

Mini Review

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New Insights into the Potential of Obicetrapib, a Cholesteryl Ester Transfer Protein Inhibitor, to Reduce Vascular Contributions to Cognitive Impairment and Dementia

Tetiana Poliakova¹ and Cheryl L. Wellington^{1*}

¹Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, The University of British Columbia, Vancouver, British Columbia, Canada, V6T 1Z3

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*Correspondence:

*Dr. Cheryl L. Wellington, Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, The University of British Columbia, Vancouver, British Columbia, Canada; Email: Cheryl.wellington@ubc.ca.

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Abstract

Alzheimer's disease (AD) remains a leading cause of dementia worldwide, with complex pathophysiology involving amyloid deposition and tau pathology that precedes cognitive decline. Cardiovascular risk factors, including hypertension, type II diabetes, and dyslipidemia, are recognized as modifiable risk factors of AD, especially during midlife, underscoring the close interplay between AD and vascular contributions to cognitive impairment and dementia (VCID). Anti-amyloid immunotherapies offer potential for disease modification; however, they can transiently increase cerebral amyloid angiopathy (CAA), which may lead to serious and potentially fatal adverse effects known as amyloid-related imaging abnormalities (ARIA). These risks are particularly elevated in apolipoprotein E4 (*APOE4*) carriers, the major genetic risk factor for late-onset AD, underscoring the urgent need for improved safety measures and patient stratification strategies. Notably, the vascular pathways implicated in ARIA may overlap with mechanisms of amyloid clearance influenced by lipid metabolism. The objective of this study is to review how lipoproteins, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), influence amyloid clearance and vascular health, and discuss how cholesteryl ester transfer protein (CETP), a key regulator of lipoprotein exchange, has emerged as a potential therapeutic target in dementia. In addition to effectively lowering LDL-C and increasing HDL-C, the CETP inhibitor obicetrapib has recently shown promising results in slowing progression of a key AD biomarker, p-tau-217, over 12-month of treatment in patients with atherosclerotic cardiovascular disease, with more pronounced effects in *APOE4* carriers. This minireview thus highlights the intersection of cardiovascular and neurodegenerative pathways and supports further exploration of lipid-modulating therapies in AD and VCID.

Main Text

Alzheimer's Disease (AD): Alzheimer's Disease (AD) is the most commonly diagnosed dementia. The typical clinical presentation of AD is impaired memory at age 65 years or later, often preceded by a period of mild cognitive impairment that is measurable but does not impair activities of daily living. Extensive research over the past two decades has shown that AD pathogenic change begins 15-20 years before clinical onset, leading to the concept of pre-clinical disease stages associated with amyloid plaque deposition, followed by formation of neurofibrillary tangles and onset of neurodegeneration that heralds the clinical disease stages of mild cognitive impairment (MCI) and dementia¹. Thus, the clinical stages of AD are preceded by a prolonged preclinical stage where interventions are likely to have their greatest efficacy. Cardiovascular risk factors (CRF), including hypertension, type II diabetes and dyslipidemia, are important modifiable AD risk factors especially at midlife², reflecting the close

relationship between AD and vascular contributions to cognitive impairment and dementia (VCID). Indeed, in addition to amyloid plaques and neurofibrillary tangles, most AD cases have cerebrovascular pathologies including cerebral atherosclerosis, arteriosclerosis, infarcts, and microbleeds when examined at autopsy, reflecting critical roles of cerebral vessels in AD pathophysiology³.

Advances in AD Biomarkers: The National Institute on Aging (NIA) and the Alzheimer's Association (AA) published revised criteria for diagnosis and staging of AD in 2024⁴ to update the "ATN" research framework, which uses biomarkers to detect the major pathological hallmarks of AD. "A" or A β biomarker tests include amyloid positron emission tomography (PET) or quantification of cerebrospinal fluid (CSF) levels of A β 42, the major peptide found in parenchymal amyloid plaques⁵. "T" or tau tests also include PET and CSF tests that measure various forms of phosphorylated tau (p-tau) found in neurofibrillary tangles. "N" biomarkers of neurodegeneration include magnetic resonance imaging (MRI) as well as CSF tests for total tau. In the 2024 update, blood biomarkers were newly recommended for AD diagnosis. Plasma biomarkers for AD pathology now include A β 42/40 as an "A" marker, p-tau-217, p-tau-181, and p-tau-231 as "T" markers, neurofilament light (NfL) as an "N" marker, and glial fibrillary acidic protein (GFAP) as an inflammatory or "I" marker. Within this framework, it is recognized that, despite being "T" markers, the most robust plasma biomarker of A β positivity is p-tau-217, which, along with p-tau-181 and p-tau-231, is believed to be an early physiological reaction to amyloid that links A β to tau proteinopathies⁴. These advances in the ATN research framework have led to global efforts to investigate appropriate use recommendations and clinical implementation of plasma biomarkers⁶. A key remaining challenge is identification of vascular, or "V" biomarkers that reflect VCID.

Anti-amyloid immunotherapies: Two anti-amyloid immunotherapies, lecanemab and donanemab, have been cleared by the Food and Drug Administration as interventions for early AD including the MCI and mild dementia stages. Although remarkably effective in removing parenchymal amyloid, both drugs have limitations including modest efficacy in slowing the rate of cognitive decline and increased risk of adverse effects known as amyloid related imaging abnormalities (ARIA) especially in carriers of apolipoprotein E4 (apoE4)⁷, the most well-established genetic risk factor for late-onset AD. ARIA includes edemic (ARIA-E) and hemorrhagic (ARIA-H) forms⁷, reflecting the key role of cerebral vessels in amyloid clearance. In healthy individuals, amyloid production in the brain is balanced by various A β removal mechanisms that include enzymatic degradation, transport across the blood brain barrier (BBB), and perivascular drainage

pathways⁸. Tracer studies show that A β first deposits in the periphery of arterioles and exits along intramural periarterial drainage pathways, similar to drainage of the brain's interstitial fluid. The glymphatic system, where cerebrospinal fluid (CSF) enters the brain along arteries, exchanges with interstitial fluid and drains through perivenous pathways is a second form of perivascular drainage. Age-related decline in efficiency of vascular amyloid clearance pathways can lead to accumulation of A β species, primarily A β 40, predominately in the media and adventitia of cortical and leptomeningeal vessels, known as cerebral amyloid angiopathy (CAA)⁹. CAA increases risk of lobar brain hemorrhage due to compromised endothelial barrier integrity, reduced cerebrovascular reactivity and, in advanced cases, replacement of the tunica media with amyloid and splitting of the vessel wall. Through processes that remain to be fully understood, anti-amyloid immunotherapies cause a transient increase in CAA as parenchymal amyloid plaques are solubilized¹⁰. Strategies to improve the safety profile of anti-amyloid immunotherapies and identify those at greatest risk of ARIA are thus highly desired.

Lipoproteins, CAA and AD: Lipoproteins play key roles in AD. ApoE is the best known, as genetic variants in *APOE* underlie most of the genetic risk factor for late-onset AD, with *APOE4* detrimental, *APOE3* neutral and *APOE2* beneficial. In the central nervous system (CNS), apoE is produced primarily from astrocytes, pericytes and microglia, and has pleiotropic functions including lipid transport, synaptic plasticity, amyloid deposition, tau-mediated neurodegeneration, BBB integrity, and inflammation¹¹. ApoE is also made by peripheral hepatocytes and macrophages and circulates in blood on peripheral lipoproteins that modulate cardiovascular disease risk. Because an intact BBB prevents the CNS and peripheral pools of apoE from mixing, peripheral lipoproteins are relatively understudied in AD research. However, it is increasingly appreciated that peripheral lipoproteins, including those containing apoE, may affect brain function by mechanisms that likely include actions on the cerebrovasculature¹². Thus, lipoproteins may affect the cerebrovasculature from both sides of the BBB; brain lipoproteins made largely from apoE from the abluminal side and peripheral lipoproteins from the luminal side.

Low density lipoprotein (LDL): High levels of low-density lipoproteins (LDL), measured by assaying LDL's cholesterol content (LDL-C), are causally related to risk of cardiovascular disease including atherosclerosis, coronary artery disease, stroke, hypertension and type II diabetes, all of which are also AD risk factors. Although apoB-containing lipoproteins do not cross the intact BBB, premorbid LDL-C levels are highly associated with AD neuropathology including Braak and CERAD scores,

immunohistochemistry for amyloid and neurofibrillary tangles, cerebral atherosclerosis, cerebral microinfarcts, cerebral microinfarcts, and CAA independent of *APOE* genotype¹³. A longitudinal analysis of 822 participants aged 60 years or older from the Framingham Heart Study revealed no association between LDL-C and incident AD, which might be attributed to older age of the participants, but confirmed the association of increased small dense LDL-C with increased incident AD¹⁴. As lowering the levels of LDL and other apoB-containing lipoproteins reduces cardiovascular events and successful management of mid-life LDL-C is associated with reduced dementia risk^{15,16}, the 2024 Lancet Commission on Dementia recognized midlife LDL-C as a modifiable dementia risk factor². Interestingly, extremely low LDL-C concentrations (<30 mg/dL, or <0.8 mmol/L) do not confer additional protection against dementia, indicating a possible threshold beyond which further reduction offers no cognitive advantage¹⁶. Moreover, LDL cholesterol exhibits an age-dependent trajectory, often increasing during midlife before declining in later years¹⁷. In older adults, higher LDL-C has been associated with reduced mortality¹⁸, whereas low LDL-C levels may reflect frailty or comorbid conditions and could exacerbate vulnerability to neurodegeneration. The relationship of LDL-C levels with ARIA risk is not known.

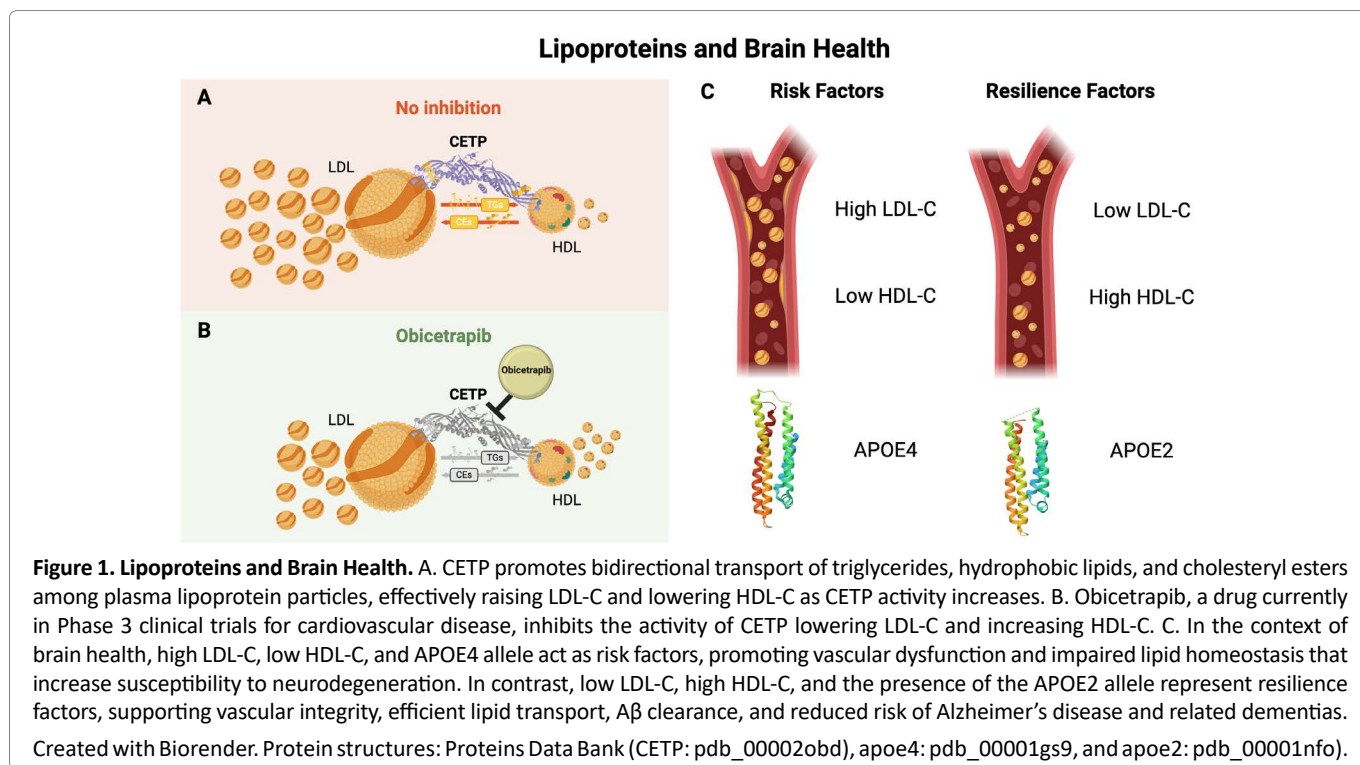
High density lipoprotein (HDL): HDL is a highly heterogeneous peripheral lipoprotein class known mainly for its ability to remove excess cholesterol from the body. In humans, over ~200 proteins and ~300 lipids have been found to associate with HDL particles¹⁹, which modify HDL's many functions including reverse cholesterol transport, reducing endothelial activation, and mitigating endothelial inflammation²⁰. Epidemiological studies on the relationship of HDL cholesterol (HDL-C) levels with dementia risk are mixed and suggest that HDL may exert its greatest influence on AD risk at mid-life, reviewed in²¹. Specifically, baseline HDL-C levels at middle age were significantly associated with AD risk, whereas baseline measures in subjects >70 years were not. Recent findings report a significant interaction between low HDL and cognitive impairment in *APOE4* carriers²². In mice, genetic and pharmacological studies have shown that HDL levels are highly associated with CAA²³⁻²⁶ and that peripheral injection of synthetic HDL particles stimulates clearance of both A β 42 and A β 40 from the brain²⁷ and attenuates CAA²⁸. In an *in vitro* scaffold-directed model of perfusable synthetic human cerebral blood vessels, HDL delivered from the "blood side" facilitates A β transport and attenuates A β accumulation in vascular tissue²⁹.

Although HDL-C is the standard clinical assay to measure HDL levels, it is increasingly appreciated that this assay does not report on HDL's unique functions that are driven mainly by its proteomic composition. For example,

peripherally-derived apoE is present on approximately 6-9% of HDL particles and is of potentially high relevance to AD. HDL containing ApoE (HDL-E) reduces vascular stiffening³⁰, stimulates reverse cholesterol transport³¹, and reduces coronary heart disease³². High HDL-apoE levels are associated with improved cognitive function as measured by the Modified Mini-Mental State Examination in the elderly (>75 years of age)³³, and high levels of plasma HDL-apoE lacking apoC-III were reported to be associated with better cognitive function and lower dementia risk in a prospective case-cohort of 1351 participants in the Ginkgo Evaluation of Memory Study³⁴. *In vitro*, HDL-E potently facilitates A β clearance and reduces vascular A β accumulation in synthetic cerebral vessels²⁹. Potential mechanisms underlying this function include attenuation of A β -induced endothelial inflammation, reducing A β binding to collagen-I by forming an HDL-A β complex, reducing collagen-I protein levels produced by smooth-muscle cells (SMC), and blocking A β uptake into arterial smooth muscle cells¹². Whether other HDL subfractions also have potentially important roles in VCID, ARIA risk, and AD, remain to be determined.

Cholesteryl ester transfer protein (CETP) and AD: CETP is a boomerang shaped glycoprotein produced mainly by the liver, with cavities at either end that enable bidirectional transfer of hydrophobic lipids, cholesteryl esters and triglycerides among plasma lipoprotein particles (Figure 1A)³⁵. Because most of the cholesteryl esters in plasma are found in the HDL fraction and most plasma triglycerides originate from very low density lipoprotein (VLDL) and chylomicrons, the net effect of CETP activity is transfer of cholesteryl esters from HDL to LDL particles and transfer of triglycerides from triglyceride-rich lipoproteins and chylomicrons into the HDL and LDL fractions.

CETP is expressed and catalytically active in humans, non-human primates, rabbits and hamsters, but is absent in most other species³⁶. Due to a deletion that leads to a nonsense mutation in exon 11 of the rodent CETP gene, neither mice nor rats express active CETP and thus have naturally high HDL and low LDL levels that increases resilience to atherosclerosis. Understanding how CETP reconstitution affects outcomes in AD mouse models is in its infancy, with evidence showing that CETP expression in hAPP transgenic (Tg) mice does not exacerbate amyloidogenic processing or alter total brain cholesterol but instead shifts hippocampal lipid distribution³⁷. Notably, treatment with the CETP inhibitor evacetrapib rescued memory decline in CETPxhAPP Tg mice despite increasing dentate gyrus cholesterol, indicating that lipid distribution rather than overall cholesterol levels may be key for cognitive outcomes. Bulk brain RNA analyses further point to vascular-associated pathways³⁷, consistent with CETP's predominant expression in endothelial cells in the human brain³⁸.



CETP has several genetic polymorphisms that regulate both its abundance and activity. Data from the UK Biobank and CARDIoGRAM plus C4D consortium show that loss of function variants have biologically equivalent effects to LDL-lowering treatments such as 3-hydroxy-3-methylglutaryl-Co-enzyme A (HMG-CoA) reductase, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition on reducing the risk of major coronary events³⁹. Human genetic and pharmacological evidence also connect low CETP activity with improved cardiovascular health and longevity⁴⁰. Recently, a Mendelian Randomization study revealed causal associations between CETP and dementia, with Parkinson Disease Dementia being particularly robust⁴¹.

Given the pivotal role of CETP in setting the plasma LDL:HDL ratio, several CETP inhibitors have been developed and evaluated in clinical trials for cardiovascular outcomes. Torcetrapib inhibited atherosclerosis in rabbits and, in early-phase studies in humans, increased HDL-C and lowered LDL-C⁴², but was discontinued due to off target effects that increased risk of death and cardiac events. Although dalcetrapib raised HDL-C levels by approximately 30% in phase 2 studies, lack of significant LDL-C lowering led to termination of clinical trials due to futility⁴³. Evacetrapib trials were also halted due to futility⁴⁴. Anacetrapib has subtle LDL-C lowering effects and significantly reduced major coronary events over 6.4 years of follow up, where continued efficacy results from its accumulation in adipose tissue leading to a long half-life⁴⁵.

Obicetrapib: Unlike the other CETP inhibitors, obicetrapib is significantly less lipophilic and shows no clinically significant off-target effects on vital signs, blood pressure, and aldosterone, sodium, potassium or bicarbonate concentrations⁴⁶. Obicetrapib lowers LDL-C, raises HDL-C, and, unique to this compound, also elevates HDL-E^{46, 47}, an HDL subfraction of interest as a vasoprotective factor in AD^{12, 24}. Obicetrapib exerts the most potent effects on LDL-C and HDL-C among the CETP inhibitors tested to date with very favourable changes in lipid profile (Figure 1B). Specifically, in a randomized phase 2 trial, obicetrapib at a 10 mg dose reduced CETP activity at steady state by 97.6%, reduced LDL-C by 50.8%, reduced apoB by 29.8%, increased HDL-C after 8 weeks by 165%, and increased apoA-I by 47.8%^{48,7}. These attributes make obicetrapib an attractive candidate to evaluate in the context of VCID, as it leads to favourable changes in *both* LDL-C and HDL-C levels. LDL-C reduction is required for lowered cardiovascular risk, which would be expected to reduce LDL-mediated effects on AD pathological changes, and elevated HDL-C is of interest with respect to its potential beneficial roles in endothelial physiology, CAA, and amyloid clearance. Moreover, obicetrapib enhances pre- β 1 HDL, a subclass central to excess cholesterol efflux, and concurrently increases key HDL-associated antioxidants, including lutein, zeaxanthin, and α -tocopherol, which further supports its potential therapeutic role in neurodegenerative disorders⁴⁸. Finally, according to Banach et al, obicetrapib has the potential to decrease the number of patients diagnosed with prediabetes and type 2 diabetes⁴⁹, a modifiable AD risk factor. A proof-of-

concept open label phase 2a trial in 13 *APOE4* carrier with MCI and biomarker-proven AD to evaluate plasma and CSF lipoprotein changes (NCT05161715) demonstrated that treatment with 10 mg obicetrapib for 24 weeks had positive effects on CSF A β levels including an 8% increase in A β 42/40 ratio, a key biomarker of AD risk, suggesting improvement in disease pathology. Moreover, the trial demonstrated 11% and 12% reductions in 24- and 27-hydroxycholesterol, respectively, indicating potential improvement of cholesterol metabolism in the brain⁵⁰.

New results from the double-blind placebo-controlled fixed dose BROADWAY Phase 3 trial were presented at the 2025 Alzheimer's Association International Conference, showing that obicetrapib stabilizes several AD plasma biomarkers including p-tau-217 especially in *APOE4* carriers (AAIC 2025 abstract 108443)⁵¹. A total of n=2,530 participants with established atherosclerotic cardiovascular disease (ASCVD) were randomized 2:1 to receive 10 mg obicetrapib daily or placebo for 12 months across *APOE* groups. Plasma AD biomarkers, including p-tau-217, p-tau-217/Ab42:40, p-tau-181, glial fibrillary acidic protein (GFAP) and neurofilament light (NFL), were measured at baseline and 12 months and correlated with lipid profile changes. Across n=1,515 participants with a mean age of 66-70 years across *APOE* genotype groups, obicetrapib significantly reduced LDL-C by 36% and raised HDL-C by 125%. In the full intention to treat cohort, p-tau-217 progression was significantly lower in the obicetrapib (1.99% increase) vs placebo (4.98% increase) groups (p=0.019). A similar reduction in the

p-tau-217/Ab42:40 ratio was observed in the obicetrapib (2.51% increase) and placebo (6.55% increase) groups (p=0.004). Remarkably, obicetrapib was highly effective in *APOE4* carriers, where p-tau-217 increased by 1.45% in the obicetrapib group and 7.19% in the placebo group (p=0.022). In *APOE4* homozygotes, p-tau-217 decreased by 7.81% in the obicetrapib group compared to a 12.67% increase in the placebo group (p=0.010). Parallel results were observed for the other AD biomarkers measured in the BROADWAY trial.

These remarkable results establish considerable potential for obicetrapib as a stand-alone or combination intervention for AD, with several important future directions. First, trials of obicetrapib in MCI and early AD will be critical to understand its efficacy in amyloid removal and protection of cognitive decline compared to anti-amyloid immunotherapies, as BROADWAY did not include cognitive status in inclusion/exclusion criteria or as an outcome. Second, further exploration into how the lipid modifying effects of obicetrapib associate with AD biomarkers and *APOE* genotype will be important. Previous obicetrapib trials for CVD reported increases in the HDL-E fraction⁴⁷, an outcome that was not included in BROADWAY. Whether *APOE* genotype modifies the ability of obicetrapib to reduce LDL-C, increase total HDL, HDL-E or other HDL fractions, remains to be determined. Third, obicetrapib's effects on CAA, whether spontaneous or induced by anti-amyloid immunotherapy, will be important to investigate.

These and other future studies could be informed by additional insights into the mechanisms by which CETP

Table 1. Effects of Obicetrapib on Lipid and Biomarker Parameters.

Parameter	Direction of change	Magnitude of change	Clinical relevance
CETP Activity	↓	97.6% ⁴⁸	Inhibition enhances reverse cholesterol transport; shifts balance toward anti-atherogenic profile.
LDL-C	↓	up to 50.8% ⁴⁸	Primary atherogenic lipoprotein; major cardiovascular risk factor; modifiable midlife risk for AD
Apolipoprotein B	↓	29.8% ⁴⁸	Key structural protein component of all major atherogenic lipoproteins
Non-HDL-C	↓	44.4% ⁴⁸	Captures all apoB-containing particles; robust predictor of cardiovascular events
Lipoprotein(a)	↓	56.5% ⁴⁸	An independent risk factor for heart disease.
HDL-C	↑	up to 165% ⁴⁸	Traditionally cardioprotective; higher levels indicate improved reverse cholesterol transport.
Pre- β 1 HDL	↑	24% ⁴⁹	A major acceptor of free cholesterol from cells
Apolipoprotein A-1	↑	47.8% ⁴⁸	Major component of HDL particles in plasma
Apolipoprotein E	↑	57% ⁴⁷	Major cholesterol transporter in the brain; pleiotropic functions; key modifier of AD risk.
α -tocopherol	↑	16% (in plasma) ⁴⁹ 58% (in HDL) ⁴⁹	HDL-associated antioxidant; supports vascular protection and reduction of oxidative stress.
Change in plasma p-tau-217	↓	1.99% increase in obicetrapib group vs 4.98% increase in placebo ⁵²	Blood-based biomarker of AD pathology; reductions suggest potential disease-modifying effect.
Change in plasma p-tau-217/Ab42:40 ratio	↓	2.51% increase in obicetrapib vs 6.55% increase in placebo ⁵²	Integrates amyloid and tau burden; predictor of AD progression.

affect AD pathophysiology. One important goal is to develop preclinical AD murine models that are reconstituted to express active CETP. Second, although LDL-C is an excellent clinical assay, the inability of HDL-C levels to report on HDL function highlights the importance of developing HDL functional assays to assess their contributions to VCID.

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