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.

Amyloid-beta oligomer receptor inhibitors (CT1812)

Evidence Summary
Preclinical, and early clinical, data suggest that the CT series of compounds may prevent Aβo-mediated toxicity.

**Neuroprotective Benefit:** Promising preclinical and very preliminary clinical data suggests CT1812 may be beneficial in Alzheimer’s patients.

**Aging and related health concerns:** Not expected to impact other age-related disease based on this mechanism of action.

**Safety:** Short-term treatment is well-tolerated, though no long-term studies have been conducted.
### What is it?

Growing evidence suggests that Aβ₀, rather than amyloid plaques themselves, are neurotoxic in Alzheimer’s disease. For instance, individuals with the Osaka mutation (a small group of individuals in Japan), develop dementia without the presence of amyloid plaques. Cerebral spinal fluid (CSF) in these patients show increased levels of high-molecular weight amyloid species, presumably Aβ₀s. Preclinical studies have implicated Aβ₀s in the development of tau pathology, impairment of axonal transport, synaptic degeneration, oxidative stress, insulin resistance, and neuroinflammation ([Cline et al., 2018](#)). The Aβ₀ hypothesis is that Aβ₀s bind to receptors on the cellular membrane causing neurotoxicity.

CT1812 binds to the sigma-2/PGRMC1 (membrane-associated progesterone receptor component 1) receptor and regulates Aβ₀-mediated toxicity. Sigma-2/PGRMC1 is not an Aβ₀ receptor, per se. Rather, CT1812 binds to sigma-2/PGRMC1 and destabilizes an unknown Aβ₀ receptor increasing the off-rate of oligomer binding ([Alzforum](#)). Preclinical and clinical studies suggest that CT1812 may protect synapses. CT1812 is being developed by [Cognition Therapeutics](#), and ADDF has supported preclinical and clinical studies of CT1812. It is currently in multiple small clinical studies.
Summary of data (Benefit, no change)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical</th>
<th>Preclinical in vivo</th>
<th>Preclinical in vitro</th>
<th>Post-mortem in situ</th>
<th>Post-mortem expression of protein</th>
<th>Pathway elucidated</th>
<th>Other modalities</th>
<th>Genetic evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT1812</td>
<td>CSF synaptic markers</td>
<td>Cognition</td>
<td>Aβo binding, synapses</td>
<td>Aβo binding</td>
<td>Sigma-2 ↑</td>
<td>siRNA, sigma-2 antibody</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Neuroprotective Benefit:** Promising preclinical and very preliminary clinical data suggests CT1812 may be beneficial in Alzheimer’s patients.

**Types of evidence:**
- Two small safety clinical trials
- Two preclinical studies with related molecules

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

**Human research to suggest benefits to patients with dementia**
A phase 1 safety study in healthy individuals suggested that the half-life of CT1812 in young participants (age 19-60; avg. age 28.5) was 12 hours. CT1812 was present in the CSF of young participants at levels predicted to achieve the 80% receptor occupancy necessary for efficacy (see below) at the two doses measured (560mg and 840mg) (Grundman et al, 2019).

In a phase 1b/2a trial in 19 patients with mild to moderate Alzheimer’s disease treated for 28 days, CT1812 improved biomarkers of synapses (neurogranin and synaptotagmin-1) with no effects on cognition (not expected due to low numbers and short duration) (Alzforum).

**Mechanisms of action for neuroprotection identified from laboratory and clinical research**
Development of CT1812 began from a high-throughput screen of molecules that could prevent Aβo-induced dysfunction of neuronal membrane trafficking. In brief, primary rat neurons were cultured for 21 days and treated with Aβos. A dye was added to the culture to investigate the dysfunction of the
trafficking of the dye into and out of cells after Aβ0 administration. Several molecules were identified
from the screen.

Several of these molecules were found to prevent Aβ0 binding and displace Aβ0s from neurons. Furthermore, they prevented the loss of synapses in neurons after Aβ0 administration. Two molecules (CT01346 and CT01344) were tested in aged Alzheimer’s animal models and improved cognition after 42
days and 5.5 months.

In a counter-screen conducted in a panel of 100 targets present in the brain, CT01346 and CT01344
were highly selective for sigma-2/PGRMC1 receptor binding. Based on the binding affinity and brain
concentrations of the drug from efficacy studies, the authors estimate CT1346 was effective at 87% but
not 50% receptor occupancy (Izzo et al, 2014).

In a complementary study, Izzo et al (2014) reported that CT0093 and CT0109 were able to displace a
sigma-2/PGRMC1 radioligand from human frontal cortex slices. In neuronal cell cultures, sigma-
2/PGRMC1 was expressed in cell bodies and at synapses, and expression increased with exposure to
Aβ0s. Neuronal cell cultures treated with an siRNA against PGRMC1 reduced sigma-2/PGRMC1 up to
28%, which reduced Aβ0 binding up to 91%.

Furthermore, in frontal cortex slices from patients with severe Alzheimer’s (CDR-sb=3 – a dementia
rating scale), where there is loss of neurons in the frontal cortex, expression of an unrelated protein,
sigma-1, was reduced, possibly because of cell loss, while sigma-2 expression was not reduced. The
authors speculate this is because of increased sigma-2 expression in neurons or glia, though they did not
count the cell density in the slices.

Previous studies showed that a 2-micron halo around amyloid plaques contained Aβ0s and devised a
method to quantitate the number of Aβ0s. Application of CT01344 to Alzheimer’s post-mortem tissue
was able to displace Aβ0s.

A working model suggests that the Cognition Therapeutics series of molecules bind to sigma-2/PGRMC1,
cause a conformational change, and displace Aβ0 (possibly through another receptor).

APOE4
None
**Safety:** Short-term treatment is well-tolerated, though no long-term studies have been conducted.

*Types of evidence:*
- A phase 1b/2a clinical trial

In a phase 1b/2a clinical trial with 19 mild to moderate Alzheimer’s patients treated with 90, 280, or 560mg of CT1812 for 28 days, side effects included nausea, vomiting, headache, fatigue, and lethargy. Side effects were slightly higher in the highest dose group; however, the drug was generally well-tolerated ([Alzforum](https://www.alzforum.org)). Future studies will be needed to determine the long-term safety of CT1812.

**Drug interactions:**
No drug interactions are currently known or predicted from the mechanism of action.

**Sources and dosing:**
CT1812 is currently in development by Cognition Therapeutics.

**Research underway:**
Three studies of CT1812 are ongoing; one looking at synaptic density (SV2A PET ligand) over 30 weeks ([NCT03493282](https://clinicaltrials.gov/ct2/show/NCT03493282), one looking at levels of CSF Aβo after 48 hours ([NCT03522129](https://clinicaltrials.gov/ct2/show/NCT03522129)), and one 30-week safety study ([NCT03507790](https://clinicaltrials.gov/ct2/show/NCT03507790)).

**Search terms:**
- Sigma-2 + Alzheimer
- CT1812

**Websites:**
- Clinicaltrials.gov
- Pubmed
Disclaimer: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the Terms & Conditions.

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.