=standard error of the mean. Note: For subjects in AROAPOC3-2001 and AROAPOC3-2002 studies, the last measurements between Month 6 and Month 9 are carried forward to Month 9; and the last measurements after Month 9 are carried forward to Month 12.

Figure 43: Pool 2: Plot of Mean Change (±SEM) in Fasting Serum Blood Glucose (Randomized Period Safety Set)



Abbreviations: Q12W=every 12 weeks; Q24W=every 24 weeks; SEM=standard error of the mean. Note: For subjects in AROAPOC3-2001 and AROAPOC3-2002 studies, the last measurements between Month 6 and Month 9 are carried forward to Month 9; and the last measurements after Month 9 are carried forward to Month 12.

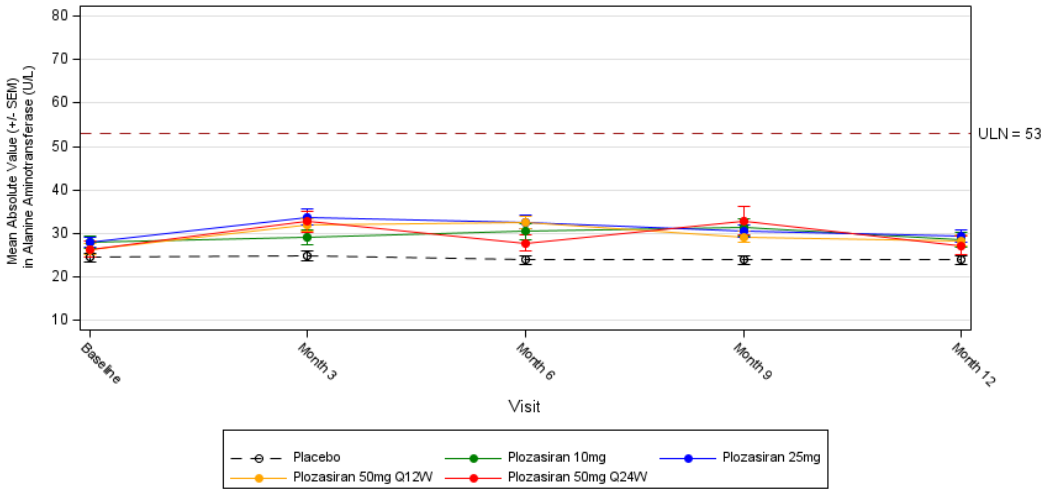
HOMA-IR also had a modest, dose-dependent increase at several timepoints, with a maximal increase from baseline of 1.257 in the plozasiran 25+50 mg dose versus a decrease of 1.203 in the placebo group at Month 3, but this measure of insulin resistance was not increased at Month 12 for those on plozasiran. C peptide levels and insulin levels did not demonstrate a consistent, dose-dependent change in relationship to study drug in Pool 2.

Liver Function Tests

The changes in LFTs noted in Pool 2 (were generally minimal. Plozasiran did not have any clinically meaningful impact on parameters such as ALP, GGT, or bilirubin, even at the plozasiran 50 mg dose.

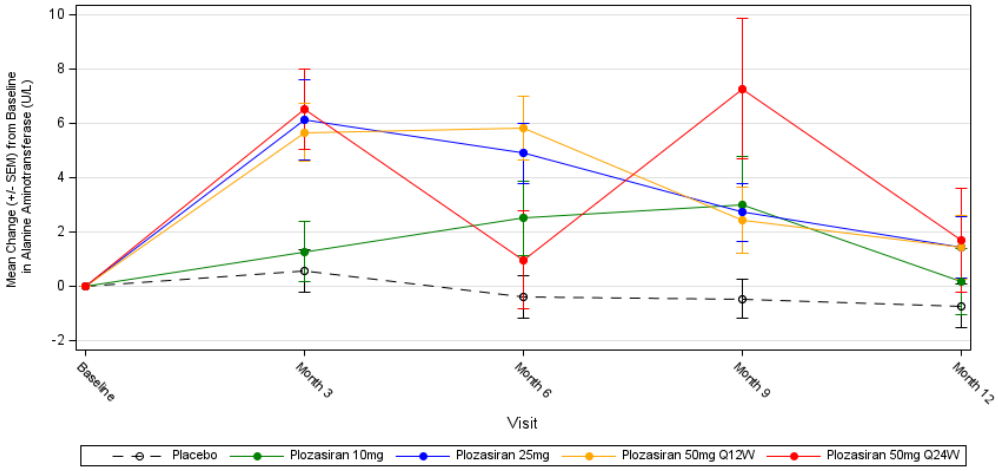
In contrast, plozasiran did appear to modestly and reversibly increase transaminases. As shown in Figure 41 and Figure 42, mean increases in ALT were less than 10 U/L. Effects on AST were even less pronounced and largely resolved by end of the study. No Grade 3 or Grade 4 shifts in ALT or AST were observed on plozasiran therapy. Generally, the dose-related effects on mean increases and shifts to >ULN observed in Pool 1 were absent in the larger Pool 2 database.

Figure 44: Pool 2: Plot of Mean Absolute Value (+/-SEM) in ALT (Randomized Period, Safety Set)



Abbreviations: ALT=Alanine aminotransferase; Q12W=every 12 weeks; Q24W=Every 24 weeks; SEM = Standard error of the mean. Note: For subjects in AROAPOC3-2001 and AROAPOC3-2002 studies, the last measurements between Month 6 and Month 9 are carried forward to Month 9, and the last measurements after Month 9 are carried forward to Month 12.

Figure 45: Pool 2: Plot of Mean Absolute Value (+/-SEM) in ALT (Randomized Period, Safety Set)



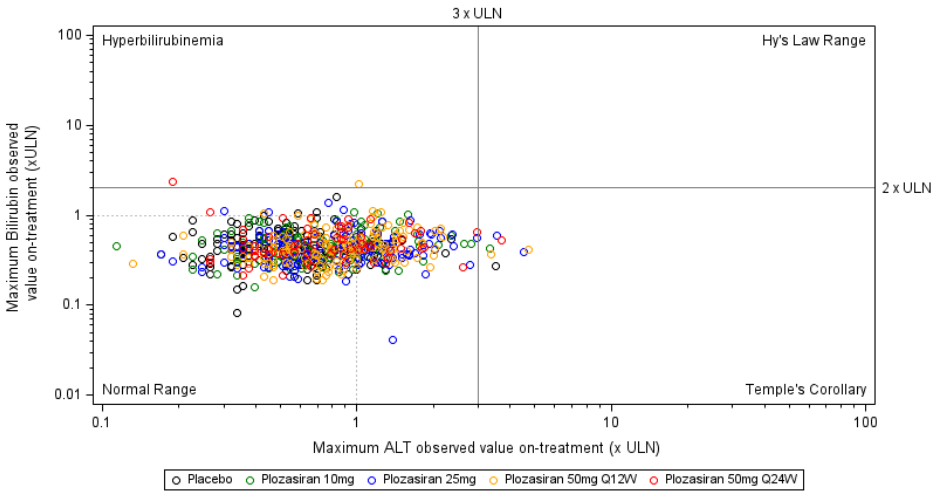
Abbreviations: ALT=alanine aminotransferase; Q12W=every 12 weeks; Q24W=every 24 weeks; SEM=standard error of the mean. Note: For subjects in AROAPOC3-2001 and AROAPOC3-2002 studies, the last measurements between Month 6 and Month 9 are carried forward to Month 9, and the last measurements after Month 9 are carried forward to Month 12.

Analysis of those with normal liver function at enrollment developing a value >ULN at any time confirmed a risk difference with CIs excluding zero for all dose groupings compared with placebo. EAIR analysis suggest that these transaminase increases were limited to abnormalities crossing the ULN, with no significant increase in more worrisome transaminitis (eg, to levels >3X ULN). Separate analyses of subjects with chronic liver disease at baseline revealed a numerical increase in risk difference for ALT (and AST, to a lesser extent), but CIs were wide and crossed zero in this subpopulation. EAIR analysis confirmed a significant increase in ALT (but not AST) above baseline in subjects with chronic liver disease for all doses of plozasiran; however, these increases did not exceed 2x the baseline value. Direct bilirubin levels also appeared to increase in subjects with chronic liver

disease, but this finding may have been spurious as total bilirubin (and all other LFT values) were not increased.

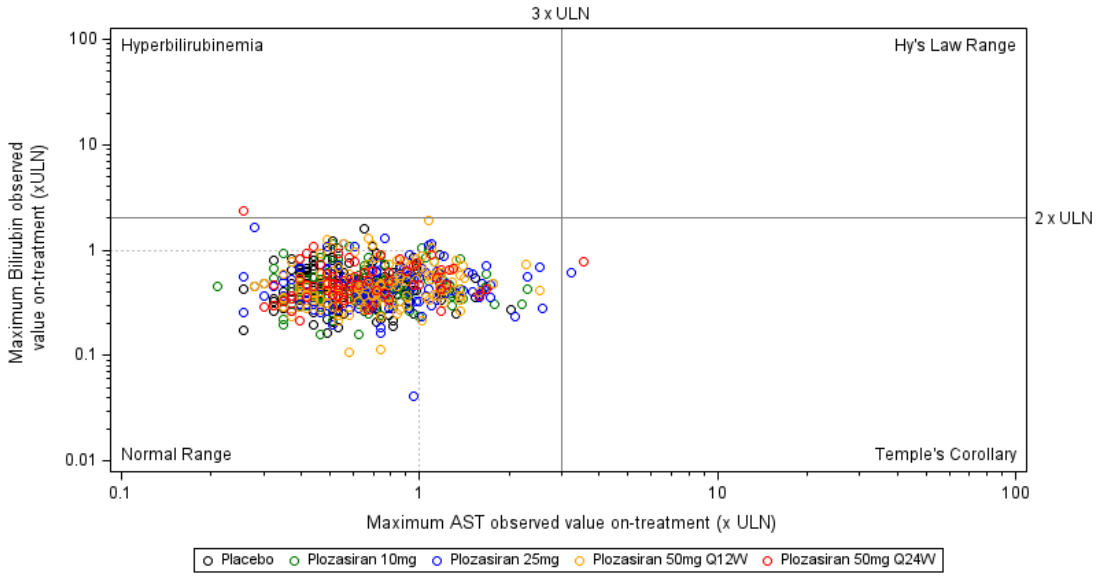
There were no cases of Hy's Law observed in Pool 2.

Figure 46: Pool 2: Scattered Plot Maximum ALT Versus Maximum Total Bilirubin (Randomized Period, Safety Set)



Abbreviations: ALT=alanine aminotransaminase; AST=aspartate aminotransaminase; ULN=upper limit of normal; Q12W=every 12 weeks; Q24W=every 24 weeks. Note: eDISH plot is using peak ALT along with bilirubin from the same visit.

Figure 47: Pool 2: Scattered Plot Maximum AST versus Maximum Total Bilirubin (Randomized Period, Safety Set)



Abbreviations: ALT=Alanine aminotransaminase; AST=Aspartate aminotransaminase; ULN=Upper limit of normal; Q12W=every 12 weeks. Q24W=every 24 weeks. Note: eDISH plot is using peak ALT/AST along with bilirubin from the same visit.

In summary, Pool 2 is consistent with the impression from Pool 1 that plozasiran has an impact on transaminases, especially ALT, but that the increases are modest, reversible, and not accompanied by

significant or sustained liver injury, cholestasis, or Hy's Law violations. Importantly, there is no evidence of disproportionate harm amongst individuals with chronic liver disease at baseline.

Renal Function Tests

As stated in the introduction to Section 7, mean eGFR and shift tables cannot be used for renal function tests parameters in Pool 2. Median values for eGFR were 60 mL/min/m2 and remained at this value throughout the quarterly testing for Pool 1, 2, and 3. This is only useful in showing that more than 50% of subjects had eGFR values above the LLN at baseline and all subsequent time points.

Unlike the situation for mean and median creatinine values at baseline in Pool 1, in Pool 2 the creatinine values were reasonably well balanced (mean creatinine ranging from 72.4 µmol/L-83.1 µmol/L [0.819-0.940 mg/dL] across the various treatment groups). Mean and median creatinine values increased modestly and similarly in the plozasiran groups at Month 3. Mean and median change from baseline values for the plozasiran 25 mg group were 2.4 µmol/L and 1.0 µmol/L (0.027 and 0.010 mg/dL), respectively. These values changed minimally through Month 12.

Regarding BUN, mean and median values were generally balanced at baseline, though modestly higher for the plozasiran 25 mg group. During the 12 months of follow-up, BUN values were generally stable or slightly lower in all dose groups.

Shifts for serum creatinine from normal baseline to Grade 1 occurred in 14.1% to 23.1% of subjects in the various treatment groups, including the placebo group, without any indication of dose-relatedness for plozasiran. Shifts to Grade 2 were rare (highest rate 2.1% with placebo. Across the subjects with abnormal creatinine values at baseline, there no shifts to Grade 3 and shift to Grade 4 were rare (1 [3.4%] subject in the placebo group and no subjects in the plozasiran groups). Of note, when assessing shifts on a quarterly basis in subjects with abnormal creatinine values at baseline, shifts from abnormal to normal creatinine values were much more common than shifts to a higher grade for placebo and for all plozasiran doses. BUN shifts did not show a different pattern. Overall, BUN and creatinine values showed mild and similar deterioration over time in Pool 2. Based on mean and median serum concentrations of BUN and creatinine and their shifts, there is not a clear difference between any dose of plozasiran and placebo.

Haematology

A review of Pool 2 suggests that plozasiran does not have a clear impact on any hematologic parameter of interest. Specifically, no anaemia, thrombocytopenia, or clear leukocyte abnormality was observed, consistent with Pool 1. Minor fluctuations in leukocytes did occur in the study (eg, an increase of 0.39 in the plozasiran 25+50 mg group and 0.14 109/L in the placebo group), but these were not clinically significant. Similarly, plozasiran did not appear to induce any coagulopathy such as a consistent alteration in international normalized ratio, prothrombin time, or fibrinogen level.

Platelets

Mean platelet counts were stable for all dose groups in Pool 2.

Urinalysis

Plozasiran usage was not associated with any clear pattern of urinalysis abnormality in clinical studies, including AROAPOC3-2001, AROAPOC3-2002, and AROAPOC3-3001.

Pool 3: Open-Label Extension Studies

Chemistry

Pool 3 results did not show that prolonged plozasiran therapy is associated with a delayed or cumulative impact on renal function. For example, the overall incidence of glomerular filtration rates (GFRs) falling below the LLN in the plozasiran 25+50 mg group was 12.4% of subjects during the OLE, compared to 13.6% of subjects in the DB phase. As was observed in Pool 2, changes in creatinine on treatment were modest, and most increases were Grade 1 (increases restricted to 1.0 to 1.5× ULN). No Grade 3 or Grade 4 changes in creatinine were observed.

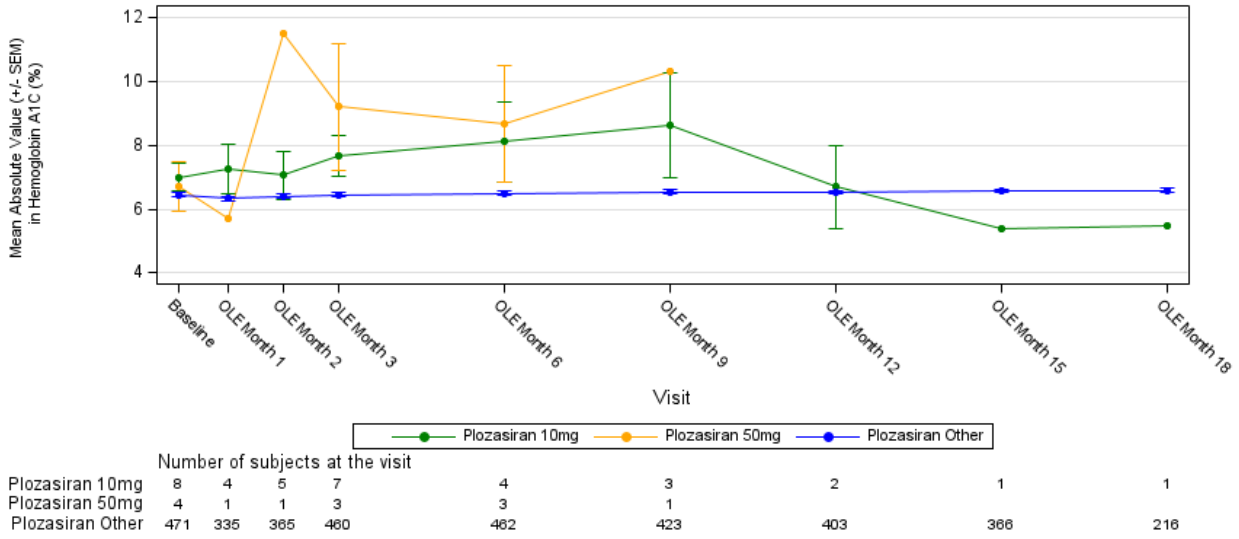
Hyperglycaemic parameters, liver function and renal function parameters are discussed below. Figures include the plozasiran 10 mg and 50 mg doses for completeness. However, because the extensions were designed to rapidly converge on the plozasiran 25 mg dose, the subject numbers are small for the plozasiran 10 mg and 50 mg doses and fall rapidly as subjects either discontinue or transition to the plozasiran 25 mg dose (labeled plozasiran other). As such, the data for the plozasiran 10 mg and 50 mg doses are not interpretable.

Hyperglycaemic Parameters

Glycaemic Control by HbA1c, Fasting Blood Glucose, and HOMA IR

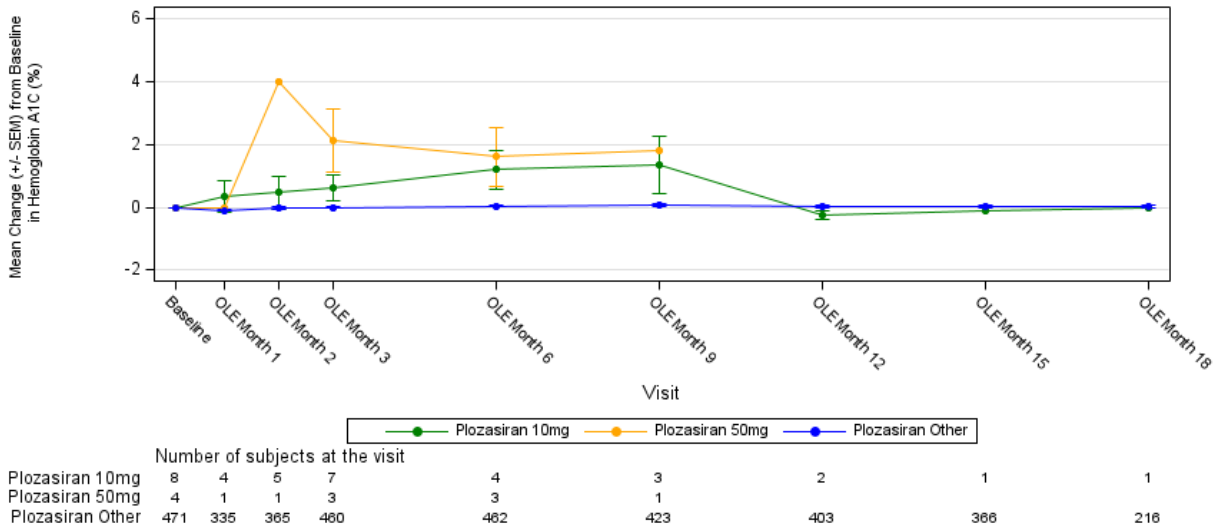
Mean HbA1c values stabilized in the plozasiran other group (ie, plozasiran 25 mg), demonstrating that glycemia is not deteriorating over time. There were not enough subjects in the 10 mg and 50 mg group to access the effect of plozasiran on mean HbA1c values. The same was observed for fasting glucose. Mean and median HOMA-IR values changed minimally. Due to a low number of subjects in the plozasiran 10 (N=8) and 50 (N=4) mg groups, no conclusions were drawn for these dose levels.

Figure 48: Pool 3: Plot of Mean Absolute Value (±SEM) in HbA1c (OLE Portion, Safety Set)



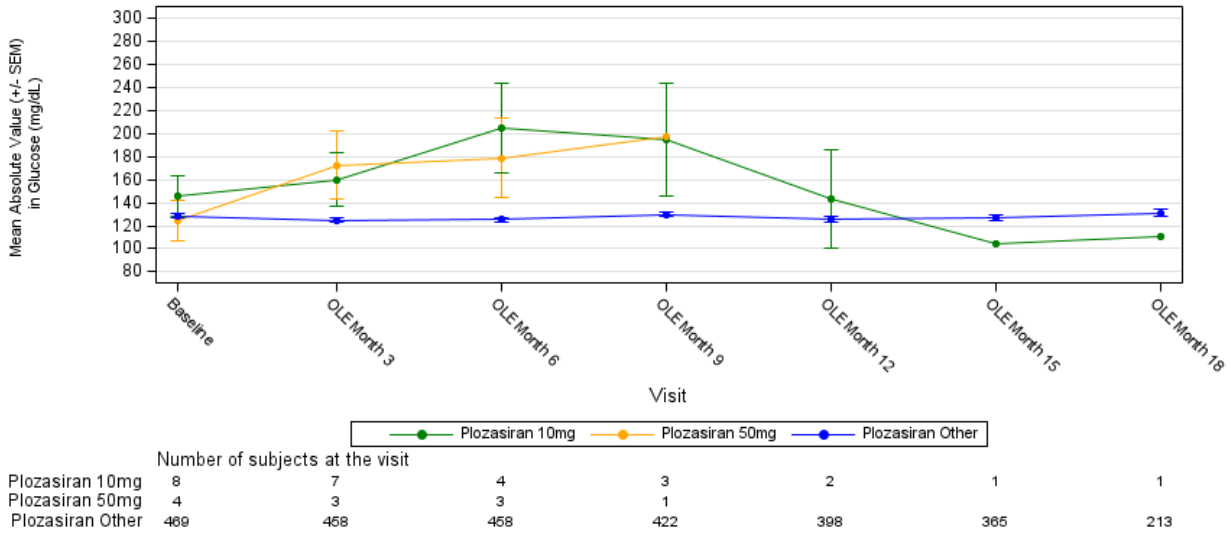
Abbreviations: HbA1c=hemoglobin A1c; SEM=standard error of the mean; OLE=open-label extension. Note: Baseline is defined as the baseline from the randomized period. Subjects who take plozasiran 25 mg through the OLE period or switch doses during the OLE period are summarized under Plozasiran Other.

Figure 49: Pool 3: Plot of Mean Change (±SEM) in HbA1c, OLE Portion, Safety Set



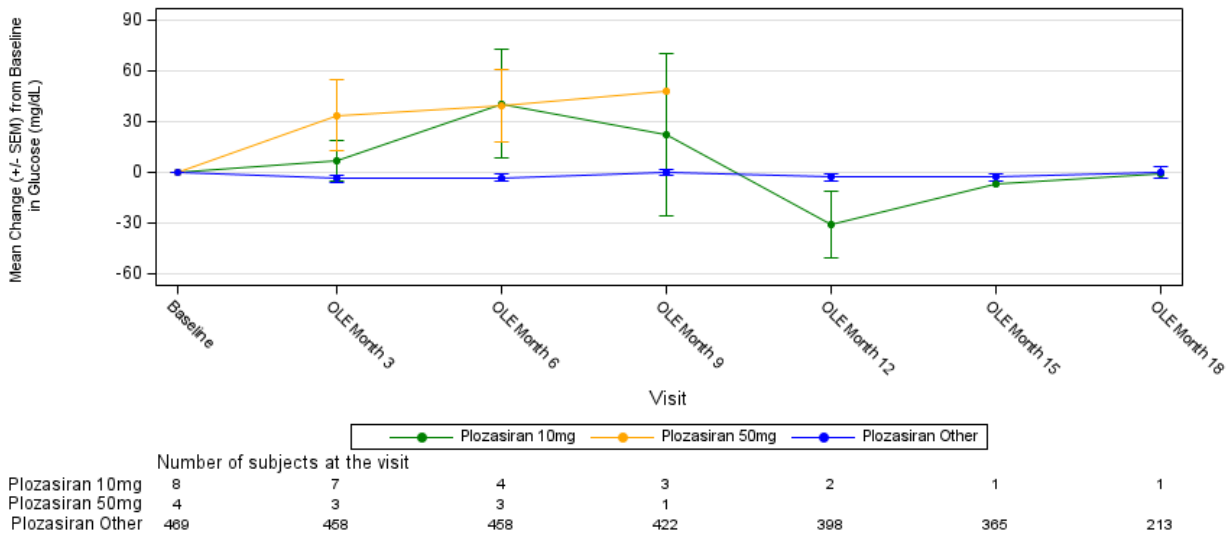
Abbreviations: HbA1c=hemoglobin A1c; SEM=standard error of the mean; OLE=open-label extension. Note: Baseline is defined as the baseline from the randomized period. Subjects who take plozasiran 25 mg through the OLE period or switch doses during the OLE period are summarized under Plozasiran Other.

Figure 50: Pool 3: Plot of Mean Absolute Value (±SEM) in Fasting Serum Blood Glucose (OLE Portion, Safety Set)



Abbreviations: SEM=standard error of the mean; OLE=open-label extension. Note: Baseline is defined as the baseline from the randomized period. Subjects who take plozasiran 25mg through the OLE period or switch doses during the OLE period are summarized under Plozasiran Other.

Figure 51: Pool 3: Plot of Mean Change (±SEM) in Fasting Serum Blood Glucose (OLE Portion, Safety Set)

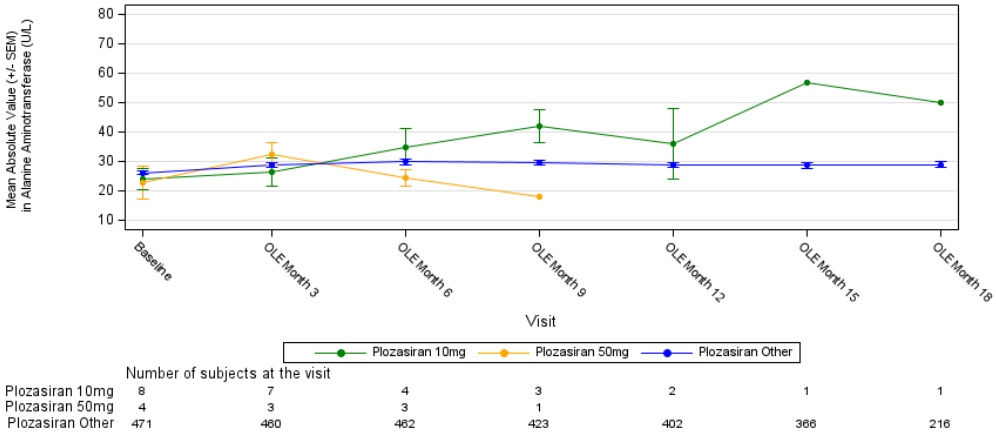


Abbreviations: SEM=Standard error of the mean; OLE=Open-label extension. Note: Baseline is defined as the baseline from the randomized period. Subjects who take plozasiran 25 mg through the OLE period or switch doses during the OLE period are summarized under Plozasiran Other.

Liver Function Tests

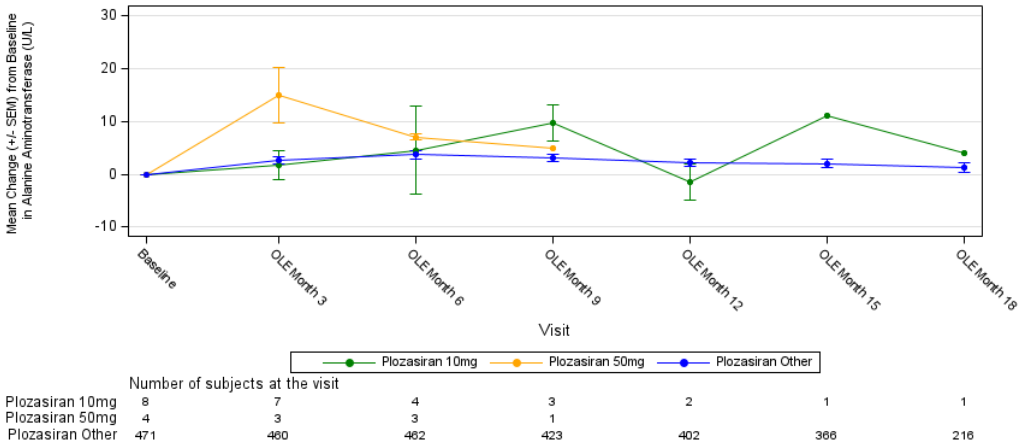
As discussed for Pools 1 and 2, plozasiran use was associated with a modest impact on transaminases with initial dosing. During the OLE, transaminase levels stabilized by Month 6 and then were essentially flat to declining for the plozasiran other group. ALT increases >ULN occurred in 11.3%, 14.6%, and 28.0% of subjects in the plozasiran 10, 25, and 50 mg groups, respectively. AST increases >ULN occurred in 6.6%, 11.3%, and 28.0% of subjects in the plozasiran 10, 25, and 50 mg groups, respectively. These increases were typically modest with a small number of subjects who experienced transaminase elevations of >3×ULN. No subjects had plozasiran dosing held or discontinued due to liver function abnormalities or met the criteria for Hy's Law during follow-up and no subject with chronic liver disease at baseline experienced more severe transaminitis than those with normal liver function at baseline.

Figure 52: Pool 3: Plot of Mean Absolute Value (±SEM) in ALT (OLE Portion, Safety Set)



Abbreviations: ALT=alanine aminotransferase; SEM=standard error of the mean; OLE=open-label extension. Note: Baseline is defined as the baseline from the randomized period. Subjects who take plozasiran 25 mg through the OLE period or switch doses during the OLE period are summarized under Plozasiran Other.

Figure 53: Pool 3: Plot of Mean Change (±SEM) in ALT (OLE Portion, Safety Set)



Abbreviations: ALT=alanine aminotransferase; SEM=standard error of the mean; OLE=open-label extension. Note: Baseline is defined as the baseline from the randomized period. Subjects who take plozasiran 25 mg through the OLE period or switch doses during the OLE period is summarized under plozasiran Other.

Renal Function Tests

eGFR remains uninterpretable except to mention that the median value remains at 60 mL/min/m^2.

At Month 3, the mean change from baseline for creatinine was 3.7 µmol/L (0.041 mg/dL) (median 3.0 µmol/L [median 0.040 mg/dL]) and remained consistent through Month 18 for subjects treated with plozasiran 25 mg. Similar trends were observed for BUN. The results indicate that renal function is not deteriorating over time in the OLEs. Due to a low number of subjects in the plozasiran 10 (N=8) and 50 (N=4) mg groups, no conclusions were drawn for these dose levels.

Haematology

No meaningful changes in haematology parameters over time were noted.

Platelets

Platelets were essentially unchanged during the period of observation to date in Pool 3.

5.4.10. Post-marketing experience

Not applicable.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

The main source for the clinical safety evaluation of plozasiran is the placebo-controlled, pivotal, phase 3 study in FCS patients (AROAPOC3-3001), supported by two phase 2, placebo-controlled studies in SHTG and moderate HTG patients (AROAPOC3-2001, AROAPOC3-2002), and a long-term phase 2b OLE study in dyslipidaemia patients (AROAPOC3-2003).
The safety evaluation is based on an integrated (pooled) safety analysis. Pool 1, i.e. 1-year data of the pivotal phase 3 study in FCS patients alone, provides the safety profile in the target population. However, the pool 1 dataset is limited and generally may not be sufficiently sensitive to signal differences between treatment groups. Pool 2, i.e. ~1-year data of the phase 2 and 3 placebo-controlled studies in FCS, SHTG and moderate HTG patients, includes patients with comparable diseases, although of different origin. This substantially larger safety dataset could better signal frequency differences between treatment arms to identify possible adverse drug reactions of plozasiran. Further, pool 3 consisted of longer-term data from the OLE period of the pivotal phase 3 study and from the OLE study in dyslipidaemia patients.

Regarding treatment exposure, in pool 1, 75 FCS patients were included in the safety analysis. Of those, 25 patients were on placebo vs 50 patients on plozasiran (n=26 plozasiran 25 mg, n=24 plozasiran 50 mg. Of the 50 on plozasiran, 90% of patients (n=45) was exposed >10-12 months.
In pool 2, 654 participants were included, of who 173 on placebo, 121 on plozasiran 10 mg, 148 on plozasiran 25 mg, 146 on plozasiran 50 mg Q12W and 66 on plozasiran 50 mg Q24W. Of the 481 patients on plozasiran, 409 (85.0%) participants received 2 injections, while only 45 patients received 4 injections and came from the pivotal phase 3 study. The majority of patients (n=410; 85.1%) was treated >4-10 months, and again, the patients (n=45, 9.4%) who were treated >10-12 months, came from the pivotal phase 3 trial.
Further, 483 patients on plozasiran were included in pool 3, i.e. n=8 (1.7%) on 10 mg, n=471 (97.5%) on 25 mg and n=4 (0.8%) on 50 mg. Of the 483 participants, the plozasiran exposure was >10 months for 422 participants (89.1%), >16 months for 309 patients (63.9%), and >22 months for 63 participants (13.0%).

In pool 1, the pivotal phase 3 study, adverse events (AEs) were frequently reported, and the incidence of AEs was slightly higher in the plozasiran groups, i.e. 88.5% and 83.3% on plozasiran 25 mg and 50 mg, compared to the placebo group, i.e. 80%. Abdominal pain (20.0% placebo vs 26.9% 25 mg, 25.0% 50 mg plozasiran), COVID-19 (0.0% placebo vs 19.2% 25 mg, 29.2% 50 mg plozasiran), headache (8.0% placebo vs 11.5% 25 mg, 20.8% 50 mg plozasiran,) and nasopharyngitis (12.0% placebo vs 19.2% 25 mg, 8.3% 50 mg plozasiran) were most commonly reported with higher frequencies in the plozasiran groups.

The findings in pool 2 were generally consistent with pool 1. The overall incidence of AEs was also slightly higher in the plozasiran groups, i.e. 73.6% on 10 mg, 70.3% on 25 mg, 79.5% on 50 mg Q12W and 74.2% on 50 mg Q24W, compared to placebo, i.e. 68.2%, showing no clear dose-dependent effect, and of which most cases were mild or moderate in severity. The most frequently reported AEs were COVID-19 (12.1% placebo vs 15.5% 25 mg, 15.8% 50 mg Q12W plozasiran), upper respiratory tract infection (7.5% placebo 9.5% vs 25 mg, 6.8% 50 mg Q12W plozasiran), type 2 diabetes mellitus (4.0% placebo vs 5.5% 25 mg, 9.6% 50 mg Q12W plozasiran), headache (4.6% placebo vs 6.8% 25 mg, 7.5% 50 mg Q12W plozasiran) and abdominal pain (4.0% placebo vs 4.7% 25 mg, 8.9% 50 mg Q12W plozasiran). Also here, the highest frequencies appeared in the plozasiran groups.
The overall AE incidences in pool 3 showed a similar AE pattern and were slightly lower with 64.4% and 61.5% in the plozasiran 25 mg and 50 mg groups, respectively.

No deaths occurred in pool 1, i.e. in patients on FCS during the pivotal phase 3 study. However, 4 deaths have been reported in pool 2, and 2 in pool 3. None of those were considered related to the use of plozasiran, as based on detailed description of these cases.

The overall incidence rate of severe adverse events (SAEs) in pool 1 was relatively low with even a lower incidence in the plozasiran groups, i.e. 19.2% plozasiran 25 mg and 8.3% plozasiran 50 mg, compared to the placebo group, i.e. 28.0%, with no dose-dependency observed. The incidence difference between the groups was mainly due to gastrointestinal-related SAEs with 20.0%, 7.7.%, and 4.2% patients in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. AEs were mostly isolated events. Only pancreatitis-related SAEs were reported in >1 subject.
In pool 2, generally similar and low findings were observed, with also a lower incidence in the plozasiran groups, i.e. 8.1% and 11.0% in 25 mg and 50 mg Q12W plozasiran, respectively, compared to the placebo group with 12.7%, which is reassuring. The most frequent reported SAEs reported with plozasiran use were pancreatitis acute (n=4 (2.3%) placebo vs n=2 (1.4%) in 25 mg, n=2 (0.7%) in 50 mg Q12W plozasiran), COVID-19 (n=1 (0.6%) placebo vs n=2 (1.4%) in 25 mg, n=1 (0.7%) in 50 mg Q12W plozasiran), osteoarthritis (n=0 (0%) placebo vs n=1 (0.8%) in 10 mg, n=0 (0%) in 25 mg and n=1 (0.7%) in 50 mg Q12W plozasiran) and acute kidney injury (AKI; n=0 (0.0%) placebo vs n=1 (0.7%) in 25 mg, n=1 (0.7%) in 50 mg Q12W plozasiran).
Further, pool 3 showed no increase in SAE incidences, i.e. 10.0%, and 15.4% of subjects in the plozasiran 25, and 50 mg groups, respectively. The exposure adjusted incidence rate (EAIR) of pool 3 with 8.8/100 PYs appeared to be similar compared to pool 2 with 9.3/100 PYs. No specific patterns for an unexpected safety signal could be identified from the current available SAE data.

Adverse events of special interest (AESI) included hyperglycaemia/ new onset diabetes mellitus, worsening of glycaemic control, local injection site reaction, and acute pancreatitis. These identified AESIs are all discussed below:

Regarding hyperglycaemia/new onset diabetes mellitus, it is known that FCS patients can become diabetic due to loss of islet cell mass caused by recurrent or severe pancreatitis.
Based on the AEs reported in pool 1, the overall incidence of hyperglycaemia/new onset diabetes mellitus (narrow SMQ) events was higher with the use of plozasiran, as compared to placebo. This was n=2 (8.0%) of subjects in the placebo group versus n=6 (23.1%) and n=5 (20.8%) of subjects in the plozasiran 25 mg, and plozasiran 50 mg groups, respectively. Glycosylated haemoglobin (HbA1c) increased was the most frequent PT, which occurred in n=0 (0%), n=3 (11.5%), and n=3 (12.5%) in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. All other PTs occurred in only 1 subject in any dose group.
This imbalance was also seen in pool 2 with a higher frequency in the plozasiran groups (n=21,

14.2% and n=30, 20.5% for 25 mg and 50 mg Q12W, respectively) compared to the placebo group (n=17, 9.8%), and the 95% CI of the risk difference excluded zero in the plozasiran 25+50 mg group (8.4% [95%CI: 2.4, 14.4]), mainly driven by the plozasiran 50 mg dose. The most common PTs were type 2 diabetes mellitus and glycosylated haemoglobin (HbA1c) increased.
Looking at the AEs of worsening of glycaemic control, based on the AEs reported in pool 1, a significantly higher incidence rate was found in the plozasiran groups (n=5 [19.2%] in 25 mg, n=5 [20.8%] in 50 mg) vs placebo (n=2 [8.0%]). This was also mainly driven by the PT of glycosylated haemoglobin (HbA1c) increased. Of the 27 subjects with diabetes at baseline (HbA1c ≥6.5%) incidences of AEs was higher in the plozasiran-treated subjects (60% in the plozasiran 25 mg and 75% in the plozasiran 50 mg group), compared to placebo (11.1%).
In pool 2, the incidence rates of AEs showed a generally similar trend and was n=18 (10.4%) for placebo, n=19 (12.8%) for plozasiran 25 mg group, and n=30 (20.5%) for plozasiran 50 mg Q12W. Type 2 diabetes and glycosylated haemoglobin (HbA1c) increased were again the most frequent PTs, with incidences of 2.3% and 4.0% for placebo, 4.1% and 5.4% for plozasiran 25 mg, and 4.8% and 9.6% for plozasiran 50 mg, respectively. Further, an additional analysis showed that the effects of plozasiran on glycaemic control were most apparent in diabetes patients, since in these groups a large difference was seen on the AE incidence rate, i.e. 31.6% in the plozasiran group versus 16.9% in the placebo group. Data from pool 3 were generally consistent.
In summary, the safety findings of the reported AESIs of hyperglycaemia/new onset diabetes mellitus and of worsening of glycaemic control, and the increases observed for the HbA1c values clearly point to a relationship with the use of plozasiran. Therefore, hyperglycaemia has been added as an ADR to section 4.8 of the SmPC. Further, a description of this ADR has been added to section 4.8 of the SmPC and a warning has been added to section 4.4. of the SmPC.

Regarding the AESI of local injection site reactions, overall, the incidence of these AEs occurred in n=1 (4.0%) subjects in the placebo group vs in n= 4 (15.4%) subjects in the plozasiran 25 mg group, and n= 1 (4.2%) subjects in the plozasiran 50 mg group.
In pool 2, the AEs of local injection site reaction were n=2 (1.2%; EAIR 1.4/100 PYs) for placebo, and higher in the plozasiran groups with n=7 (4.7%; EAIR 5.9/100 PYs) for plozasiran 25 mg, and n=6 (4.1%; 5.2/100 PYs) for plozasiran 50 mg Q12W. The most common PT was injection site pain.
In pool 3, the OLE period, EAIR for the EASI was 2.1/100 PYs in the plozasiran 25 mg group, which was lower than pool 2. Data show that the number of subjects with ISR AEs pointed to be highest after the first injection and did not increase over time, which has been added to the description of selected ADRs in section 4.8 of the SmPC.

Regarding the AESI of acute pancreatitis, in the safety data of pool 1, the incidence rate of acute pancreatitis was low, and lower in the plozasiran groups (n=2, 7.7% and n=2, 8.3% in the 25 and 50 mg), as compared to the placebo group (n=6, 24%). Also based on the AEs reported in pool 2, the AE frequency was lower in the plozasiran groups (n=2, 1.4% and n=3, 2.1% in plozasiran 25 mg and 50 mg Q12W) compared to the placebo group (n=9, 5.2%) during the on-treatment period. These findings are consistent with the long-term data in pool 3.
Current data do not provide concerns regarding acute pancreatitis with the use of plozasiran and were consistent with the efficacy findings.

Since renal safety have been an important issue for earlier oligonucleotides, the applicant assessed the cases on acute kidney injury (AKI), and 5 cases have been identified of which one was a duplet and the last case seemed to be erroneous, since no abnormal creatinine values were reported. Of note, no cases were revealed from the pivotal phase 3 study, only from the phase 2 studies. Of the three cases left, no relationship of AKI and plozasiran use has been identified.

Further, regarding renal function laboratory parameters in pool 1, the mean change from baseline of creatinine values at month 3 was 8.3 µmol/L, 3.5 µmol/L and 9.2 µmol/L, for placebo, plozasiran 25 mg and 50 mg, respectively, indicating an increase, which remained over time. At month 12, the mean change from baseline of creatinine values were 5.8 µmol/L, 8.4 µmol/L, 10.5 µmol/L for placebo, plozasiran 25 mg and 50 mg, respectively. A similar effect was observed for BUN. In pool 2, the mean creatinine values also increased in the plozasiran groups at month 3 and values remained consistent through month 12, while the effect was lower for placebo. A similar effect was seen with the changes on the BUN values. No new safety signals were received from pool 3. Subsequently no clinical consequences on renal safety have been observed yet in the patients using plozasiran. However, although the AKI cases did not identify any safety concerns, moderate elevated creatinine values have been shown with the use of plozasiran, as compared to placebo. Further, adverse effects on the kidney have also been observed in the non-clinical studies. Based on this information, renal toxicity on the long term is covered by 'long-term safety' as missing information in the RMP and 'renal toxicity' has been added as a safety concern in the PSURs for further follow-up of this safety concern.

Liver function laboratory tests (LFTs) have been assessed. In pool 1, increases in ALT and AST have been identified in the patients on plozasiran, while no such an effect was seen in placebo. No patients had a peak liver function value >3×ULN and no cases with Hy's Law criteria were observed. The incidence rate of ALT levels >ULN increased with 4.0%, 30.8%, and 45.8% patients in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. This was also seen with the AST levels >ULN with 8.0%, 19.2%, and 37.5% subjects in the placebo, plozasiran 25 mg, and plozasiran 50 mg groups, respectively. Only one AE on ALT increase seemed to be reported. No cases of DILI were identified.
Also in pool 2, an increase in ALT and AST has been observed, consistent with pool 1. The increases seemed to be limited to >ULN or grades 1 and 2, no cases with Hy's Law criteria were observed and the figures do not show a dose-dependent effect, which was seen in pool 1, with no new signals from pool 3.
Overall, modest elevated AST and ALT values have been shown with the use of plozasiran. Further, adverse effects on the liver have been observed with rats and monkeys in the non-clinical studies. Therefore, both "ALT increased" and "AST increased" as ADRs to section 4.8 of the SmPC.

The incidence of subjects who discontinued due to an AE was low, which point out to acceptable tolerability.

Comparisons of the safety in special populations were made by the applicant in pools 1 and 2 of the integrated safety analysis, which is acceptable. Subgroup analyses were performed in age, BMI, sex, race, ethnicity, baseline diabetes disease state, baseline liver disease state, confirmation of FCS, and in the extrinsic factor geographic region. None of the subgroups provided concerning data, new relevant notable patterns and no clinically meaningful differences were observed.

Regarding use in pregnancy and lactation, the performed non-clinical studies of plozasiran demonstrated no concerns around foetal toxicity in animals with clinically relevant exposures (see non-clinical assessment on developmental and reproductive toxicology). Of note, use in pregnant or breast-feeding women is included as missing information in the RMP.

No significant safety signals have been observed in the overdose, medication errors or drug abuse cases. No specific studies on the effects of plozasiran on the ability to drive or operate machinery have been performed, which is acceptable.

Regarding clinical chemistry laboratory values in pools 1 and 2, were mostly within normal limits, except for hyperglycaemic parameters and liver and renal function tests, which have been discussed earlier.
No meaningful changes or trends on urinalysis parameters were noted.
Regarding the haematology and coagulation laboratory values in pools 1 and 2, no clinically meaningful changes have been identified. Regarding platelets, changes in mean and median platelet counts were not clinically relevant. One AE of thrombocytopenia was reported in 1 subject randomized to plozasiran 50 mg in pool 1, but no association could have been revealed with the use of plozasiran.

Regarding vital signs, in pools 1 and 2, there were no notable trends presented for blood pressure, pulse and weight. No safety signals were observed for electrocardiograms done in pools 2, and 1 and 3. A formal thorough QT/QTc study showed that plozasiran did not have a statistically or clinically significant effect on the QTcF interval or morphology of ECG waveforms at the supratherapeutic dose of plozasiran 100 mg dosed SC (see section on clinical pharmacology). Further, the safety pools did not identify any meaningful prolongations in QT.

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

Based on the frequencies and the relevant imbalances of AEs between the treatment groups, i.e. a difference of >2% AEs in plozasiran 25 mg compared to placebo within pool 2, hyperglycaemia, headache, nausea, local injection site reaction and liver disorder (ALT increased, AST increased) included as adverse drug reactions (ADRs) to section 4.8 of the SmPC.

Table 74: Adverse draug reactions included in the SmPC

System organ class	*Adverse reaction*	*Frequency*
Metabolism and nutrition disorders	Hyperglycaemiaa	Very common
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Nausea	Common
Hepatobiliary disorders	Liver disorder (ALT increased, AST increased)	Uncommon
General disorders and administration site conditions	Injection site reactiona	Common

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
a See section "Description of selected adverse reactions"

5.4.11.2. Conclusions on clinical safety

The clinical safety data set for plozasiran in FCS patients is limited as expected due to its orphan designation. However, based on the currently available safety data in patients with FCS and in patients with SHTG and moderate HTG, considered as comparable diseases although of different origin, plozasiran appeared to be generally well tolerated with only 1.4% patients, who discontinued

plozasiran during the treatment period. The most commonly reported AEs were hyperglycaemia, headache, nausea, local injection site reaction. Headache and nausea were mild or moderate of nature. These findings were supported by longer-term findings with generally similar outcomes.

6. Risk management plan

6.1. *Safety specification*

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 75: Summary of safety concerns in proposed RMP, version 0.4.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant or breast-feeding women Long term safety

6.1.2. Discussion on proposed safety specification

Regarding use in pregnant or breast-feeding women, there are currently very limited data on the effect of plozasiran in pregnant women as the clinical studies excluded pregnant women and enforced contraception methods. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. It is unknown whether plozasiran or metabolites are excreted in human milk. Since there are currently no available data of patients, as plozasiran could be used in fertile women in the future, as a precautionary measure, it is mentioned in section 4.6 of the SmPC, that the use of plozasiran during pregnancy and breast-feeding is preferable to be avoided. The use in pregnant or breast-feeding women is included as missing information in the RMP.

Also, since the pivotal clinical trial covered a limited period of time but the treatment is intended for a long-term basis, long-term safety has been included as missing information in the RMP.

6.2. *Pharmacovigilance plan*

6.2.1. Proposed pharmacovigilance plan.

Routine Pharmacovigilance Activities

Routine pharmacovigilance activities including adverse reactions reporting, signal detection and pregnancy follow-up to outcome will be employed.

Additional Pharmacovigilance Activities

Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
AROAPOC3-3001 Open-Label Extension (ongoing)	The aim of the study is to collect further long-term safety and efficacy data on plozasiran in patients with FCS	Long term safety in patients with FCS	Final CSR	April 2027

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6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The proposed routine pharmacovigilance activities are acceptable.

6.2.2.2. Additional pharmacovigilance activities

OLE study was included as a Category III study as missing information, which is acceptable.

6.3. *Plans for post-authorisation efficacy studies*

Not applicable

6.4. *Risk minimisation measures*

6.4.1. Proposed risk minimisation measures

Routine Risk Minimization Measures

Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Use in pregnant or breast-feeding women	Routine risk communication and routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.6 There are no data on the effect of Redemplo in pregnant women as the clinical studies excluded pregnant women and enforced contraception methods (SmPC Section 4.6). As a precautionary measure, it is preferable to avoid the use of this medicinal product during pregnancy. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. If the patient becomes pregnant or breast-feeding, suspected to be pregnant, or planning to have a baby, ask your doctor or pharmacist for advice before using this medicine (Patient Leaflet Section 2). There are no data on the effect of plozasiran in pregnant women as the clinical studies excluded pregnant women and enforced contraception methods (SmPC Section 4.6).

	It is unknown whether plozasiran or metabolites are excreted in human milk. It is recommended to discuss breast-feeding with the doctor to see what is best for the patient and child. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicines
Long-term safety	**Routine risk communication:** SmPC Sections: 4.8. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information**:** Legal status: Prescription only medicines

Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures are proposed.

Summary of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in pregnant or breast-feeding women	**Routine risk communication:** As a precautionary measure, it is preferable to avoid the use of this medicinal product during pregnancy (SmPC 4.6). Patient Leaflet, Section 2 states the following: If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. There is no information on the use of this medicine in pregnant women. Therefore, do not use Redemplo during pregnancy, unless advised to do so by your doctor. It is not known if Redemplo passes into breast milk. It is recommended that you discuss breast-feeding with your doctor to see what is best for you and your child. **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	No additional risk minimization measures.	
Long-term safety	**Routine risk communication:** SmPC Section 4.8. **Additional risk minimization measures:** No additional risk minimization measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AROAPOC3-3001 OLE: Final CSR complete ~April 2027

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The safety specification and routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

6.4.2.2. Additional risk minimisation measures

No additional risk minimisation measures are deemed necessary at this stage.

6.5. *RMP summary and RMP annexes overall conclusion*

The RMP Part VI and the RMP Annexes are acceptable

6.6. *Overall conclusion on the Risk Management Plan*

The CHMP and PRAC consider that the risk management plan version 0.4 is acceptable.

7. Pharmacovigilance

7.1. *Pharmacovigilance system*

The CHMP rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. *Periodic safety update reports (PSURs) submission requirements*

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 18 November 2025.

8. Product information

8.1. *Summary of product characteristics (SmPC)*

See attached edited product information including both Rapporteur and Co-Rapporteur assessments, as endorsed by the CHMP.

8.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical trials.

8.1.2. SmPC section 5.1 justification

Information on the pivotal studies supporting the indication is included in the SmPC section 5.1.

8.2. *Labelling*

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.3. *Additional monitoring*

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Redemplo (plozasiran) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. *Therapeutic context*

9.1.1. Disease or condition, proposed therapeutic indication

Familial chylomicronaemia syndrome (FCS) is a severe and ultrarare genetic disease that is present from childhood and is characterized by extremely high fasting triglyceride (TG) levels, typically over 10 mmol/L. Patients with FCS have inherited recessive defects that limit or impair functionality of LPL, an essential enzyme in hydrolysis of plasma TGs, resulting in chylomicronemia and consequently leading to extremely high fasting TG levels (>10 mmol/L).

The severe elevations in TG in FCS patients lead to various serious complications and debilitating symptoms including acute pancreatitis, which can be fatal, chronic and even daily abdominal pain, diabetes mellitus, and hepatic steatosis. Quality of life and cognitive issues include difficulty concentrating, 'brain fog', anxiety, fear, and worry. The overall associated mortality rate for recurrent acute pancreatitis is 5% to 6% and increases to 30% for patient subgroups with severe complications (infected pancreatic abscess or persistent multiple organ failure that can result in pancreatic necrosis).

The risk of acute pancreatitis increases relative to the elevation in serum TG levels, with the incidence of acute pancreatitis increasing 3% to 4% for every 100 mg/dL (1.13 mmol/L) increase in TG levels (Gelrud 2017; Scherer 2014). Thus, the current goal of treatment in FCS is to reduce and maintain TG values well below 10 mmol/L (885 mg/dL), the threshold above which the risk of acute pancreatitis significantly increases (Blom 2018).

The final agreed therapeutic indication is the same as the initially proposed indication by the applicant, with exception to addition of the reference to section 4.2 for patient selection criteria.

Agreed therapeutic indication:

"*Redemplo is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with familial chylomicronaemia syndrome (FCS) (see section 4.2 for patient selection criteria).*"

For a detailed description of the therapeutic context, please see section 2.1 of this document.

9.1.2. Available therapies and unmet medical need

Patients with FCS are on strict dietary fat restriction. Traditional lipid-lowering medications used to treat hypertriglyceridemia (HTG), such as fibrates, statins and fish oils, and niacin (not authorised anymore in the EU) are only minimally effective in patients with FCS. Gene therapy (Glybera (alipogene tiparvovec) was approved for FCS patients but restricted to those with LPL deficiency, who suffer from severe or multiple pancreatitis attacks and detectable levels of LPL protein with genetic confirmed testing. However, this product has been withdrawn from use in the EU since October 2017.

Further, an antisense oligonucleotide inhibitor of APOC3 (volanesorsen sodium, Waylivra) is approved in the EU with a conditional marketing authorisation for use as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and TG lowering therapy has been inadequate. Tryngolza (olezarsen) is an antisense oligonucleotide-

triantennary N-acetylgalactosamine conjugate approved as an adjunct to diet in adult patients for the treatment of genetically confirmed FCS.

As such, the therapeutic options to adequately treat FCS in the EU are limited.

At the time of marketiting authorisation of plozasiran, there are no products authorised in the EU for the treatment of patients with FCS without the restriction to genetically confirmed diagnosis of FCS, which underpins the unmet medical need.

9.2. *Main clinical studies*

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2 of this document.

The main body of evidence supporting the efficacy of plozasiran in patients with FCS is the pivotal study AROAPOC3-3001 (PALISADE), which is a Phase 3, randomized, double-blind, and placebo-controlled study to evaluate the efficacy and safety of plozasiran in adults with genetically confirmed or clinically diagnosed FCS maintained on a low-fat diet. The study included a 12-month randomized double-blind placebo-controlled (DBPC) period and a 24-month 2-part open-label (OLE) extension period (ongoing). A total of 75 subjects distributed across 54 different sites in 18 countries were randomized (2:1:2:1) to the dose cohorts plozasiran 25 mg, volume-matched placebo, plozasiran 50 mg, and volume matched placebo and received 5 doses Q3M. Randomization was stratified by level of fasting TG at screening (≥2000 mg/dL versus <2000 mg/dL). Participants who completed the randomized period were eligible to continue to the 2-part extension period, where all participants were receiving plozasiran. The primary study endpoint was the percent change from baseline at Month 10 in fasting TG. The alpha-controlled key secondary endpoints were the percentage change from baseline at Months 10 and 12 (averaged) in fasting TG; the percent change from baseline at Month 10 and Month 12 in fasting APOC3 protein; and finally, the incidence of positively adjudicated events of acute pancreatitis.

All subjects have completed the 12-month DBPC period.

Supportive efficacy data are obtained from the 2 randomized dose-finding phase 2b studies (AROAPOC3-2001 and AROAPOC2-2002) and an open-label extension (OLE) study (AROAPOC3-2003) in related populations, including severe hypertriglyceridaemia (SHTG) and mixed hyperlipidaemia.

The safety evaluation is based on an integrated (pooled) safety analysis. Pool 1, i.e. 1-year data of the abovementioned pivotal phase 3 study in FCS patients alone, provides the safety profile in the target population. Pool 2, i.e. ~1-year data of the phase 2 and 3 placebo-controlled studies in FCS, SHTG and moderate HTG patients, includes a larger group of patients with comparable diseases, although of different origin. Further, pool 3 consisted of longer-term data from the OLE period of the pivotal phase 3 study and from the phase 2b OLE study in dyslipidaemia patients.

9.3. *Favourable effects*

Primary endpoint. In the pivotal study AROAPOC3-3001, treatment with 25 mg and 50 mg plozasiran Q3M demonstrated a substantial median fasting TG reduction of -80% and -78%, respectively, compared to -17% in placebo at Month 10, resulting in a between-group LS median difference vs placebo of -59% and -52% ($p < 0.0001$ and $p < 0.0002$, respectively). This

corresponded to an absolute median TG reduction of -17.7 mmol/L and -14.0 mmol/L to 5.01 mmol/L and 7.5 mmol/L levels at Month 10 for 25 mg and 50 mg Q3M plozasiran, respectively. The effect was consistent in the prespecified sensitivity analyses and subgroup analyses including genetic confirmation of FCS (yes/no). The results of the key (alpha-controlled) secondary endpoint of median reduction in TG levels from baseline at Month 10 and 12 (averaged) is similar to the primary analysis, with between-group differences versus placebo of -60% (p<0.0001) and -51% (p=0.0007) for 25 mg and 50 mg plozasiran Q3M, respectively.

The substantial reductions in TG maintained up to Month 24 as indicated by the interim data of the OLE part of the pivotal AROAPOC3-3001 study.

The beneficial effect in TG was supported by the 2 randomized dose-finding Phase 2b studies (AROAPOC3-2001 and AROAPOC3-2002) and their OLE study (AROAPOC3-2003).

Key secondary endpoints (alpha-controlled). Treatment with plozasiran resulted in a significant reduction in the risk for acute pancreatitis, with 2 positively adjudicated events in 2 patients in the pooled plozasiran groups compared with 7 positively adjudicated events in 5 patients in the placebo group (OR=0.169; p=0.0292). Additionally, in the placebo group, most of the positively adjudicated events were severe, whereas in the plozasiran groups, none of the positively adjudicated events were severe.

Treatment with plozasiran also resulted in a substantial decrease in ApoC3 levels, with a between-group difference of -91% and -93% at Month 10 and -87% and -88% at Month 12 for 25mg and 50 mg Q3M plozasiran, respectively (p<0.0001 for all comparisons).

Mechanism of action. The mechanism of action was also reflected by the substantial decrease in fasting ApoC3, which showed a between-group difference of -91% and -93% at Month 10 and -87% and -88% at Month 12 for 25mg and 50 mg Q3M plozasiran, respectively (p<0.0001 for all comparisons).

Other secondary endpoints (non-alpha controlled). A numerically higher proportion of subjects in the 25 mg and 50 mg plozasiran group compared with placebo reached TG levels of < 10 mmol/L (75% and 55% vs. 21%, respectively) and < 5.65 mmol (50% and 46% vs. 5%, respectively).

Exploratory endpoints. Treatment with plozasiran also resulted in numerically favourable outcomes in other lipid parameters including non-HDL-C, ApoB, and VLDL-C along with increases in HDL-C and LDL-C. The increases in LDL-C, which remained below the ULN (<1.4mmol/L), was accompanied by a decrease in non-HDL-C. For patient reported outcomes (PROs: EORTC QLQ-C30, EORTC QLQ-PAN26, and EQ-5D-5L), numerically improvements were shown for appetite loss, insomnia, cognitive functioning, emotional functioning, and role functioning in the plozasiran treated subjects compared to placebo.

9.3.1. Uncertainties and limitations about favourable effects

Clinical endpoints. Despite the significant effect on risk reduction of acute pancreatitis, the numbers were very limited and this effect has only been demonstrated for subjects with a history of acute pancreatitis of which the majority had a history of recurrent pancreatitis, whereas the effect in patients without a history of acute pancreatitis remains unknown (see importance of favourable and unfavourable effects).

The TG lowering effects of 50 mg plozasiran did not offer a therapeutic benefit over the

recommended 25 mg dose.

No clear effect on the clinically relevant outcome of abdominal pain (exploratory endpoint) has been shown. Only, a trend toward less frequent occurrence of hospitalization for abdominal pain was observed with 1 patient in each 25 mg and 50 mg plozasiran Q3M group compared with 5 patients in the placebo group which support the acute pancreatitis endpoint (OR (95%CI): 25 mg 0.175 (0.020, 1.54); 50 mg 0.193 (0.022, 1.65).

Elderly. A limited number of FCS patients $\geqslant$ 65 years of age was included (n=9 (12%)). These limited data show a similar efficacy in patients $\geqslant$ 65 years of age compared with patients $\leqslant$ 65 years of age.

9.4. *Unfavourable effects*

The complete treatment exposure was considered appropriate to assess the safety profile of plozasiran, since in pool 1, 45 of the 75 FCS patients were exposed with plozasiran >10-12 months, in pool 2, 410 were treated with plozasiran >4-10 months, and in pool 3, 422, 309 and 63 were exposed >10 months, >16 months and >22 months, respectively.

In pool 1, the incidence rates of adverse events (AEs) were slightly higher in the plozasiran groups, i.e. 88.5% and 83.3% on 25 mg and 50 mg, resp., compared to 80% in placebo. Abdominal pain (20.0% placebo vs 26.9% 25 mg, 25.0% 50 mg plozasiran), COVID-19 (0.0% placebo vs 19.2% 25 mg, 29.2% 50 mg plozasiran), headache (8.0% placebo vs 11.5% 25 mg, 20.8% 50 mg plozasiran) and nasopharyngitis (12.0% placebo vs 19.2% 25 mg, 8.3% 50 mg plozasiran) were most commonly reported with higher frequencies in the plozasiran groups. The findings in pool 2 were generally consistent with pool 1, showing percentages of incidence rates in the same range and with a similar increase in the plozasiran groups, i.e. 70.3% on 25 mg and 79.5% on 50 mg Q12W, compared to 68.2% placebo. Most cases were mild or moderate in severity.

The overall incidences of severe adverse events (SAEs) in pool 1 were relatively low with even a lower incidence in the plozasiran groups, i.e. 19.2% on 25 mg and 8.3% on 50 mg, compared to 28.0% in placebo. In pool 2, generally similar findings were observed, with also a lower incidence in the plozasiran groups, i.e. 8.1% and 11.0% in 25 mg and 50 mg Q12W, resp., compared to 12.7% in placebo. The most frequently reported SAEs were pancreatitis acute (2.3% placebo vs 1.4% in 25 mg, 0.7% in 50 mg Q12W), COVID-19 (0.6% placebo vs 1.4% in 25 mg, 0.7% in 50 mg Q12W), osteoarthritis (0% placebo vs 0.8% in 10 mg, 0% in 25 mg and 0.7% in 50 mg Q12W) and acute kidney injury (AKI; 0.0% placebo vs 0.7% in 25 mg, 0.7% in 50 mg Q12W).

No deaths have been reported in pool 1. Four deaths have been reported in pool 2, and 2 in pool 3. None of those were considered related to the use of plozasiran.

The following adverse events of special interest (AESIs) were discussed:

- Regarding worsening of glycaemic control, based on the AEs reported in pool 1, a significantly higher incidence rate was found in the plozasiran groups (19.2% in 25 mg, 20.8% in 50 mg) vs placebo (8.0%). In pool 2, the incidence rates of AEs showed a generally similar trend with 10.4% for placebo vs 12.8% for 25 mg, and 20.5% for 50 mg Q12W plozasiran. Further, an additional analysis showed that the effects were most apparent in diabetes patients, i.e. 31.6% in the plozasiran group vs 16.9% in the placebo group. The incidence of hyperglycaemia AEs in pool 1 was higher with the use of plozasiran

(23.1% and 20.8% in 25 mg and in 50 mg), as compared to placebo (8.0%). In pool 2, the incidence rate of AEs was also higher with the use of plozasiran (12.8% and 20.5% in 25 mg and in 50 mg), as compared to placebo (10.4%) with the effects most apparent in the diabetes group. These data were supported by the hyperglycaemic parameters, in which increases from baseline were observed for the HbA1c values with the use of plozasiran, compared to placebo. Hyperglycaemia is addressed in the SmPC section 4.4 and included as an ADR in section 4.8 of the SmPC.

- Regarding the AESI of local injection site reactions, an imbalance of events between the treatment groups has been observed with the use of plozasiran in pool 1: 15.4% in 25 mg, and 4.2% in 50 mg, compared to 4.0% in placebo group. In pool 2, this was 4.7% in 25 mg, and 4.1% in 50 mg Q12W plozasiran vs 1.2% for placebo. Data are supported by findings in animals from non-clinical toxicity studies. The number of subjects with injection site reaction events was highest after the first and second injections. Local injection site reactions included as an ADR in section 4.8 of the SmPC.
- No safety signals with respect to the AESIs acute pancreatitis and medical device AEs have been observed.
- Although the AKI cases did not identify any safety concerns, moderate elevated creatinine values have been shown with the use of plozasiran, as compared to placebo. Further, adverse effects on the kidney have also been observed in the non-clinical studies. Based on this information, renal toxicity on the long term is covered by 'long-term safety' as missing information in the RMP and 'renal toxicity' has been added as a safety concern in the PSURs for further follow-up of this safety concern.
- Modest elevated AST and ALT values have been shown with the use of plozasiran, while it is unknown whether this is reversible of permanent. Further, adverse effects on the liver have been observed with rats and monkeys in the non-clinical studies. Liver safety has been addressed in the SmPC sections 4.2 and 4.8.

Regarding tolerability, the incidence of subjects who discontinued due to an AE was low. In pool 2, only 7 subjects had AEs leading to study drug discontinuation (n=2, 1.2% placebo; n=1, 0.8% 10 mg, n=2, 1.4% 25 mg, n=2, 1.4% 50 mg Q12W plozasiran), of which 3 of them were also included in pool 1, i.e. the phase 3 study.

9.4.1. Uncertainties and limitations about unfavourable effects

Since plozasiran is indicated for an orphan disease, i.e. patients with FCS, the documented safety exposure of this specific target population remains limited with a relatively small sample size and short study duration, which does not cover long-term experience (and experience in elderly) with plozasiran. Of the 75 FCS patients in pool 1, 25 were on placebo and 50 were on plozasiran, i.e. 26 on 25 mg, 24 on 50 mg. Of the 50 patients on plozasiran, only 45 were exposed >10-12 months. Additional safety data came from pools 2 and 3, which included patients with comparable diseases, but of different origin, i.e. SHTG and moderate HTG and dyslipidaemia.

9.5. *Effects table*

Table 76: Effects Table for Plozasiran for the treatment of FCS, based on study 3001.

Favourable effects				
Plozasiran dose	**25 mg (N=26)**	**50 mg (n=24)**	**Placebo (n=25)**	
Median % change from baseline in TG at Month 10	-80.1	-77.6	-17.0	Difference vs placebo (95%CI): 25 mg: -58.7% (-89.6, -27.9); 50 mg: -52.5% (-83.1, -21.9) **SoE:** • Consistent across sensitivity and subgroup analyses. • Supported by Phase 2b studies AROAPOC3-2001 and 2002 • Numerically higher proportion of responders with target TG level < 10 mmol/L (75% and 55% vs 21%; OR vs placebo (95%CI): 25 mg: 15 (3.3, 72.8).; 50 mg: 5.7 (1.3, 24.6). **Unc:** None
Patient with on-treatment acute pancreatitis (N= subjects/ n= events)	Total nr of subjects N=50 2/2		5/7	OR vs placebo of 0.169; p=0.0292 **SoE:** • Pre-specified • Most events in the placebo group were severe vs none severe in the pooled plozasiran group **Unc:** • Limited number of events • Effect only observed in subgroup of patients with a history of acute pancreatitis
Unfavourable effects				
AEs worsening of glycaemic control (AMQ) – n/N (%)	5/26 (19.2%)	5/24 (20.8%)	2/25 (8.0%)	**SoE:** • Consistent with data in pool 2, i.e. 10.4% placebo vs 12.8% 25 mg , and 20.5% 50 mg Q12W • Similar findings with hyperglycaemia/new onset diabetes mellitus (narrow and broad SMQ) • Supported by an increase on mean HbA1c values and on fasting serum blood glucose levels with plozasiran **Unc:** Low numbers
AEs local injection site reactions (AMQ) – n/N (%)	4/26 (15.4%)	1/24 (4.2%)	1/25 (4.0%)	**SoE:** • Consistent with data in pool 2, i.e. 1.2% placebo vs 4.7% 25 mg, and 4.1% 50 mg Q12W • Supported by findings in animals from non-clinical toxicity studies **Unc:** Low numbers

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence. Pool 2 consists of phase 2 and 3 placebo-controlled studies in FCS, SHTG and moderate HTG patients.

9.6. *Benefit-risk assessment and discussion*

9.6.1. Importance of favourable and unfavourable effects

Treatment with plozasiran is targeted at patients with familial chylomicronemia syndrome (FCS). These patients have extremely high levels of TG (and chylomicrons), which are associated with several clinical symptoms including abdominal pain and acute pancreatitis.

The current application is based on the results of a single pivotal phase 3 study AROAPOC3-3001 in patients with FCS, supported by data from 2 phase 2b dose-finding studies AROAPOC3-2001 and 2002 and their open-label extension study AROAPOC3-2003 in related populations but different SOC, including severe hypertriglyceridaemia (SHTG) and mixed hyperlipidaemia.

Primary analyses show a substantial reduction in fasting TG upon treatment with 25 mg and 50 mg plozasiran Q3M compared with placebo (median: -59%; p< 0.0001 and -52; p< 0.0002, respectively). This corresponded to an absolute median TG reduction of -17.7 mmol/L and -14.0 mmol/L to 5.01 mmol/L and 7.5 mmol/L levels at Month 10 for 25 mg and 50 mg Q3M plozasiran. The ESC guideline classifies patients with TG levels > 10 mmol/L (880 mg/dL) as patients with high TG being at increased risk for pancreatitis. Due to the substantial treatment effect in reduction of TG, a large proportion of patients treated with plozasiran was able to reach this target TG level of < 10 mmol/L (75% for 25 mg and 55% for 50 mg vs. 21% for placebo). The primary result was robust to sensitivity analyses, consistent in subgroup analyses, including genetically confirmed FCS (yes/no), and consistent to results observed in the 2 Phase 2b dose-finding studies.

Whether the increased proportion of patients reaching the target TG level will translate in clinically meaningful reductions in acute pancreatitis is challenging to demonstrate, because of the rare occurrence of these events (approximately 3.5% during 5 years of follow-up (Brahm 2015)), the limited number of patients investigated and the currently limited follow-up (one year). Nevertheless, in the pivotal study, treatment with plozasiran resulted in a significant reduction in the risk of acute pancreatitis, with 2 positively adjudicated events in 2 patients in the pooled plozasiran groups compared to 7 positively adjudicated events in 5 patients in the placebo group (OR=0.169; p=0.0292). Although the numbers of acute pancreatitis are limited, observed in a limited time frame of assessment on-treatment (i.e. one year), and not supported by clear effects on abdominal pain and PROs, these results are suggestive for the clinical relevance of reducing TG by plozasiran.

These acute pancreatitis events were only observed in subjects with a history of acute pancreatitis of which the majority had a history of recurrent pancreatitis. Thrombocytopenia seen with previously approved treatments for FCS has not been observed with plozasiran and the unmet medical need is high in FCS patients. The risk of acute pancreatitis increases relative to the elevation in serum triglycerides, with the incidence of acute pancreatitis increasing 3% to 4% for every 1.13 mmol/L (100 mg/dL) increase in triglycerides (Murphy 2013; Rashid 2016). Further, already the first episode of acute pancreatitis can be life threatening (Frosmark 2016, Nawaz 2015). Therefore, it is considered appropriate to extrapolate the significant reduction in the risk of acute pancreatitis observed in FCS patients with a history of acute pancreatitis to FCS patients without a history of acute pancreatitis and to reflect it as the broad indication “FCS patients”, i.e. without the restriction to “patients with FCS and at high risk for pancreatitis”.

In the pivotal study of plozasiran both genetically confirmed FCS and clinical FCS have been included and a substantial reduction in TG has been demonstrated regardless of these subgroups.

The clinical safety dataset can be considered generally appropriate to assess the safety aspects associated with the treatment of plozasiran, although the safety exposure of the specific target population remains limited in terms of sample size and study duration, since plozasiran is proposed to be indicated for an orphan disease, i.e. patients with FCS. Plozasiran appeared to be generally well tolerated with most frequently reported AEs of hyperglycaemia, headache, nausea, and injection site reactions, and with a low frequency of discontinuations. Further, the renal and liver safety are addressed in the SmPC.

Notably, the differences between the 25 mg and 50 mg plozasiran Q12W doses were negligible or showed a higher effect size with the 25 mg plozasiran dose, whereas generally a small difference in safety profile between both doses were observed. The lowest dose of 25 mg Q3M is the recommended treatment dose for plozasiran in the authorised indication. The TG lowering effects of 50 mg plozasiran did not offer a therapeutic benefit over the recommended 25 mg dose.

9.6.2. Balance of benefits and risks

The benefits of plozasiran in terms of substantial reductions in TG levels pointing to a reduction in the risk for acute pancreatitis, compared to placebo, are accompanied by limited risks.

Further, the use of plozasiran appeared to be well tolerated with an acceptable safety profile.

Overall, plozasiran can reduce TG levels to a considerable extent which translate in clinically meaningful effects accompanied by acceptable risks.

9.7. *Benefit-risk conclusions*

9.7.1. CHMP conclusions

The benefit-risk balance of plozasiran in the claimed indication is positive.