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.

Volanesorsen (Waylivra)

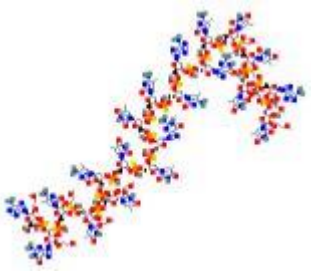
Evidence Summary

Volanesorsen is an antisense-oligonucleotide (ASO) that targets ApoC3 and effectively lowers triglycerides and raises HDL, but safety issues surrounding the drug may limit its use to rare diseases.

Neuroprotective Benefit: There is no rationale for the use of volanesorsen in the treatment of Alzheimer's disease.

Aging and related health concerns: Volanesorsen effectively lowers triglyceride levels, though potential safety issues may limit its use to rare diseases.

Safety: Volanesorsen is associated with several side-effects, some potentially serious.

Availability: Not available, currently in clinical trials	**Dose**: Currently being tested at once-weekly subcutaneous 300mg doses	**Molecular Formula:** $C_{230}H_{320}N_{63}O_{125}P_{19}S_{19}$ **Molecular weight:** 7,165 g/mol **Source:** Pubchem 
Half-life: 2-4 weeks	**BBB**: Unknown, likely not penetrant	
Clinical trials: 2 ongoing, open-label extension Approach phase 3 study in familial chylomicronemia, BROADEN phase 2/3 study in familial partial lipodystrophy	**Observational studies**: None	

What is it?

Volanesorsen is a second-generation antisense oligonucleotide that targets ApoC3. It is being developed by Akacea and Ionis for rare diseases, such as familial chylomicronemia syndrome and familial partial lipodystrophy. Targeting ApoC3 can reduce levels of plasma triglycerides.

Plasma triglycerides are a marker of remnant lipoproteins, such as very-low density lipoproteins (VLDLs), intermediate-density lipoproteins, and chylomicron remnants. ApoC3 is a component of these remnant lipoproteins. It inhibits lipoprotein lipase, thus preventing the hydrolysis of triglyceride-rich lipoproteins, and prevents the uptake of these lipoproteins by the liver. Intracellularly, ApoC3 can promote triglyceride synthesis and VLDL assembly and secretion. All these mechanisms may increase the levels of triglycerides in the plasma (Jorgensen et al, 2014).

Reducing ApoC3 is one of the additional ways to target residual cardiovascular risk in a post-statin era and joins other potential targets such as PCSK9, ANGPTL3, and Lp(a) (Nordestgaard et al, 2018).

Neuroprotective benefit: There is no rationale for the use of volanesorsen in the treatment of Alzheimer's disease.

Types of evidence:

- Three biomarkers studies

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

One study reported that ApoC3 levels were positively correlated with cognition, but only in the oldest of old (95-105) females (Muenchhoff et al, 2017).

Human research to suggest benefits to patients with dementia:

In a study of 53 Alzheimer's patients with cardiovascular disease (CVD) or a single CVD risk factor and 52 Alzheimer's patients without CVD risk factors, Adunksy et al (2002) found no difference in blood levels of ApoC3 between the groups. Both groups had levels below normal, though the authors acknowledge that normal levels are still not well established. In a study with 147 Alzheimer's patients and 160 healthy controls, blood levels of ApoC3 were lower in Alzheimer's patients and inversely correlated with clinical severity (Lin et al, 2015).

Mechanisms of action for neuroprotection identified from laboratory and clinical research

N/A

APOE4 Interactions:

N/A (volanesorsen has not been tested in AD populations)

Aging and related health concerns: Volanesorsen effectively lowers triglyceride levels, though potential safety issues may limit its use to rare diseases.

Types of evidence:

- Two clinical studies (hypertriglyceridemia and familial chylomicronemia syndrome)
- One pilot study in diabetes
- One phase 1 study in healthy adults
- One meta-analysis of genetic polymorphisms in gain-of-function ApoC3
- Three genetic studies on loss-of-function mutations in ApoC3

- Two genetic lifespan studies
- One biomarker lifespan study
- One biomarker study of ApoC3
- Preclinical studies in rodent and primate models

Lifespan

Two studies in Caucasian populations reported no association between ApoC3 mutations and longevity (Novelli et al, 2008; Soerensen et al, 2016). Another study reported that ApoC3 levels linearly decline with age (Muenchhoff et al, 2017).

Cardiovascular disease

In a cohort of 75,725 participants, Jorgensen et al (2014) 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 reduced risk of ischemic vascular disease (HR = 0.43; 95%CI 0.35-0.54) and a reduced risk of ischemic heart disease (HR = 0.40; 95%CI 0.31-0.52). Similar results were obtained when comparing quintiles.

They 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. Heterozygotes for these mutations had a 44% (0.77 mmol/L) decrease in levels of non-fasting triglycerides. Heterozygotes also had a 16% reduction in ApoB, 24% increase in HDL, and a 9% increase in ApoA1. Heterozygotes also had reduced risks of ischemic vascular disease (HR 0.59; 95%CI 0.41-0.86) and ischemic heart disease (HR = 0.64; 95%CI 0.41-0.99). 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. 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 was also lower in mutation carriers than non-carriers (OR = 0.60; 95%CI 0.47-0.75) (The TG and HDL Working Group of the Exome Sequencing Project, NHLBI, 2014).

Another study found that a null mutation in *APOC3* reduced levels of triglycerides, increased HDL-c, and lowered LDL-C. In addition, mutation carriers were protected from subclinical atherosclerosis (measured by coronary artery calcification) (Pollin et al, 2008).

Finally, 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 an increased risk of coronary heart disease (OR = 1.30; 95%CI 1.10-1.55) (Li et al, 2016). Another study of plasma apolipoproteins and the risk of coronary artery disease, peripheral artery disease, and carotid artery plaques reported that after controlling for several factors, including lipids, ApoC3 levels were only associated with a significantly increased risk of carotid artery plaques (OR = 1.30; 95%CI 1.06-1.58) (Dittrich et al, 2018).

Volanesorsen (previously ISIS 304801)

Volanesorsen is a second-generation ApoC3 antisense oligonucleotide being developed for hypertriglyceridemia and familial chylomicronemia syndrome.

Hypertriglyceridemia

In multiple mouse models, administration of volanesorsen reduced levels of ApoC3, plasma triglycerides, VLDL, and chylomicron particles. In primates fed fructose (to cause hypertriglyceridemia), volanesorsen reduced plasma triglycerides and VLDL/chylomicron levels and increased levels of HDL. In a placebo-controlled phase 1 study in healthy volunteers, volanesorsen reduced levels of ApoC3 and triglycerides in a dose-dependent manner (Graham et al, 2013).

Gaudet et al (2015) conducted a phase 2 RCT dose-finding study of 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.

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 volanseorsen or the placebo. 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 . There were additionally 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 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, 3) a change in the secretion or catabolism of LDL particles.

Add-on to fibrate therapy
In the add-on to fibrate therapy group, patients received a single dose of either 200mg or 300mg and then were randomly assigned drug or placebo in a 2:1 ratio at the same dosing regimen. Similar results were obtained, though there was no increase in LDL-c, possibly because fibrates can counteract the increase in LDL-c found when volanesorsen was given as a monotherapy.

Familial Chylomicronemia Syndrome
A phase 3, 52-week study in 66 patients with familial chylomicronemia syndrome tested the effects of volanesorsen (300mg, subcutaneously, weekly) versus placebo. At 3 months, volanesorsen reduced levels of ApoC3 (-84% vs. +6.1% for placebo) and fasting triglycerides (-77% vs. +18%). These results were also significant at 6- and 12- months (Witztum et al, 2019).

Diabetes
In a pilot study with 15 patients with type 2 diabetes and hypertriglyceridemia randomized 2:1 to receive either volanesorsen (300mg 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). There was a significant inverse relationship between insulin sensitivity and plasma ApoC3 (r=-0.61) and triglycerides (r=-0.68) (Digenio et al, 2016).

Safety: Volanesorsen is associated with several side-effects, some potentially serious.

Types of evidence:
- One phase 3 study in patients with familial chylomicronemia syndrome (FCS)
- One phase 2 study in patients with hypertriglyceridemia

In the phase 3 study in patients with FCS, 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) (Witztum et al, 2019).

Volanesorsen was ultimately rejected by the FDA in this indication, possibly because of the drop in platelet counts in patients (the company never explained the reason). It is thought that the drop in platelet count may be due to the delivery methodology (the type of ASO) (Taskinen et al, 2019).

In the phase 2 study in patients with hypertriglyceridemia (Gaudet et al, 2015), injection site reactions occurred in 13%-15% of patients in the treated groups and none in the placebo group. 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 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.

Larger studies will be required to determine whether it is safe for patients without severe disease. Potentially other ApoC3-targeted therapies, when developed, could be safer.

Drug interactions: Not known, though volanesorsen could interact with other drugs that lower triglycerides.

Sources and dosing: Volanesorsen is being developed by Akacea and Ionis. It is in clinical trials and not currently commercially available. Doses of up to 300 mg once-weekly (subcutaneous) have been tested in clinical trials.

Research underway:

There are two ongoing studies of volanesorsen.

- Approach open-label extension phase 3 study in patients with familial chylomicronemia syndrome
- BROADEN phase 2/3 study in patients with familial partial lipodystrophy

Search terms:

ApoC3 + Alzheimer, longevity, cardiovascular, neuropathy, hypotension, cancer
volanesorsen

Websites visited:

- Clinicaltrials.gov
- Pubmed