Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

ApoC3 Therapies

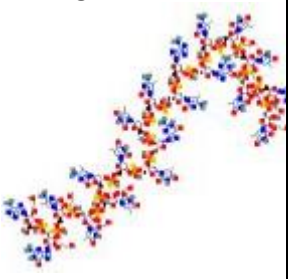
Evidence Summary

ApoC3 lowering therapies reduce triglycerides and may help reduce residual cardiovascular risk. Liver targeted therapies show better safety. They are currently approved for a rare form of hyperlipidemia.

Neuroprotective Benefit: Circulating ApoC3 levels tend to decline in dementia, likely due to altered lipid composition and impaired homeostatic processes. ApoC3 lowering may potentially improve cerebrovascular health in those with high cardiovascular risk.

Aging and related health concerns: ApoC3 therapies effectively lower levels of triglycerides, and atherogenic particles, such as ApoB and non-HDL-C. They may help reduce residual cardiovascular risk, but benefits may be impacted by ethnicity.

Safety: Volanesorsen is associated with thrombocytopenia. Liver-targeted olezarsen and plozasiran have less impact on platelets, but may still modestly increase liver enzymes. Volanesorsen and plozasiran may impact glycemic control.

Availability: ***Olezarsen*** is available via Rx (Tryngolza™) in the US. ***Volanesorsen*** is available via Rx (Waylivra®) in Europe. ***Plozasiran*** is currently in clinical testing.	**Dose**: ***Olezarsen:*** the FDA recommended dose in patients with Familial chylomicronemia syndrome (FCS) is 80 mg monthly, administered via subcutaneous injection. ***Volanesorsen:*** the EMA recommended starting dose in patients with FCS is 285 mg weekly for three months, and then every two weeks, administered via subcutaneous injection. ***Plozasiran*** has been tested in clinical trials at doses of 25 or 50 mg every three months, via subcutaneous injection.	**Volanesorsen** **Molecular Formula:** $C_{230}H_{320}N_{63}O_{125}P_{19}S_{19}$ **Molecular weight:** 7,165 g/mol  **Source:** Pubchem
Half-life: ***Olezarsen***: about 4 weeks ***Plozasiran:*** not available ***Volanesorsen:*** >2 weeks	**BBB**: Unlikely to reach the brain. Olezarsen and Plozasiran are targeted to the liver.	
Clinical trials: ***Volanesorsen*** was tested in Phase 2 trials in hypertriglyceridemia (n=15; n=45; n=114), a Phase 2/3 trial in FPLD (n=40), and a Phase 3 trial in FCS (n=66). ***Olezarsen*** has been tested in Phase 2 trials in hyperlipidemia (n=114; n=154), and Phase 3 trials in hyperlipidemia (n= 1,478) and FCS (n=66). ***Plozasiran*** has been tested in Phase 2 trials in hyperlipidemia (n=229) and mixed dyslipidemia (n=353), and a Phase 3 trial in FCS (n=75).	**Observational studies**: Gene association and Mendelian randomization studies indicate that ApoC3-lowering gene variants are associated with a lower risk for cardiovascular disease in European cohorts.	

What is it?

Apolipoprotein C-III (ApoC-III, also written as ApoC3) is primarily produced in the liver, and to a lesser degree, in the intestine [1]. This small apolipoprotein is largely bound to triglyceride-rich particles (TRLs) and high-density lipoproteins (HDLs), and to a lesser extent on low-density lipoproteins (LDLs). ApoC3 is interchangeable between these pools, such that high levels of triglycerides (and TRLs) are often coupled with lower levels of HDLs, and vice versa. TRLs include liver-derived very-low density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), and intestine-derived chylomicrons. The presence of ApoC3 can hinder the breakdown and clearance of the TRLs. The incomplete breakdown of TRLs can result in the formation of TRL remnants, which are highly atherogenic, and are thought to contribute to residual cardiovascular risk.

ApoC3 is implicated in a variety of mechanisms that increase the level of triglycerides in the plasma. ApoC3 inhibits lipoprotein lipase (LPL), thus preventing the hydrolysis of TRLs, and prevents the uptake of these lipoproteins by the liver [2]. Intracellularly, ApoC3 may also promote triglyceride synthesis and VLDL assembly and secretion.

Targeting ApoC3 can reduce levels of plasma triglycerides, TRLs, and TRL remnants [3]. Gene association studies have identified a relationship between ApoC3 lowering gene variants, and reduced cardiovascular risk, at least in certain ethnic groups. This led to the clinical development of ApoC3-lowering therapies for the treatment of hypertriglyceridemia as well as rare conditions characterized by severe hypertriglyceridemia, such as familial chylomicronemia syndrome.

Reducing ApoC3 is one of several novel mechanisms aimed at reducing residual cardiovascular risk in a post-statin era and joins other potential targets such as PCSK9, ANGPTL3, and Lp(a) [4].

EMA approved, but rejected by the FDA:

Volanesorsen (ISIS 304801) is a second-generation antisense oligonucleotide that targets ApoC3. It was developed by Akacea Therapeutics and Ionis Pharmaceuticals, and has been clinically tested for rare diseases, such as familial chylomicronemia syndrome and familial partial lipodystrophy, as well as for more common indications, such as hypertriglyceridemia. Its application for familial chylomicronemia syndrome was rejected by the FDA in 2018 due to safety concerns, but it was approved for this indication, in conjunction with a low-fat diet, by the EMA in 2019 (EMA). It is marketed under the tradename Waylivra® by Ionis Pharmaceuticals (Akacea is a wholly owned subsidiary of Ionis).

FDA approved:

Olezarsen (ISIS 678354; AKCEA-APOCIII-LRx) is a third-generation antisense oligonucleotide that targets ApoC3. It contains the same sequence as volanesorsen, but it is conjugated to N-acetylgalactosamine (GalNaC), which provides liver-specific targeting. This targeted delivery allowed for the use of lower doses and an improved safety profile, relative to volanesorsen. Olezarsen was developed by Akacea Therapeutics and Ionis Pharmaceuticals and has been tested in a Phase 3 trial for familial chylomicronemia syndrome. It is currently undergoing Phase 3 testing for hyperlipidemia. The improved benefit-to-risk profile facilitated its FDA approval for familial chylomicronemia syndrome in conjunction with a low-fat diet in 2024. It is marketed by Ionis Pharmaceuticals under the tradename Tryngolza™.

Anticipated approval:

Plozasiran (ARO-APOC3) is a first-generation small interfering RNA (siRNA) targeting ApoC3 that is conjugated to GalNaC for liver-specific uptake. It was developed by Arrowhead Pharmaceuticals. To date, it has been tested in Phase 2 trials for hyperlipidemia and mixed dyslipidemia, and a Phase 3 trial for familial chylomicronemia syndrome. The company has submitted a new drug application for the use of plozasiran in the treatment of familial chylomicronemia syndrome, with a decision expected in late 2025. Plozasiran is currently undergoing Phase 3 clinical testing for hyperlipidemia.

Neuroprotective benefit:. Circulating ApoC3 levels tend to decline in dementia, likely due to altered lipid composition and impaired homeostatic processes. ApoC3 lowering may potentially improve cerebrovascular health in those with high cardiovascular risk.

Types of evidence:

- Six biomarkers studies assessing ApoC3 levels

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

The impact of ApoC3 levels on cognition appears to be complex, and is likely indirect. ApoC3-lowering gene variants have not been implicated in dementia risk [5]. ApoC3-lowering therapies could potentially impact the risk for vascular dementia by reducing vascular damage, though this has not been assessed in any of the clinical trials testing ApoC3-targeted therapies to date.

Several studies described below have found that circulating ApoC3 levels are decreased in the context of dementia, which could imply a protective role for ApoC3. However, it could also be indicative of altered lipid metabolism, an established feature of Alzheimer's disease and many other dementias. A key complication is that the impact of ApoC3 may differ depending on which type of particle it is associated with. As such, changes in the relative distribution of ApoC3 across particles, as well as the ratio of free to particle-bound ApoC3, may be more informative than the absolute levels.

One study reported that ApoC3 levels were positively correlated with cognition, but only in the oldest of old (95-105) females [6]. This could be related to age-related changes in lipid metabolism and homeostasis, such that higher levels of ApoC3 may be indicative of more intact lipid regulation. It could also be related to frailty, such that the decreases in ApoC3 in late life may be related to unintended weight loss [7].
A separate nested case-control study including 1,516 participants aged 75+ from the Ginkgo Evaluation of Memory Study similarly found that higher total plasma ApoC3 levels were associated with better cognitive function (difference in Modified Mini-Mental State Examination scores tertile 3 vs. tertile 1: 0.60, 95% Confidence Interval [CI] 0.23 to 0.98) and a lower risk for dementia (adjusted hazard ratio [HR] per standard deviation [SD] increase in ApoC3 in plasma: 0.86, 95% CI 0.74 to 1.01) [7]. The association with dementia was not significant after adjusting for triglycerides. Since declines in triglycerides in late life (likely stemming from the loss of lipid homeostasis and nutrient malabsorption) have been associated with dementia risk [8], the findings with ApoC3 may be a bystander effect due to the generally strong link between triglyceride and ApoC3 levels.

In an assessment of HDL particles, a higher proportion of ApoE-containing HDL was associated with better cognition in a cohort of 1,351 community-dwelling participants [9]. ApoC3 appears to counteract the presence of ApoE on lipoproteins. Consistent with this, the beneficial association of ApoE-containing HDL with cognitive function was only observed in the absence of ApoC3. HDL containing both ApoE and ApoC3 were not associated with cognition.

Human research to suggest benefits to patients with dementia:
A study including 53 Alzheimer's patients with cardiovascular disease or a single cardiovascular risk factor and 52 Alzheimer's patients without cardiovascular risk factors, found no difference in blood levels of ApoC3 between the groups [10]. Both groups had levels below normal. Another study including 147 Alzheimer's patients and 160 healthy controls, found that blood levels of ApoC3 were lower in Alzheimer's patients and inversely correlated with clinical severity [11].

One small study found that urinary levels of ApoC3 were elevated in patients with Alzheimer's disease relative to controls, however, due to its low abundance, accurate detection may be a challenge, and could potentially skew the results in studies with small sample sizes [12]. If validated, this finding could indicate a shift in the relative distribution of free to lipoprotein-bound ApoC3. Under physiological conditions, ApoC3 is largely bound with lipoproteins, which are cleared via the liver [1]. Free ApoC3, on the other hand, is eliminated via the kidneys, and thus may be detectable in the urine.

Mechanisms of action for neuroprotection identified from laboratory and clinical research

There is some preliminary evidence to suggest that ApoC3 may act as an amyloid binding protein. Recombinant ApoC3 has been shown to promote amyloid-like fibril formation *in vitro*, and a rare variant (D25V) with altered stability is associated with amyloidosis [13]. ApoC3 is not implicated in amyloid fibril formation under physiological conditions, but it is unclear whether this may occur under pathophysiological conditions, such as in the context of increased levels of free (i.e. non-lipoprotein bound) ApoC3.

APOE4 Interactions: Not established.

Aging and related health concerns: ApoC3 therapies effectively lower levels of triglycerides, and atherogenic particles, such as ApoB and non-HDL-C. They may help reduce residual cardiovascular risk, but benefits may be impacted by ethnicity.

Types of evidence:

- Four clinical trials for volanesorsen (hypertriglyceridemia and FCS)
- Four clinical trials for olezarsen (hyperlipidemia and FCS)
- Four clinical trials for plozasiran (hyperlipidemia, mixed dyslipidemia, and FCS)
- Five analyses from clinical trials
- Nine genetic association studies for ApoC3 and cardiovascular disease
- Four gene association studies for ApoC3 variants and lifespan
- Two meta-analyses of gene association studies for ApoC3 variants and NAFLD
- Seven biomarker studies of ApoC3

- Preclinical studies in rodent and primate models

Lifespan: POTENTIAL MODEST ASSOCIATION OF LIFESPAN WITH GENETIC APOC3 LOWERING
Two studies in Caucasian populations reported no association between ApoC3 mutations and longevity [14; 15]. A Mendelian randomization study in a Caucasian population found a trend toward a longer lifespan with ApoC3-lowering variants of an additional 0.89 years per standard deviation reduction in triglycerides (95% CI 0.01 to 1.78, p=0.047) in women and an additional 0.75 years per standard deviation [SD] reduction in triglycerides (95% CI -0.02 to 1.53, p=0.06) in men [16]. A separate Mendelian randomization analysis utilizing three genome-wide association study (GWAS) cohorts also found an association between ApoC3-lowering variants and increased parental lifespan (+0.06 years per SD reduction in ApoC3, 95% CI 0.03 to 0.09 years [5].
The impact of age on ApoC3 appears to be complex, as several studies find that levels increase from childhood through middle-age, but may then decline in late life [6; 17; 18].

Cardiovascular disease: POTENTIAL BENEFIT
Gene association and observational studies indicate that elevated ApoC3 is associated with increased cardiovascular risk, while ApoC3 lowering variants are associated with cardioprotection. These findings have spurred the development of ApoC3 lowering therapies for cardiovascular disease, particularly for the treatment of hypertriglyceridemia. This class of therapies may be beneficial for residual cardiovascular risk by reducing levels of remnant cholesterol stemming from the incomplete clearance of triglyceride-rich particles.

Normal levels of ApoC3 are around 10 mg/dL [19].

An analysis of a cohort of 75,725 participants reported that when comparing those with non-fasting triglyceride levels below 1.00 mmol/L to those above 4.00 mmol/L, low levels of triglycerides were associated with a lower risk of ischemic vascular disease (HR: 0.43, 95% CI 0.35 to 0.54) and a lower risk of ischemic heart disease (HR: 0.40, 95% CI 0.31 to 0.52) [2]. Similar results were obtained when comparing quintiles.
Researchers sequenced *APOC3* in these participants and found three rare variants (R19X, IVS2+1G->A, and A43T) which were associated with significantly lower levels of non-fasting triglycerides [2]. Heterozygotes for these mutations had a 44% (0.77 mmol/L) lower level of non-fasting triglycerides. Heterozygotes also had 16% lower ApoB, 24% higher HDL, and 9% higher ApoA1. Heterozygotes also had lower risks of ischemic vascular disease (HR: 0.59, 95% CI 0.41 to 0.86) and ischemic heart disease (HR:

0.64, 95% CI 0.41 to 0.99). These results were no longer significant after controlling for non-fasting triglyceride levels (suggesting possibly that more than ApoC3 alone controls triglyceride levels).

Another study published in the same year found four mutations in *APOC3* associated with lower levels of triglycerides (R19X, IVS2+IG1->A, IVS3+1G->T, A43T). These mutations were present in about 1 in 150 people [20]. Triglyceride levels in mutation carriers were 39% lower than noncarriers, and ApoC3 levels were 46% lower in mutation carriers. The risk of coronary heart disease (CHD) was also lower in mutation carriers than non-carriers (Odds Ratio [OR]: 0.60, 95% CI 0.47 to 0.75).

Another study found that a null mutation in *APOC3* reduced levels of triglycerides, increased HDL-C, and lowered LDL-C [21]. In addition, mutation carriers were protected from subclinical atherosclerosis (measured by coronary artery calcification).

A meta-analysis of 29 studies of carriers of the SstI polymorphism in *APOC3*, which increases levels of ApoC3 and triglycerides, found that carriers of the SstI polymorphism (S2 versus S1) had a higher risk of CHD (OR:1.30, 95% CI 1.10 to 1.55) [22]. A separate study of plasma apolipoproteins and the risk of coronary artery disease (CAD), peripheral artery disease, and carotid artery plaques reported that after controlling for several factors, including lipids, ApoC3 levels were only associated with a significantly higher risk of carotid artery plaques (OR: 1.30, 95% CI 1.06 to 1.58) [23].

Mendelian randomization studies provide evidence that ApoC3 plays a causal role in the regulation of triglyceride levels and risk for cardiovascular disease. A study including 401,548 participants of European ancestry from the UK Biobank found that genetically lower ApoC3 was associated with a lower risk for CHD (OR: 0.96, 95% CI 0.93 to 0.98) [24]. The magnitude of CHD risk reduction per 10 mg/dL decrease in ApoB (OR: 0.70, 95% CI 0.59 to 0.83) was similar to that of PCSK9 lowering variants, and the effect of ApoC3 lowering had an additive effect on CHD risk reduction when combined with LDL-C lowering variants (i.e. PCSK9 and HMGCR), suggesting that they impact CHD via distinct mechanisms. Based on 15 genetic proxies for ApoC3 levels from three GWAS studies of ApoC3 blood levels (deCODE, n = 35,378; Fenland, n = 10,708; and ARIC, n = 7,213), genetically-predicted lower ApoC3 levels were associated with lower levels of triglycerides, ApoB, LDL-C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), as well as higher levels of HDL-C [5]. Genetically predicted ApoC3 lowering was also associated with reduced risk for aortic stenosis (OR per 1 SD reduction in ApoC3 levels: 0.82, 95% CI 0.73 to 0.93), and CAD (OR per 1 SD reduction in ApoC3 levels: 0.86, 95% CI 0.80 to 0.93). A drug-target Mendelian randomization study including multiple GWAS including participants (ranging from 1.3M to 400K) of

European descent found that genetically proxied ApoC3 inhibition was associated with a decreased risk for aortic stenosis (OR per standard deviation decrease in triglycerides: 0.78, 95% CI 0.70 to 0.88)[25]. Notably, variants of genetically proxied LDL-C lowering were also associated with a lower risk for aortic stenosis, while other genetically proxied variants of triglyceride lowering, such as ANGTPL3 and PPARA, were not associated with lower risk. The study authors note that the discrepancy between the impact of lifelong genetic lowering and clinical performance of drugs that act on the same pathways may be the timing of intervention, and that earlier initiation of these therapies may be needed for a meaningful impact on aortic stenosis progression.

In contrast, an analysis including participants from the CARDIOGRAMplusC4D consortium and the UK Biobank found that common variants, which have more modest effects on ApoC3 levels relative to the loss-of-function variants, impact circulating levels of triglycerides, and VLDL, but do not alter levels of LDL-C or ApoB, and are not associated with risk for CAD [26]. The lack of impact on CAD risk is similar to what has been observed with common variants for the triglyceride-modulating gene, ANGPTL3. This suggests that therapeutics targeting ApoC3 may need to achieve the potent lowering in line with the loss-of-function variants coupled with a reduction in ApoB to have a meaningful impact on cardiovascular risk.
It should also be noted that these relationships between genetic ApoC3 lowering and cardioprotection have largely been driven by cohorts of European descent, and this relationship is not consistent across other ethnic groups [3].

Observational studies have found that plasma ApoC3 levels are associated with cardiovascular risk, but that the relationship can vary depending on demographic and clinical features [3; 27]. These disparities may be related to variation in the composition of ApoC3 proteoforms.
Total plasma ApoC3 may not be an optimal biomarker for cardiometabolic risk because ApoC3 can undergo posttranslational modifications which impact its function and association with cardiovascular risk [28]. The best studied modification for ApoC3 is glycosylation. Various differentially glycosylated forms (proteoforms) have been identified, four of which have been studied in some detail. These include a non-glycosylated form ($ApoC3_{0a}$) and three O-glycosylated forms with either zero ($ApoC3_{0b}$), one ($ApoC3_1$), or two sialic acids ($ApoC3_2$) [28]. Higher levels of the mono-sialylated form ($ApoC3_1$) are positively associated with triglycerides, insulin resistance, and cardiovascular risk, while a shift toward a higher ratio of the dual sialylated form ($ApoC3_2$) relative to the mono-sialylated form ($ApoC3_1$) is inversely associated with these features [3].

Impact of ethnicity: A multi-ethnic analysis including 5,790 participants found that levels of $ApoC3_1$ tended to be higher in White and Hispanic participants, while $ApoC3_2$ levels tended to be higher in Black and Chinese participants [27]. A compositional shift was also observed in the context of menopause, with a shift towards a higher $ApoC3_1$ to $ApoC3_2$ ratio, indicative of increased cardiovascular risk.
The prevalence of the $ApoC3_2$ form likely accounts for why those of African ancestry tend to have lower levels of circulating triglycerides and higher levels of HDL, and why cardiovascular risk is largely uncoupled from ApoC3 levels in this population [29]. African Americans tend to have elevated rates of CAD despite relatively lower levels of triglycerides and ApoC3. The cardioprotection observed with ApoC3 loss-of-function variants in European cohorts has not been consistently observed in other ethnic groups, which may stem from ethnic differences in ApoC3 proteoform composition [3].
This suggests that ApoC3-lowering therapies may offer preferential benefit in certain ethnic groups, though this has not yet been addressed in the clinical trials, which to date, have predominantly enrolled the ethnic groups most likely to benefit based on their ApoC3 profiles, namely Caucasians and Hispanics.

Mechanisms of cardioprotection

Regulation of triglyceride hydrolysis: ApoC3 is an inhibitor of lipoprotein lipase (LPL), which is the rate-limiting enzyme in the hydrolysis of triglycerides from lipoproteins [1]. Triglycerides are primarily transported as part of triglyceride-rich lipoproteins (TRLs), such as very-low density lipoproteins (VLDL) formed in the liver and chylomicrons formed in the intestine. ApoC3 is not a direct inhibitor of LPL, but instead appears to block access to its substrate and/or displace it from the surface of the lipoproteins. Reducing ApoC3 augments LPL, which allows for increased lipolysis and hepatic clearance of TRLs. One reason mono-sialylated $ApoC3_1$ and dual-sialylated $ApoC3_2$ proteoforms are differentially linked with cardiovascular risk may stem from differences in triglyceride hydrolysis activity. ApoC3 complexes containing $ApoC3_2$ have lower capacity to inhibit LPL activity or negatively impact hepatic clearance of lipoproteins relative to complexes containing $ApoC3_1$ [30].

Regulation of TRL clearance rates: The hydrolysis of triglycerides from TRLs by LPL results in the formation of smaller, denser particles that are more enriched in cholesterol, called TRL remnants or remnant cholesterol [3]. The remnants can be cleared by liver via the LDLR and LRP1 receptors. VLDL can also be converted to IDL and eventually LDL. Thus, enhancing the clearance of TRL has the potential to reduce levels of both remnant cholesterol and LDL-C. ApoC3 has been shown to slow the rate of TRL clearance. ApoE is important for LDLR/LRP1 mediated clearance of lipoproteins, such that the inclusion of ApoE on TRLs speeds up their clearance. ApoC3 acts to counteract the effects of ApoE, such that TRLs (and LDLs) that contain ApoC3 are slow to be taken up and cleared by the liver [3].

Lipoprotein analysis from individuals with ApoC3 loss-of-function mutations indicates that loss of ApoC3 results in faster rates of TRL clearance, and thus shorter time in circulation, leading to lower concentrations of circulating TRLs and TRL remnants [31].
The clearance rate and mechanism also depend on the ApoC3 proteoforms. Mono-sialylated $ApoC3_1$-containing lipoproteins are preferentially cleared via the LDLR/LRP1 pathway, whereas di-sialylated $ApoC3_2$-containing lipoproteins are preferentially cleared in a slower manner via heparan sulfate proteoglycans (HSPGs) [32]. A study found that treatment with a ApoC3-lowering therapy (volanesorsen) led to a shift toward a greater reduction in $ApoC3_1$ relative to $ApoC3_2$, suggesting that lowering ApoC3 primarily accelerates hepatic clearance via the LDLR/LRP1 pathway [32].
Slowed clearance of TRL remnants is especially problematic because these particles are highly enriched in cholesterol and have increased capacity to traverse into walls of blood vessels. The presence of ApoC3 also enhances the update of oxidized LDL by macrophages, leading to the formation of atherosclerotic plaques [3]. The extra time in circulation means that the highly atherogenic TRL remnants are more likely to form fatty deposits and promote inflammation in vessels. Therefore, simply increasing the rate of TRL hydrolysis would not be beneficial unless it was coupled with enhanced clearance of the remnants. Reducing levels of ApoC3 on TRLs is protective because it increases rates of both hydrolysis and clearance.

Inflammation: There is evidence to suggest that ApoC3 may promote inflammation. While most ApoC3 is associated with lipoproteins, preclinical studies suggest that lipid-free ApoC3 can trigger pro-inflammatory signaling cascades, which may be relevant locally within atherosclerotic lesions [1]. ApoC3 levels have also been found to be positively associated with levels of pro-inflammatory glycoproteins [33].

Enhancement of HDL: ApoC3 is primarily found on TRL and HDL particles, and to a lesser extent on LDL particles [3]. The pool of ApoC3 is readily exchangeable between these particles. When triglyceride levels increase, ApoC3 is transferred from HDL to TRL, and when triglyceride levels decrease, ApoC3 is transferred from TRL to HDL. The impact of ApoC3 on the functionality of HDL is not fully understood, but there is evidence to suggest that it slows particle clearance and may counteract some of the cardioprotective functions of HDL, such that a higher proportion of ApoC3 containing HDL is associated with a worse cardiovascular risk profile [3]. Studies testing ApoC3 lowering therapies provide evidence for a shift toward more HDL particles [34; 35]. Reducing levels of ApoC3 may have a beneficial effect by enhancing the protective functions of HDL, though this has not been well studied to date.

Lipoprotein particle size shift: Particle size and composition can be more informative about atherogenic potential than total lipoprotein levels. Small dense LDL-C are more atherogenic, therefore, shifts in particle size can influence cardiovascular risk, even in the absence of changes in total levels. NMR lipoprotein profiling of participants treated with ApoC3-lowering therapies also provides evidence for a shift in the particle profile toward less atherogenic forms, such as larger LDL particles [34; 35]. Analysis from *APOC3* loss-of-function carriers indicates effects on VLDL particle sizes that may be independent of LPL activity [36]. There tends to be a shift away from the larger triglyceride-rich VLDL particles, which may stem, in part, from the enhanced clearance of ApoC3$_1$-containing TRLs.

Residual cardiovascular risk: To date, the impacts of triglyceride-lowering therapies, such as fibrates, on cardiovascular risk have been quite modest [37]. A meta-analysis of prior triglyceride-lowering trials found that a 40 mg/dL reduction in triglycerides was associated with only a 4 to 5% decrease in cardiovascular risk [38]. It is thought that degree of triglyceride and ApoC3 lowering in those studies had been inadequate to offer meaningful clinical benefit. It is expected that potential benefits will be linked to the reduction of atherogenic ApoB-containing particles, particularly remnant cholesterol (i.e. TRL remnants). Using data from Mendelian randomization studies, it is anticipated that a 10-mg/dL reduction in ApoB and 70-mg/dL reduction in triglycerides would translate to a 23% reduction in major adverse cardiovascular events (MACE) [37]. Additionally, the Copenhagen General Population Study found that due to the high atherogenic nature of remnant cholesterol, a smaller level of reduction was needed (32 mg/dL) compared with the level of LDL-C reduction needed to achieve an equivalent 20% relative risk reduction in recurrent MACE [39]. Cardiology working groups have suggested that instead of relying on triglycerides for inclusion criteria, additional measures should also be taken into consideration, such as ApoB ≥80 to 85 mg/dL or non–HDL-C ≥100 to 120 mg/dL (in the context of maximal LDL-lowering therapy) [37]. This further posits that ApoB/non-HDL-C/remnant cholesterol would be more informative outcomes measures for understanding the impact of these therapies on residual risk.

Diabetes: POTENTIAL BENEFIT FOR VASCULAR COMPLICATIONS

ApoC3 may be particularly relevant for cardiovascular complications in the context of diabetes. Hepatic ApoC3 expression is induced by glucose and suppressed by insulin [3]. Under conditions of insulin resistance, this balance gets disrupted, and hyperglycemia results in the persistent expression of ApoC3 on TRLs, resulting in the slowed clearance of TRLs and their remnants. Individuals with diabetes also show evidence for a shift in the glycosylation pattern of ApoC3, which may impact their risk for a variety of micro and macrovascular complications [40]. A multi-ethnic cohort study including 5,743 participants,

724 of whom had type 2 diabetes found that baseline ApoC3 levels were more strongly correlated with cardiovascular risk in participants with diabetes (HR per 1 SD ApoC3: 1.21, 95% CI 1.01 to 1.45), relative to those with normal fasting glucose levels (HR per 1 SD ApoC3: 0.98, 95% CI 0.89 to 1.08) [41].

ApoC3-lowering therapies: The impact on long-term cardiovascular risk has not yet been evaluated for any of these therapies, so the different therapies cannot yet be compared on that metric.

Antisense oligonucleotide

To date, two ASOs targeting ApoC3 have undergone Phase 3 clinical testing. Volanesorsen and olezarsen. Both contain the same ASO sequence and are being developed by Ionis and Akacea. Volanesorsen is not site directed, whereas olezarsen is GalNaC conjugated to facilitate selective uptake to the liver, which allows for higher potency -lower doses and fewer side effects. The superior safety profile of olezarsen paved the way for its approval by the FDA for familial chylomicronemia syndrome in late 2024. Volanesorsen was rejected by the FDA for this indication in 2018, though it was approved for use in Europe by the EMA in 2019.

Volanesorsen

Volanesorsen (previously ISIS 304801) is a second-generation ApoC3 antisense oligonucleotide (ASO) that has been clinically tested for hypertriglyceridemia and familial chylomicronemia syndrome (FCS).

A pooled analysis of Phase 2 and Phase 3 trials testing volanesorsen in patients with FCS (n=66) or severe hypertriglyceridemia (n=173) found that, relative to placebo, treatment with volanesorsen at a dose of 300 mg weekly (administered via subcutaneous injection) for three months was associated with significant reductions in levels of ApoC3 (Mean Difference [MD]: -80.0%, 95% CI -97.5% to -62.5), triglycerides, (MD: -73.9%, 95% CI -93.5% to -54.2), VLDL-C (MD: -71.0%, 95% CI -76.6% to -65.4%), and Apo-B48, a marker of plasma chylomicrons (MD: -69.03%, 95%CI -98.59.4% to -39.47%) [42]. Volanesorsen was also associated with significant increases in levels of HDL-C (MD: +45.92%, 95%CI +37.24% to +54.60%) and LDL-C (MD: +68.6%, 95%CI +7.0% to +130.1%). But, volanesorsen treatment did not significantly impact levels of Apo-B100 (MD: +4.58%, 95%CI -5.64% to +14.79%), suggesting that the increase in LDL-C reflects a shift in the profile of ApoB containing particles, consistent with increased breakdown of VLDL-C.

Hypertriglyceridemia

In multiple mouse models, administration of volanesorsen reduced levels of ApoC3, plasma triglycerides, VLDL, and chylomicron particles [43]. In primates fed fructose (to cause hypertriglyceridemia), volanesorsen reduced plasma triglycerides and VLDL/chylomicron levels and increased levels of HDL [43]. In a placebo-controlled phase 1 study in healthy volunteers, volanesorsen reduced levels of ApoC3 and triglycerides in a dose-dependent manner [43].

A phase 2 RCT dose-finding study tested volanesorsen in untreated patients with fasting triglycerides between 4.0 mmol/L and 22.6 mmol/L and in patients on stable fibrate therapy with fasting triglycerides between 2.5 mmol/L and 22.6 mmol/L; 57 patients were enrolled in the monotherapy cohort and 28 patients were enrolled in the fibrate-treated cohort [44].

Monotherapy cohort: Patients received a single subcutaneous dose of 100, 200, or 300 mg of volanesorsen then were randomly assigned in a 3:1 ratio to receive either the active agent or the placebo [44]. The drug was administered subcutaneously once per week for 13 weeks. Volanesorsen reduced ApoC3, reduced triglycerides, and increased HDL in a dose-dependent manner. These changes persisted over time. Additionally, there were decreases in VLDL-ApoB (a marker of VLDL particle number), decreases in ApoB-48 (a marker of chylomicron particle number), and increases in LDL-C. However, non-HDL-C and total ApoB levels remained relatively stable.
The study authors give three possibilities for the increase in LDL-c in this study: 1) an increase in the conversion of VLDL to LDL, 2) remodeling of lipoprotein content by CETP, and/or 3) a change in the secretion or catabolism of LDL particles.

Add-on to fibrate therapy cohort: In the add-on to fibrate therapy group, patients received a single dose of either 200 mg or 300 mg volanesorsen and then were randomly assigned drug or placebo in a 2:1 ratio at the same dosing regimen [44]. Similar results were obtained, compared with monotherapy, except there was no increase in LDL-C, possibly because fibrates can counteract the volanesorsen-related increase in LDL-C.

Hypertriglyceridemia + Diabetes

In a pilot study with 15 patients with type 2 diabetes and hypertriglyceridemia randomized 2:1 to receive either volanesorsen (300 mg weekly subcutaneous) or placebo over 15 weeks, treatment with volanesorsen reduced triglycerides (-69%), improved whole-body insulin sensitivity by 57%, and improved HbA1c (-4.9 mmol/mol, volanesorsen versus +8.5 mmol/mol, placebo) [45]. There was a

significant inverse relationship between insulin sensitivity and plasma ApoC3 (r=-0.61) and triglycerides (r=-0.68).

Familial Chylomicronemia Syndrome

Familial chylomicronemia syndrome (FCS) is a rare, autosomal recessive genetic disorder that results in severely elevated levels of plasma triglyceride and recurrent episodes of pancreatitis [46]. It typically results from mutations in LPL, though cases stemming from mutations in other genes have also been reported. In contrast to other triglyceride-lowering therapies that involve the augmentation of LPL activity, such as ANGPTL3 inhibitors, therapies targeting ApoC3 show efficacy in lowering triglyceride levels in FCS patients, suggesting that ApoC3 lowering can also impact triglycerides in an LPL-independent manner.

A Phase 3, 52-week study (APPROACH) in 66 patients with FCS tested the effects of volanesorsen (300 mg, subcutaneously, weekly) versus placebo [47]. At three months, volanesorsen treatment reduced levels of ApoC3 (-84% vs. +6.1% for placebo) and fasting triglycerides (-77% vs. +18%). These results were also significant at six and 12 months.

A Phase 3 open-label extension study including 49 FCS patients who participated in the Phase 3 APPROCH or COMPASS trials as well as 19 treatment-naïve FCS patients assessed the safety and efficacy of subcutaneous volanesorsen at a dose of 300 mg per week for at least 52 weeks (NCT02658175) [48]. Treatment resulted in sustained triglyceride reductions in all groups, with mean decreases in fasting plasma triglycerides of -50%, -66% and -46%, at 24 months for those in the APPROACH, COMPASS, and treatment-naïve groups, respectively. Mean percent LDL-C levels also increased, but the absolute increase was small, as levels increased from baseline levels of 4 mg/dL to 33 mg/dL, which are quite low, to 31 mg/dL to 43 mg/dL following 12 months of treatment, which are still within the normal range.

Olezarsen

Olezarsen (ISIS 678354; AKCEA-APOCIII-LRx) is a third-generation ASO targeting ApoC3. It contains the same nucleotide sequence as volanesorsen, but is conjugated to N-acetylgalactosamine (GalNaC), which allows for targeted uptake by hepatocytes in the liver, so it allows for silencing of ApoC3 specifically in the liver [3]. It has been tested in Phase 3 trials for FCS and hypertriglyceridemia.

A meta-analysis of four RCTs testing olezarsen assessed the lipid-lowering dose-response effect to determine the optimal dose [49]. The dose-modeling analysis indicates that 50 mg every four weeks is

likely the optimal dose, as triglyceride-lowering capacity increases steadily and then begins to plateau afterwards, such that increasing doses result in diminishing returns. At the 50 mg dose, triglycerides were reduced by an average of -49.84 % (95 % CI -70.42 to -22.37), which was similar to the degree of lowering observed with the 80 mg dose (MD: -52.32 %, 95% CI -58.25 to -46.40). This trend models the reduction in ApoC3 levels with increasing doses. A similar trend is observed with respect to the olezarsen-induced elevation in HDL levels, while LDL levels were not meaningfully changed at any dose level.

Hypertriglyceridemia

Olezarsen was tested in a randomized, double-blind, placebo-controlled, dose-ranging Phase 2 trial in 114 patients with hypertriglyceridemia (fasting serum triglycerides 200-500 mg/dL) and at high risk for or with established atherosclerotic cardiovascular disease (ASCVD) (NCT03385239) [50]. Participants were treated with placebo or olezarsen, administered subcutaneously, at a dose of 10 or 50 mg every 4 weeks (q4w), 15 mg every two weeks (q2w), or 10 mg every week (qw) for six to 12 months (median of 232 days). Median fasting triglyceride levels were 262 mg/dL, while mean levels of ApoC3 (16.2 mg/dL), and VLDL-C (54.9 mg/dL) were also elevated approximately two times the normal range. The study met its primary endpoint of percent change in fasting triglyceride levels from baseline to six months. Olezarsen-treated participants also experienced significant reductions in levels of ApoC3, VLDL-C, ApoB, and non-HDL-C at the higher doses. HDL-C levels increased, while there were no significant effects on LDL-C levels (see table).

Placebo-adjusted % change at 6 months (95% CI)	10 mg q4w	15 mg q4w	10 mg qw	50 mgq4w
Triglycerides	-27% (-41 to -10)	-58% (0.34 to -48)	-63% (-70 to -54)	-62% (-29 to –53)
ApoC3	-30% (-47 to -8)	-68% (-76 to -58)	-74% (-80 to -65)	-74% (-80 to -66)
VLDL-C	-25% (-39 to -9)	-47% (-56 to -35)	-54% (-62 to -44)	-57% (-64 to -48)
Non-HDL-C	-7% (-18 to +6)^{NS}	-24% (-34 to -14)	-15% (-26 to -4)	-20% (-29 to -9)
ApoB	+2% (-7 to +13)^{NS}	-16% (-24 to –7)	-5% (-14 to +5)^{NS}	-10% (-19 to -1)
HDL-C	+12% (+1 to +24)	+34% (+21 to +49)	+42% (+28 to +57)	+30% (+18 to +44)
LDL-C	+14% (-3 to +35)^{NS}	-1% (-12 to +17)^{NS}	+23% (+4 to +45)	+10% (-8 to +30)^{NS}

NMR lipid profile analysis found that in addition to reducing overall levels of atherogenic lipoprotein particles, olezarsen treatment is associated with a shift in their size and composition that generally

reflects a less atherogenic profile [35]. At the 50 mg q4w dose, levels of TRL-particles (VLDL and chylomicrons) by -51% with the largest reductions in large-size and medium-sized particles. Large VLDL-particles are more likely to undergo hydrolysis leading to the formation of atherogenic remnants, while the smaller VLDL-C more readily undergo conversion to LDL-C. The increase in LDL-C sometimes observed with ApoC3-lowering therapies may then reflect the shift toward more of the small VLDL-P. The impact on the highly atherogenic TRL remnants was not specifically assessed, but this shift in profile suggests that remnant formation should decrease. The HDL-particle concentration increased by 15%. While the total LDL-particle concentration was not changed, there was a shift toward larger LDL-P and less small LDL-particles. This shift is considered beneficial, since the small-dense LDL-P tend to be the most atherogenic.

The randomized, placebo-controlled Bridge–TIMI 73a Phase 2b trial (NCT05355402) included 154 participants with moderate hypertriglyceridemia (triglyceride level 150 to 499 mg/dL) and elevated cardiovascular risk or with severe hypertriglyceridemia (triglyceride level, ≥500 mg/dL) [51]. Participants received placebo or olezarsen at a dose of 50 mg or 80 mg administered via subcutaneous injection once per month (q4w) for 12 months. The primary outcome was the percent change in the triglyceride level from baseline to six months. Both doses of olezarsen significantly reduced triglyceride levels, relative to placebo. Significant reductions were also observed on measures of ApoC3, VLDL-C, non-HDL-C, ApoB, and remnant cholesterol. Levels of HDL-C were increased, and there were no significant effects on LDL-C (see table). These effects remained consistent at 12 months.

Placebo-adjusted % change at six months (95% CI)	50 mg	80 mg
Triglycerides	-49.3% (-39.5 to -59.0)	-53.1% (-43.4 to -62.9)
ApoC3	-64.2% (-53.6 to -74.7)	-73.2% (-62.5 to -83.9)
VLDL-C	-46.2% (-56.7, -35.7)	-49.7 (-60.3 to -39.2
Non-HDL-C	-25.4% (-36.3, -14.5)	-23.1% (-34.0 to -12.1)
ApoB	-18.2% (-27.1 to -9.4)	-18.5% (-27.4 to -9.6)
HDL-C	+39.6% (+26.7 to +52.6)	+39.6% (+26.6 to +52.6)
LDL-C	-9.9% (-26.3 to +6.6)^{NS}	-7.7% (-24.2 to +8.7)^{NS}
Remnant cholesterol	-46.6% (-57.1 to -36.1)	-50.1% (-60.7 to -39.6)

Olezarsen has also been tested in the randomized, double-blind, placebo-controlled Phase 3 Essence-TIMI 73b trial (NCT05610280) in 1,478 patients with moderate hypertriglyceridemia (triglycerides 200-499 mg/dL) and increased cardiovascular risk, or with severe hypertriglyceridemia (triglycerides ≥500 mg/dL) [52]. The primary endpoint is the percent change in triglyceride levels from baseline to six months. The study also includes a coronary computed tomography angiography (CTA) sub-study (n=555), which will assess changes in noncalcified plaque volume from baseline to 12 months.
The trial was recently completed (in mid-2025), and topline results have been released by the study sponsor (Ionis). The trial met its primary endpoint with significant placebo-adjusted reductions in triglyceride levels at six months of 61% and 58% for the 50 mg and 80 mg doses of olezarsen, respectively. Key secondary endpoints, including change in triglyceride levels at 12 months, the proportion of patients achieving fasting triglycerides <150 mg/dL and percent changes in ApoC3, remnant cholesterol, non-HDL-C and ApoB, were also met (Press release).

Olezarsen is currently being tested in the CORE-TIMI-72a and CORE-TIMI-72b Phase 3 trials in patients with severe hypertriglyceridemia.

Familial Chylomicronemia Syndrome
Olezarsen was tested in the randomized, double-blind, placebo-controlled Phase 3 BALANCE trial in 66 patients with genetically confirmed FCS and fasting triglycerides ≥880 mg/dL [53]. Baseline triglyceride levels were approximately 2,600 mg/dL and 71% of the FCS patients had a history of acute pancreatitis. Participants were randomized to placebo or olezarsen administered via subcutaneous injection at a dose of 50 mg or 80 mg q4w for 53 weeks. The primary endpoint was the placebo-adjusted % change in fasting triglycerides from baseline to six-months, while secondary endpoints included changes in 12-month triglyceride levels and ApoC3 levels, as well as the incidence of acute pancreatitis events. The study met its primary endpoint at the 80 mg dose, with significant reductions in placebo-adjusted triglyceride levels of -43.5% (95% CI -69.1 to -17.9) at six months, and -59.4% at 12 months. There was a non-significant trend toward a reduction of triglycerides with the 50 mg dose at six months (-22.4%, 95% CI -47.2 to 2.5). ApoC3 levels were significantly reduced at both doses, with placebo-adjusted reduction of -73.7% 95% CI, -94.6 to -52.8) at the 80 mg dose, and a reduction of -65.5% (95% CI, -82.6 to -48.3) at the 50 mg dose. Rates of acute pancreatitis were also reduced with olezarsen, as there were 11 cases in the placebo group and only one case in the pooled olezarsen group (RR: 0.12; 95% CI, 0.02 to 0.66). Based on the results of this study, olezarsen received FDA approval at a dose of 80 mg per month (s.c.) as an adjunct to diet for the reduction of triglycerides in patients with FCS (FDA).

An analysis from the BALANCE trial in FCS patients assessed the impact of olezarsen on ApoC3 associated with lipoprotein pools for ApoB (ApoB-48 + ApoB-100), ApoA-I, and Lp(a) [54]. The most pronounced ApoC3 reductions were in the total ApoB (by -47.1 % and -65.8 %, at the 50 mg and 80 mg doses, respectively) and ApoA-1 (by -53.6% and -76.1%, respectively) lipoprotein pools. This likely reflects the predominance of (ApoB-48) chylomicrons, and ApoC3-containing HDL particles in patients with FCS. The magnitude of the impact of the different particle classes likely reflects the baseline distribution of the lipoprotein pools, and thus may differ in the context of different types of hyperlipidemias.

siRNA

Plozasiran is a first-in-class GalNaC conjugated siRNA targeting liver ApoC3 in clinical development by Arrowhead Pharmaceuticals. It has been tested in Phase 2 clinical trials for hyperlipidemia and mixed dyslipidemia, and a Phase 3 trial for familial chylomicronemia syndrome.

Hypertriglyceridemia
Plozasiran was tested in the randomized, placebo-controlled, double-blind, dose-ranging, Phase 2b SHASTA-2 trial in 229 patients with severe hypertriglyceridemia (fasting triglyceride levels 500 to 4,000 mg/dL) (NCT04720534) [55]. Participants were treated with placebo or plozasiran at a dose of 10, 25, or 50 mg, administered subcutaneously on day 1 and at week 12 (i.e. three months). The mean baseline triglyceride level was 897 mg/dL, and the mean plasma ApoC3 level was 32 mg/dL, which is around three times higher than normal. The study met its primary endpoint of placebo-subtracted difference in the means of percentage triglyceride change at week 24. Plozasiran treatment was also associated with dose-dependent increases in HDL-C and LDL-C. However, the effect on LDL-C likely reflects the increased breakdown and conversion of TRLs, since it was accompanied by decreases in levels of chylomicrons and non-HDL-C. Notably, treatment also led to durable reductions in levels of highly atherogenic remnant cholesterol (see table).

Placebo-adjusted % change at week 24 (95% CI)	10 mg every 12 weeks	25 mg every 12 weeks	50 mg every 12 weeks
Triglycerides	-48.8% (-64.0 to -33.7)	-53.1% (-68.1 to -38.0)	-57.0% (-71.9 to -42.1)
ApoC3	-67.7% (-79.6 to -55.8)	-71.5% (-83.2 to -59.7)	-77.4% (-89.1 to -65.8)
Non-HDL-C	-27.9%	-26.9%	-20.2%

ApoB	-2.0%^{NS}	-13.3%^{NS}	-7.3%^{NS}
HDL-C	+43.5%	+52.2	+57.0%
LDL-C	+31.0%	+25.8^{NS}	+60.3%
Remnant cholesterol	-61.8%	-63.6%	-58.8%

A Phase 1 trial (NCT03783377) included a cohort of 40 patients with hypertriglyceridemia. Participants were treated with subcutaneous injections of placebo or plozasiran, administered on days 1 and 29, at doses of 10, 25, 50, or 100 mg [56]. Mean levels of ApoC3 decreased from baseline to day 113 with plozasiran treatment by -62.0%, -81.7%, -90.1%, and -94.4%, respectively, compared with -1.6% with placebo. This was accompanied by median changes in triglyceride levels of -65.6%, -69.9%, -81.2%, and -81.0%, respectively, compared with -2.8% with placebo. There were dose-dependent increases in HDL-C ranging from 44.2% to 83.4%, while mean levels of non-HDL-C decreased by approximately 30% in each of the plozasiran-treated groups.
In the cohort of 52 healthy participants, there were dose-dependent reductions from baseline in median ApoC3 levels up to about -94% with single dose administration (to day 85) and repeat dose administration (to day 113) [56]. This was accompanied by median dose-related reductions in triglyceride levels up to approximately -69%, though there was a plateauing of the effect size at higher doses. Reductions in non-HDL-C, ApoB, VLDL-C, and LDL-C were also observed. The reduction in LDL-C in this healthy cohort lends further support for the notion that the increase observed in participants with severe hypertriglyceridemia reflects increased conversion of TRLs (e.g. VLDL-C) when baseline levels of TRLs are very high.

Mixed hyperlipidemia
Plozasiran was tested in the randomized, double-blind, placebo-controlled Phase 2b MUIR trial (NCT04998201) in 353 patients with mixed dyslipidemia (triglycerides 150 to 499 mg/dL and either LDL-C ≥70 mg/dL or non-HDL-C 100 mg/dL) [57]. Participants in three cohorts received placebo or plozasiran at a dose of 10, 25, or 50 mg on day 1 and at week 12 (i.e. every three months), administered via subcutaneous injection, while participants in the fourth cohort received placebo or 50 mg of plozasiran on day 1 and at week 24 (i.e. every six months). The primary endpoint was the percent change in fasting triglyceride level at week 24. Plozasiran exhibited dose-dependent reductions in triglyceride levels with quarterly (i.e. every 12 weeks) dosing, which were related to reductions in levels of ApoC3 (see table below). Significant reductions were also observed for levels of ApoB, non-HDL-C, and remnant cholesterol. Levels of HDL-C were increased, whereas LDL-C levels were largely unchanged, except for a

modest decrease at the 50 mg quarterly dose. The effect sizes with 50 mg half-yearly dosing were dampened relative to quarterly dosing at week 24, however, they were generally similar at week 48, with placebo-adjusted reductions of triglycerides by -56.7%, ApoC3 by -70.3%, non-HDL-C by -21.8%, ApoB by -15.2%, and remnant cholesterol by -53.8%.

Placebo-adjusted % change at week 24 (95% CI)	10 mg every 12 weeks	25 mg every 12 weeks	50 mg every 12 weeks	50 mg every 24 weeks
Triglycerides	-49.8% (-59.0 to -40.6)	-56.0% (-65.1 to -46.8)	-62.4% (-71.5 to -53.2)	-44.2% (-53.4 to -35.0)
ApoC3	-57.3% (-66.6 to -48.1)	-72.5% (-81.7 to -63.3)	-78.5% (-87.8 to -69.3)	-56.1% (-65.3 to -46.9)
Non-HDL-C	-16.7% (-24.3 to -9.0)	-17.5% (-25.1 to -9.8)	-24.2% (-31.9 to -16.6)	-7.7% (-15.3 to 0.0)
ApoB	-10.3% (-17.9 to -2.6)	-13.0% (-20.6 to -5.4)	-19.1% (-26.7 to -11.5)	-6.5% (-14.1 to +1.2)[NS]
HDL-C	+33.1% (23.2 to 43.1)	+42.0% (32.1 to 52.0)	+45.8% (35.8 to 55.7)	+28.0% (18.0 to 38.0)
LDL-C	-4.1% (-13.9 to +5.7)[NS]	-2.7% (-12.4 to +7.0)[NS]	-13.6% (-23.3 to -3.8)	+2.8% (-6.9 to 12.6)[NS]
Remnant cholesterol	-42.9% (-56.8 to -29.0)	-48.9% (-62.7 to -35.2)	-47.5% (-61.4 to -33.7)	-36.5% (-50.3 to -22.6)

NMR lipoprotein particle analysis from the Phase 2 SHASTA-2 (hyperlipidemia) and MUIR (mixed dyslipidemia) trials (n=403) found that plozasiran led to dose-dependent reductions in TRL particles (-46% and -48%, respectively) [34]. There was also a shift in the size of the LDL particles, with an increase in large and medium sized particles, and a decrease in the highly atherogenic small-dense LDL particles. Plozasiran was also associated with a shift toward larger HDL particles. This indicates that plozasiran treatment shifts the lipoprotein particle distribution in a manner consistent with reduced cardiovascular risk.

Plozasiran is currently being tested in the Phase 3 MUIR-3 trial in patients with hypertriglyceridemia, and the Phase 3 SHASTA-3, SHASTA-4, and SHASTA-5 trials in patients with severe hypertriglyceridemia.

Familial Chylomicronemia Syndrome
Plozasiran was tested in the randomized, double-blind, placebo-controlled Phase 3 PALISADE trial in 75 patients with persistent chylomicronemia (with or without a genetic diagnosis) (NCT05089084) [58]. The median baseline triglyceride level was 2,044 mg/dL. Participants were treated with subcutaneously administered placebo or plozasiran at a dose of 25 mg or 50 mg every three months for 12 months. The study met its primary endpoint of the median percent change from baseline in the fasting triglyceride level at 10 months, with reductions of -80% in the 25-mg group, -78% in the 50-mg group, compared with -17% in the placebo group. Median ApoC3 levels were reduced by -93% in the 25-mg group, by -96% in the 50-mg group, and by -1% in the placebo group. Rates of acute pancreatitis were lower in the plozasiran-treated groups (2 cases in 2 out of 50 patients) relative to the placebo-treated group (7 cases in 5 out of 25 patients) (OR: 0.17).
Based on the results of this trial, Arrowhead Pharmaceuticals has submitted a New Drug Application (NDA) to the FDA for the use of plozasiran in FCS. The application has been accepted and a Prescription Drug User Fee Act (PDUFA) date, which is the deadline set for the FDA to review and make a decision on a drug application, is in November 2025 (Press release).

Fatty liver disease: APOC3 VARIANTS ASSOCIATED WITH RISK IN SOME ETHIC GROUPS
Gene association studies suggest that gene variants which impact ApoC3 levels or activity can influence the risk for non-alcoholic fatty liver disease (NAFLD also called MASLD), but the relationship is modified by ethnic background.
A meta-analysis including eight studies (1,750 cases and 2,181 controls) assessing the impact of the rs2854116 (T455C in the promoter region) ApoC3 variant, which is associated with (~30%) higher ApoC3 levels, found an association with increased NAFLD risk under the dominant model (OR: 1.16, 95% CI 1.01 to 1.33) [59]. However, another variant which is in strong linkage disequilibrium (tends to be inherited together), rs2854117 (C482T in the promoter region) was not significantly associated with NAFLD risk based on six case-control studies including 1,523 cases and 1,568 controls. It should be noted that nearly all of the included studies assessed ethnically Chinese participants. A separate meta-analysis including eight case-control studies (1,511 cases and 1,900 controls) similarly found that the rs2854116 (T455C) variant, but not the rs2954117 (C482T) variant, was associated with increased risk for NAFLD, and the association was modified by ethnicity [60]. The ApoC3 variant was associated with NAFLD risk in non-Asian cohorts, but not in Asian cohorts. Since ApoC3 glycated proteoform composition and association

with cardiovascular risk varies based on ethnicity (i.e. genetic background), the associations with other metabolic traits may also vary.

Clinical studies involving interventions that reduce ApoC3 levels also provide evidence that modulating ApoC3 may impact liver fat accumulation. In the context of dietary intervention, reductions in ApoC3 were associated with reductions in levels of liver and pancreatic fat [61].
An analysis including 220 patients with hypertriglyceridemia, familial partial lipodystrophy (FPL) or familial chylomicronemia syndrome (FCS) from clinical trials testing volanesorsen found that treatment with the ApoC3-lowering therapy for six months reduced the absolute hepatic fat fraction by -3.02% (95% CI -5.60 to -0.60) [62]. Due to the progressive increase in liver fat accumulation in untreated participants, the magnitude of change is greater in placebo-adjusted analysis (-24.2%). The degree of reduction was related to the baseline hepatic fat fraction, such that individuals with the highest hepatic fat fraction at baseline experienced a greater degree of reduction.

Cancer: APOC3 MAY BE A PROGNOSTIC MARKER FOR SOME TYPES OF CANCER
ApoC3 has been identified as a prognostic marker for some types of cancer.
Gastric cancer: A study using the GEO and TGCA databases identified cholesterol metabolism as a factor in the development of gastric cancer [63]. A set of lipid metabolism genes, including ApoA1, ApoC3, NPC2, CD36, and ABCA1 were found to act as prognostic factors. High expression of ApoC3, NPC2, CD36, and ABCA1 was associated with worse prognosis.
Breast cancer: A Mendelian randomization study including 139,274 participants found that ApoC3 lowering was associated with reduced risk of breast cancer via impacts on triglycerides (OR: 0.91, 95% CI 0.86 to 0.98) and ApoB (OR: 0.74, 95% CI 0.64 to 0.85) [64].
Endometrial cancer: A Mendelian randomization study including 240,027 participants found that ApoC3 lowering was associated with reduced risk of endometrial cancer via impacts on triglycerides (OR: 0.60, 95% CI 0.47 to 0.78) and ApoB (OR: 0.30, 95% CI 0.18 to 0.52) [64].
Colorectal cancer: Serum levels of O-glycosylated ApoC3, particularly the di-sialylated form ($ApoC3_2$), was shown to be increased in the context of colorectal cancer [65].

Safety: Volanesorsen is associated with thrombocytopenia. Liver-targeted olezarsen and plozasiran have less impact on platelets, but may still modestly increase liver enzymes. Volanesorsen and plozasiran may impact glycemic control.

Types of evidence:

- Four clinical trials for volanesorsen (hypertriglyceridemia and FCS)
- Four clinical trials for olezarsen (hyperlipidemia and FCS)
- Four clinical trials for plozasiran (hyperlipidemia, mixed dyslipidemia, and FCS)

Volanesorsen

Volanesorsen was ultimately rejected by the FDA due to safety concerns, including the drop in platelet counts in patients. It is thought that the drop in platelet count may be due to the delivery methodology (the type of ASO)[66].

The EMA label contains special precautions for reductions in platelet counts leading to thrombocytopenia. Monitoring for renal and hepatic toxicity is also recommended. The label also notes that elevations of LDL-C within the normal range may also occur.

In the phase 2 study in patients with hypertriglyceridemia, injection site reactions occurred in 13% to 15% of patients in the treated groups and none in the placebo group [44]. The most common adverse events possibly related to the study drug in the monotherapy group included fatigue (14%), musculoskeletal pain (10%), nausea (10%), chills (7%), myalgia (7%); and in the add-on to fibrate therapy included diarrhea (10%), upper abdominal pain (10%), fatigue (10%), and a feeling of relaxation (10%). 10% of the patients treated with volanesorsen discontinued treatment because of adverse events. There were two serious adverse events (SAE) in the treated groups (a serum sickness-like reaction and an SAE associated with arterial graft stenosis). There was no indication of significant effects on renal or liver function.

In the phase 3 study in patients with FCS, volanesorsen was associated with an increased risk of thrombocytopenia, in some cases severe thrombocytopenia [47]. Injection site reactions were more common in the volanesorsen group (12% vs. 0%). Platelet counts fell below the normal level (140,000 per microliter) in 76% of patients in the volanesorsen group versus 24% of patients in the placebo group. There were two cases of severe thrombocytopenia in the volanesorsen group leading to a more rigorous monitoring of platelet counts. These patients recovered after drug withdrawal. There were more

dropouts in the volanesorsen group (14 patients – 9 due to adverse events – versus 2 patients in the placebo group).

Olezarsen

According to the FDA label, the most common adverse events (incidence > 5%) observed in clinical trials testing olezarsen that occurred at higher frequency (>3%) than placebo were injection site reactions, decreased platelet count, and arthralgia (joint pain).

Hypertriglyceredmia: In a Phase 2 dosing trial in patients with hypertriglyceridemia and cardiovascular risk factors testing olezarsen at subcutaneous doses up to 50 mg q4w for 6-12 months, the most common adverse events occurring at a higher frequency with olezarsen were injection site erythema (15.6% vs. 0%), arthralgia (12.2% vs. 0%), nasopharyngitis (12.2% vs. 8.3%), and upper respiratory tract infection (11.1% vs. 8.3%) [50]. Rates of injection site redness (erythema) were highest in the group that received the greatest number of injections (10 mg weekly). Rates of injection-related flu-like reactions were similar between the olezarsen and placebo groups (8.9% vs 8.3%). There were no clinically significant differences in liver chemistry tests, renal function, or other laboratory measures such as glycemic parameters, or high-sensitivity C-reactive protein levels, vital signs, or electrocardiographic measures.

In the Phase 2b Bridge–TIMI 73a trial in patients with moderate to severe hypertriglyceridemia, elevations in liver enzymes (ALT or AST) were more common with olezarsen [51]. Cases of liver enzyme elevations at least three times the upper limit of the normal range occurred in 4 patients (7%) in the olezarsen 50-mg group, 1 patient (2%) in the 80-mg group, and none of the patients in the placebo group. Changes in kidney function (based on eGFR and creatinine measures) were not increased with olezarsen relative to placebo. The incidence of platelet count reductions to below 100,000 per microliter was not significantly higher with olezarsen relative to placebo with rates of 0%, 5%, and 3% in the 50-mg, 80-mg, and placebo groups, respectively. There were no significant changes in the systemic inflammatory marker C-reactive protein, or glycemic parameters, such as glycated hemoglobin (HbA1c).

Full safety results have not yet been released from the Phase 3 Essence-TIMI 73b trial in patients with moderate hypertriglyceridemia and elevated cardiovascular risk. Topline results indicate that the most common adverse event occurring at higher frequency with olezarsen relative to placebo was injection-site reactions (Press release).

Familial chylomicronemia syndrome: Olezarsen generally had a favorable safety profile in the Phase 3 BALANCE trial in patients with FCS [53]. Rates of serious adverse events were higher in the placebo group, primarily driven by higher rates of pancreatitis. There were no clinically meaningful cases of platelet reductions or cases of hepatic or renal toxicity.

Plozasiran

Hypertriglyceridemia: In a Phase 2 trial in patients with severe hypertriglyceridemia testing subcutaneous doses up to 50 mg (two doses administered on days 1 and 12), rates of adverse events and serious adverse events were similar across groups [34]. Cases of worsening glycemic control were reported in some participants with diabetes, with one participant in the 50 mg plozasiran group discontinuing the study due to worsened glycemic control. An increase in HbA1c was observed at the 50 mg dose at week 24 (LS mean difference vs placebo: 0.5, 95% CI 0.2 to 0.8), but not at the lower doses of plozasiran. However, there were no significant changes on the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). The study authors speculate that impact on glycemic control may be related to accelerated delivery of substrate to the liver to drive gluconeogenesis, stemming from the enhanced hydrolysis of triglyceride-rich lipoproteins.

In a Phase 1 single and multiple ascending dose trial, the most common treatment-emergent adverse events were mild, transient, injection site reactions, such as erythema, pain, bruising, and rash [56]. Treatment-emergent cases of asymptomatic, transient, mild elevations in liver enzymes (ALT and AST) occurred in 10 participants treated with plozasiran and were more prevalent at the higher doses (50 and 100 mg). Eleven participants had ALT levels of greater than three times the upper limit of normal and total bilirubin levels greater than twice the upper limit of normal. In all cases, liver enzymes returned to normal by the end of the study. There were no cases of thrombocytopenia, and the incidence of platelet count reductions was similar between plozasiran and placebo-treated groups.

Mixed dyslipidemia: In a Phase 2b trial in patients with mixed dyslipidemia treated with doses of plozasiran up to 50 mg every 12 weeks, rates of adverse events at week 24 were generally similar across treatment groups [57]. Of the most common adverse events (occurring in ≥ 5 participants), worsening glycemic control is the only event occurring at a higher frequency with plozasiran. The impact on glycemic control was only observed at the higher doses (50 mg every 12 weeks and 50 mg every 24 weeks), with incidence rates of 20% and 21%, respectively, compared with 10% in the placebo group. Changes in glycated hemoglobin (HbA1c) over the course of the trial were more common in those with diabetes. However, this effect was not accompanied by changes on HOMA-IR, suggesting that insulin

sensitivity was not impacted. The effect is thought to be related to postprandial glycemia stemming from increased breakdown of TRLs. There were no clinically meaningful cases of liver enzyme elevations or low platelet counts.

Familial chylomicronemia syndrome: In the Phase 3 PALISADE trial in patients with FCS testing doses of plozasiran administered every three months of 25 mg and 50 mg, the most common adverse events were abdominal pain, nasopharyngitis, headache, and nausea, with rates similar across plozasiran and placebo groups [58]. Rates of serious adverse events were lower with plozasiran, driven by decreased rates of pancreatitis. Cases of hyperglycemia were observed in the subset of participants with diabetes or prediabetes.

Drug interactions:
There are currently no known/established drug interactions for ***olezarsen*** or ***plozasiran***, however, since both are liver targeted drugs, caution may be warranted when used in conjunction with other drugs which could influence liver function.
Drug interactions for ***volanesorsen*** have not been established clinically, but due to potential impacts on platelet counts, there may be an increase in bleeding when used in conjunction with antithrombotic agents (EMA label). There could potentially also be interactions with drugs that impact renal or hepatic function.
Impacts on glycemic control have been observed in diabetic trial participants treated with ***volanesorsen*** or ***plozasiran***, suggesting that dose adjustments of antidiabetic medications may be needed in some patients.

Sources and dosing:
Olezarsen is FDA approved for use in adults with familial chylomicronemia syndrome, as an adjunct to a low-fat diet. The recommended dose is 80 mg monthly, administered via subcutaneous injection (FDA label). It is marketed by Ionis Pharmaceuticals under the tradename Tryngolza™. It has been clinically tested for hypertriglyceridemia at doses of 50 mg or 80 mg, monthly, but is not yet approved for that indication.
Plozasiran is not yet approved for any indication. It is in clinical development by Arrowhead Pharmaceuticals. In clinical trials it has been tested at doses of 25 or 50 mg every three months, administered via subcutaneous injection.
Volanesorsen is EMA approved for use in adults with familial chylomicronemia syndrome, as an adjunct to a low-fat diet. The recommended starting dose is 285 mg weekly, administered via subcutaneous

injection, for the first three months, and then 285 mg every two weeks (EMA label). It is marketed by Ionis Pharmaceuticals under the tradename Waylivra®.

Research underway:
There are currently no active clinical trials testing **volanesorsen**.

According to ClinicalTrials.gov, there are currently 5 active clinical trials testing **olezarsen**.

Olezarsen is being tested in a two Phase 3, multi-center, randomized, double-blind, placebo-controlled CORE-TIMI studies in 446 participants and 617 participants, respectively, with severe hypertriglyceridemia (fasting triglycerides ≥ 500 mg/dL) (NCT05552326 and NCT05079919). The studies include a 53-week treatment period, and a 13-week post-treatment evaluation period or transition to open-label extension (OLE) study with up to 1-year treatment. They have estimated completion dates in late 2025.
CORE-OLE is the open-label extension study for the patients from the double-blind trials testing olezarsen in patients with severe hypertriglyceridemia (NCT05681351), which has an estimated completion date in 2027.

Olezarsen is being tested in an open-label extension study in 60 patients with Familial Chylomicronemia Syndrome (FCS) (NCT05130450), which has an estimated completion date in 2028. It is also being tested in an open-label study in 24 patients with FCS previously treated with volanesorsen (NCT05185843), which has an estimated completion date in 2027.

According to ClinicalTrials.gov, there are currently 6 active clinical trials testing **plozasiran**.

The Phase 3 PALISADE trial testing ***plozasiran*** in 75 adult patients with Familial Chylomicronemia Syndrome (FCS) (NCT05089084) had a primary completion date in 2024. Participants continued into a 2-year open-label extension period, which has a completion date in 2026.

Plozasiran is being tested in in the Phase 3 MUIR-3 trial in 1,456 patients with hypertriglyceridemia (mean fasting triglyceride level ≥150 mg/dL and ≤499 mg/dL) (NCT06347133), which has an estimated completion date in 2026.

Plozasiran is being tested in two Phase 3 trials (SHASTA-3 and SHASTA-4) in patients (n=446 and n=311, respectively) with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL) (NCT06347003 and NCT06347016), which have expected completion dates in 2026.
Participants from these studies have the option of entering the 24 month SHASTA-10 open-label extension study (NCT06822790), which has an estimated completion date in 2028.
Plozasiran will also be tested in a double-blind, placebo-controlled, Phase 3 trial (SHASTA-5) in patients with severe hypertriglyceridemia at high risk of acute pancreatitis (NCT06880770).

Search terms:

Pubmed, Google: ApoC3, volanesorsen, olezarsen, plozasiran +

- Alzheimer's disease, longevity, cardiovascular, diabetes, cancer, GWAS, clinical trial, safety

Websites visited:

- Clinicaltrials.gov (Olezarsen, Plozasiran, Volanesorsen)
- PubChem (Volanesorsen)
- Drugs.com (Olezarsen)
- Drugbank.ca (Olezarsen, Plozasiran, Volanesorsen)

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