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)

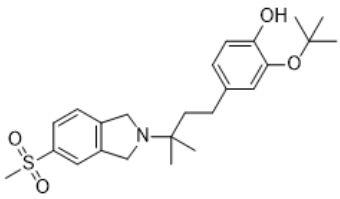
Evidence Summary

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**.**

Availability: Currently under development from Cognition Therapeutics	**Dose**: Ongoing trials using 100mg or 300mg per day	**Chemical formula:** $C_{24}H_{33}NO_4S$ **MW:** 431.591 **Source:** Drug Approval List 
Half life: 12 hours	**BBB**: Penetrant (in humans, at doses of 560mg and 840mg)	
Clinical trials: 3 trials completed, 3 trials ongoing	**Observational studies**: 0	

What is it?

Growing evidence suggests that Aβo, 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 Aβos. Preclinical studies have implicated Aβos in the development of tau pathology, impairment of axonal transport, synaptic degeneration, oxidative stress, insulin resistance, and neuroinflammation (Cline et al, 2018). The Aβo hypothesis is that Aβos binds to receptors on the cellular membrane causing neurotoxicity.

CT1812 binds to the sigma-2/PGRMC1 (membrane-associated progesterone receptor component 1) receptor and regulates Aβo-mediated toxicity. Sigma-2/PGRMC1 is not an Aβo receptor, per se. Rather, CT1812 binds to sigma-2/PGRMC1 and destabilizes an unknown Aβo 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)

Drug	Clinical	Preclinical in vivo	Preclinical in vitro	Post-mortem in situ	Post-mortem expression of protein	Pathway elucidated	Other modalities	Genetic evidence
CT1812	CSF synaptic markers	Cognition	Aβo binding, synapses	Aβo binding	Sigma-2 ↑		siRNA, sigma-2 antibody	

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 Aβo administration. Several molecules were identified from the screen.

Several of these molecules were found to prevent Aβo binding and displace Aβos from neurons. Furthermore, they prevented the loss of synapses in neurons after Aβo 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 Aβos. Neuronal cell cultures treated with an siRNA against PGRMC1 reduced sigma-2/PGRMC1 up to 28%, which reduced Aβo 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 Aβos and devised a method to quantitate the number of Aβos. Application of CT01344 to Alzheimer's post-mortem tissue was able to displace Aβos.

A working model suggests that the Cognition Therapeutics series of molecules bind to sigma-2/PGRMC1, cause a conformational change, and displace Aβo (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). 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), one looking at levels of CSF Aβo after 48 hours (NCT03522129), and one 30-week safety study (NCT03507790).

Search terms:

Sigma-2 +
Alzheimer
CT1812

Websites:
Clinicaltrials.gov
Pubmed

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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.