



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.

Apabetalone (RVX-208)

Evidence Summary

Apabetalone modestly increases circulating levels of ApoA1. Whether it is effective for cardiovascular disease might depend on the patient population (e.g. diabetics).

Neuroprotective Benefit: No trial for Alzheimer's disease, but epidemiology suggests that increased ApoA1 levels are associated with cognitive health.

Aging and related health concerns: Two phase 2b trials suggest apabetalone may prevent a major coronary event, but a larger phase 3 study failed to show benefit on the primary endpoint.

Safety: Transient increases in liver enzymes have been reported in ~7% of patients.

What is it?

Apabetalone is a small molecule developed by ResVerlogix that increases the expression of ApoA1. It is a bromodomain and extraterminal (BET) protein antagonist which displaces these proteins from chromatin, causing epigenetic changes that increase ApoA1 gene transcription. Previous studies suggested that ApoA1 induction is mediated by the BET family member, BRD4 ([Nikolic et al, 2015](#)).

Neuroprotective Benefit: No trial for Alzheimer's disease, but epidemiology suggests that increased ApoA1 levels are associated with cognitive health.

Types of evidence:

- 1 randomized controlled trial (RCT) for cognitive improvement in patients with cardiovascular disease (CVD)
- 2 RCTs that examined plasma A β 40
- Plasma biomarkers from CVD trials
- Epidemiology and biomarker data for the rationale

Epidemiology data suggests that individuals with higher levels of plasma ApoA1 may be at a decreased risk of dementia ([Saczynski et al 2007](#)), and biomarker data suggests that plasma ApoA1 levels may correlate with Alzheimer's disease severity ([Merched et al 2000](#)). It is unknown whether these benefits are due to lifelong increased ApoA1 levels but increasing ApoA1 later in life may potentially prevent dementia or benefit patients with Alzheimer's disease.

However, there is minimal data suggesting that apabetalone can prevent dementia or benefit patients with Alzheimer's disease. A small (n=24) pilot study in Alzheimer's disease patients and a larger (n=299) phase 2b study in patients with coronary artery disease showed that apabetalone treatment increased levels of plasma A β 40 ([Nikolic et al, 2015](#)). Unfortunately, plasma A β 40 alone may not be a good Alzheimer's disease biomarker ([Koyama et al, 2012](#)). In CVD studies, apabetalone decreased components of the complement cascade ([Wasiak et al, 2017](#)).

In one cardiovascular study over two years, apabetalone improved cognition in patients with mild cognitive impairment ([link](#)). However, this study will need to be replicated in a larger group of patients.



Aging and related health concerns: Two phase 2b trials suggest apabetalone may prevent a major coronary event, but a larger phase 3 study failed to show benefits on the primary endpoint.

Types of evidence:

- 9 RCTs
- Preclinical animal work in mice and monkeys

A phase 1 study with 24 healthy volunteers taking 2-8 mg/kg/day of apabetalone reported a 42% increase in pre-beta-HDL (the primary acceptor of cholesterol from ABCA1) and an 11% increase in ABCA1-mediated cholesterol efflux ($p < 0.05$) ([Bailey et al, 2010](#)).

Apabetalone was tested in two phase 2b clinical trials to examine changes in atheroma volume in patients with established cardiovascular disease scheduled to undergo coronary angiography ([NCT01067820](#), ASSURE I) and to examine changes in baseline lipid parameters in patients with stable coronary artery disease ([NCT01423188](#), SUSTAIN). Each trial enrolled patients with low HDL-c, most of whom were taking statins. In ASSURE I, apabetalone failed to meet its primary endpoint – a change in atheroma volume. However, in SUSTAIN it met its primary endpoint – to increased HDL-c levels. Pooled data suggested that apabetalone increased HDL-c (7.63%; $p < 0.001$), ApoA-1 (6.5%; $p < 0.01$), large HDL particles (26.6%; $p < 0.01$), and average HDL particle size (1.16%; $p < 0.05$). Major Cardiovascular Events (MACE) were a secondary endpoint in ASSURE I but not a pre-specified endpoint in SUSTAIN, but when Gilham et al (2016) went back in a post-hoc analysis and combined the data, they found that apabetalone led to a -55% ($p = 0.02$) relative risk reduction in MACE. There were no changes in LDL-C, glucose, or hsCRP ([Gilham et al, 2016](#), [Wong et al, 2015](#)).

The pooled data from ASSURE I and SUSTAIN also suggested that in diabetic patients specifically, apabetalone decreased the relative risk for MACE even greater (-77%, $p = 0.01$) and lowered glucose levels significantly ([Wong et al, 2015](#)). Also, in patients with high levels of hCRP ($> 2\text{mg/L}$), apabetalone decreased the relative risk for MACE by 69% ($p = 0.007$).

However, in a phase 3 study (BET-on-MACE), apabetalone failed to reduce the risk of MACE compared to placebo in diabetic patients. There were trends toward benefits in several secondary outcomes ([link](#)).

In a cross-over trial in 20 males with prediabetes, [Siebel et al \(2016\)](#) reported that apabetalone for 30 days improved glucose tolerance after an oral glucose tolerance test.



Mechanism of action from preclinical studies:

Preclinical work in African green monkeys suggests that apabetalone increased circulating ApoA1 and HDL-C levels by 60% and 97%, respectively ([Kingwell et al, 2014](#)). In a mouse model of hyperlipidemia (ApoE[-/-]), apabetalone (150mg/kg twice/day) for 12 weeks significantly reduced aortic lesion formation and increased HDL-C two-fold ([Jahagirdar et al, 2014](#)).

Safety: Transient increases in liver enzymes have been reported in ~7% of patients.

Types of evidence:

- 1 phase 2b study

In a phase 2b study (ASSURE I), [Nicholls et al \(2016\)](#) reported that 100mg twice/day of apabetalone over six months resulted in a greater incidence of transient increases in liver enzymes over placebo (7.1 vs 0%; p=0.009). The reasons for the increase are unclear, although it was primarily observed in patients treated with simvastatin, high-dose statin therapy, and those with elevated liver enzymes at baseline ([Nikolic et al, 2015](#)). Data from a large 2,400 patient trial that is currently recruiting patients will hopefully shed more light on the etiology of this increase.

Sources and dosing:

Apabetalone is developed by [ResVerlogix](#) (Calgary, Canada). Previous studies used 100mg twice/day for up to six months.

Research Underway

Resverlogix announced their topline results for their BET-on-MACE trial earlier in 2019. The trial failed, though subgroups of patients showed some benefits. It is unclear what the future development plan of apabetalone is.

Search Terms:

- RVX-208 (pubmed and clinicaltrials.gov and google)



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