*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.*

# CSL112

**Evidence Summary**

Because of the degree to which CSL112 increases ApoA1 levels and HDL cholesterol efflux capacity, it might be beneficial in preventing future cardiovascular events. However, there is still little clinical data to confirm this.

**Neuroprotective Benefit:** Preclinical evidence suggests that short-term treatment of CSL111 might reduce levels of soluble amyloid beta, but it probably does not affect amyloid plaques and may not affect vascular amyloid plaques.

**Aging and related health concerns:** CSL112 increases levels of ApoA1 and cholesterol efflux capacity for up to seven days which may be beneficial for cardiovascular disease, but no large-scale clinical trials of CSL112 or CSL111 have been reported.

**Safety:** Minor adverse events are related to the infusion procedure itself, but there are no major short-term adverse events. Long-term treatment has not been studied.

**What is it?**
CSL112 is a reconstituted HDL (rHDL) particle composed of native ApoA1 purified from human plasma and phosphatidylcholine that can be intravenously infused. It is a reformulation of an initial product, CSL111, which was discontinued because of potential liver toxicity. CSL112 is redesigned to improve safety and particle uniformity (Du et al, 2015). It is designed to mimic the poorly lipidated, small HDL-vs particles that are the preferred substrate for ABCA1, and thus designed to improve reverse cholesterol transport and potentially remove cholesterol from atherosclerotic plaques.

Most of the clinical and preclinical work to date has used CSL111. Therefore, some of the CSL111 data will be provided along with CSL112.

**Neuroprotective Benefit:** Preclinical evidence suggests that short-term treatment of CSL111 might reduce levels of soluble amyloid beta, but it probably does not affect amyloid plaques and may not affect vascular amyloid plaques.

*Types of evidence:*

- Epidemiology studies of ApoA1
- Two preclinical studies

*Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:*
None

*Human research to suggest benefits to patients with dementia:*
None

*Mechanisms of action for neuroprotection identified from laboratory and clinical research:*
Epidemiology studies suggest that low ApoA1 levels may be a risk factor for dementia or MCI, and mouse studies suggest that overexpression of ApoA1 may protect against cerebral amyloid angiopathy (CAA – amyloid plaques around blood vessels) Saczynski et al 2007, Lewis et al ,2010). Sutkas et al (2014) infused rhApoA1 (provided by the company that developed CSL112) to shown that it rapidly accumulates in the brain via the choroid plexus (the barrier between the blood and the cerebral spinal fluid). Robert et al, (2016) infused a single injection of CSL111 in an aged, symptomatic Alzheimer's mouse model, APP/PS1, and reported a nearly 50% reduction in soluble amyloid-beta 40 and 42 at 24

hours later. There was no effect, however, on amyloid plaques. When animals were examined seven days after one month of treatment, CSL111 failed to alter levels of soluble amyloid beta 40 and 42, vascular or cerebral amyloid burden, or markers of inflammation. By that time CSL111 was already cleared from the plasma. This suggests that the effect of CSL111 or CSL112 may be acute.

**Aging and related health concerns:** CSL112 increases levels of ApoA1 and cholesterol efflux capacity for up to seven days which may be beneficial for cardiovascular disease, but no large-scale clinical trials of CSL112 or CSL111 have been reported.

*Types of evidence:*

- 10 phase 0 trials of CSL111
- 1 phase 2 trial of CSL111
- 5 Phase 1-2 RCTs (3 reported) of CSL112

In a trial of 20 patients scheduled for femoral artery surgery, CSL111 decreased lipid content in femoral artery plaques (Shaw et al, 2008). In addition, a phase 2 RCT with 145 patients who recently had an acute coronary syndrome tested multiple infusions of CSL111 at either 40mg/kg or 80mg/kg. The low dose CSL111 did not change atheroma volume over placebo (though it did decrease atheroma volume from baseline, -3.4%; $p<0.001$), but it did improve plaque characterization (Tardif et al, 2007). The high dose, however, was discontinued early because of liver function abnormalities (Tardif et al, 2007). Therefore, CSL111 was reformulated. CSL112 is the new formulation and has less phosphatidylcholine and showed no signs of liver function abnormalities in two phase I and one phase 2a trial, even at four weekly doses higher than the CSL111 dose that caused liver function abnormalities (Diditchenko et al, 2013; Easton et al, 2013; Tricoci et al, 2015).

Low HDL cholesterol efflux capacity or low ApoA1 levels may be predictive of future cardiovascular events. Therefore an increase in these two may help prevent future cardiovascular disease (Ishikawa et al, 2015, Rohatgi et al, 2014, Boekholdt et al 2013).

In a single ascending dose, phase 1 study with CSL112 (135mg/kg), Gille et al (2014) reported a profound 3,596% increase in HDL-vs, a 300% increase in ApoA1, a 630% increase in ABCA1-dependent cholesterol efflux capacity over baseline after infusion. In a phase 2a study, Tricoci et al (2015) reported that a single infusion of CSL112 (6.8g -~113 mg/kg) increased plasma ApoA-1 levels over baseline by 145% (in 6.8g group, only a 25% increase in the 1.7g group) and increased serum cholesterol efflux capacity by 310%.

Plasma cholesterol levels were also increased, suggesting that cholesterol was being removed from peripheral tissue.

CSL112 increases ApoA1 levels and serum cholesterol efflux capacity, two actions that epidemiology suggests might be beneficial in cardiovascular disease. However, these levels return to baseline after about seven days in patients with the highest doses (>~100mg/kg) (Gille et al (2014). A phase 2b study in 1,267 patients, will give patients who recently had an acute myocardial infarction four infusions of CSL112 once/week. The patients will be followed for 16 weeks to assess whether they have a major adverse cardiovascular event. This information will hopefully provide some insight to whether infusions of CSL112 can be beneficial.

**Safety*:*** Minor adverse events are related to the infusion procedure itself, but there are no major short-term adverse events. Long-term treatment has not been studied.

CSL Behring discontinued CSL111 because of a transient increase in liver enzymes that suggested liver toxicity. However, 38 patients have received CSL112 doses higher than those that showed elevated liver enzymes in CSL111 without reports of liver toxicity. In addition, there were no increases in proatherogenic lipids. It should be noted that CSL112 is composed of ApoA1 derived from human plasma which may increase the risk of viral transmission. However, there has been no indication of this. Adverse events are generally related to the infusion procedure (bruising at the infusion site, etc.), although in one study CSL112 patients did report mild headaches, fatigue, nausea, and vessel puncture-site reactions not at the infusion site.

In a multiple ascending dose study, HDL-C levels remained elevated for >72 hours, and in the 6.8g group remained elevated before subsequent weekly infusions, raising possible concerns about accumulation of the drug. Future studies will have to optimize dosing schedules. (Gille et al, 2014, Tricoci et al, 2015).

Although the long-term effects of CSL112 infusion are unknown, short-term use of CSL112 appears safe for healthy adults and those with stable atherosclerotic disease. The potential safety in other vulnerable populations remains to be shown.

**Sources and dosing:**
Studies report doses of 6.8g CSL112/week or 2x3.4g/week for four weeks. Occasional infusions of CSL112 might be a useful prophylactic procedure. Efficacy results from a phase IIb study are expected within the next year.

**Research underway:**
A phase 2b study in 1,267 patients, will give patients who recently had an acute myocardial infarction four infusions of CSL112 once/week. Primary outcomes are liver injury and renal injury, but the patients will be followed for 16 weeks to assess whether they have a major adverse cardiovascular event (NCT02108262). The trial is complete and should give a better indication on the efficacy of CSL112. Results are expected in the second half of 2016. A second phase II study is expected to start recruiting in July 2016 (NCT02742103) to investigate renal safety in 81 patients with moderate renal impairment and acute myocardial infarction, and an additional phase III study is being planned.

**Pubmed:**

- Atherosclerosis + Alzheimer (Observational, Clinical trial, Systematic Review, Meta-Analysis)
- ApoA1 + Alzheimers
- ApoA1 + drug development
- CSL112
- CSL111
- RVX-208
- apolipoptrotein + atherosclerosis (meta-analysis, systematic review)
- apolipoprotein A + dementia (meta-analysisi, clinical trial, observational, systematic review)
- apolipoprotein a + aging
- apolipprotein a + longevity

**Clinicaltrials.gov:**

- CSL111
- CSL112

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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.*