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.

CT1812 (Elayta)

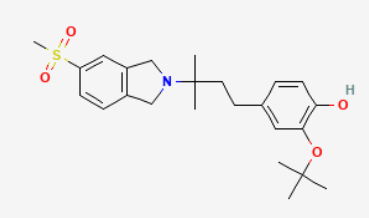
Evidence Summary

While CT1812 treatment clears Aβ oligomers from the brain and improves some biomarkers, it has not translated to improved cognitive function or synapse count in Alzheimer's patients.

Neuroprotective Benefit: In Alzheimer's patients, CT1812 treatment clears Aβ oligomers from the brain and reduces markers of neurodegeneration. No benefits in cognition or synapse count were observed after 6 months of treatment.

Aging and related health concerns: There are plans for a phase 2 trial of CT1812 in patients with geographic atrophy secondary to dry age-related macular degeneration. There are no peer-reviewed publications on the effects of CT1812 in age-related diseases.

Safety: Most completed studies of CT1812 have been short-term treatments, and adverse events included headache, gastrointestinal disturbances, and lymphocytopenia. Long-term safety is to be determined in ongoing clinical trials.

Availability: in clinical development	**Dose**: Dosage has not been established for any condition. Several clinical trials have tested doses of 100 or 300 mg per day, orally.	**Chemical formula:** $C_{24}H_{33}NO_4S$ **MW**: 431.591  Source: PubChem
Half-life: 12 hours	**BBB**: penetrant	
Clinical trials: The phase I study in healthy people included a total of 93 participants.	**Observational studies**: none	

What is it?

CT1812 is an orally bioavailable, brain-penetrant antagonist to the sigma-2 receptor complex, which includes the progesterone receptor membrane component 1 subunit (PGRMC1) and TMEM97 (Izzo et al., 2021). The sigma-2 receptor complex regulates the plasma membrane surface expression of neighboring Aβ oligomer receptor complexes (consisting of PrPc, Nogo receptor, and LilrB2). By CT1812 binding to the sigma-2 receptor complex, it allosterically destabilizes the binding site of the Aβ oligomer receptor complex, displacing Aβ oligomers from the synapse (increasing the off-rate of the oligomers). Thus CT1812 is a negative allosteric modulator of Aβ oligomers binding to synaptic receptors. The displaced Aβ oligomers are then cleared into the cerebral spinal fluid. Aβ oligomers are thought to be one of the most toxic forms of amyloid and have been shown to cause synaptotoxicity, disruption of synaptic plasticity (e.g., long-term potentiation), and failure of new memory formation (reviewed in Selkoe and Hardy, 2016). Protective effects from lower binding affinity of Aβ oligomers to synaptic receptors is seen in the Icelandic A673T mutation, where carriers are four times less likely to get Alzheimer's disease compared to noncarriers (Limegrover et al., 2020).

CT1812 and other related compounds were discovered through an unbiased phenotypic neuronal trafficking assay to screen for drug-like compounds that blocked the binding and synaptotoxic effects of Aβ oligomers (Izzo et al., 2014; Rishton et al., 2021). CT1812 is currently under development by Cognition Therapeutics for the treatment of Alzheimer's disease, Parkinson's disease, Lewy body dementia, and dry age-related macular degeneration.

Neuroprotective Benefit: In Alzheimer's patients, CT1812 treatment clears Aβ oligomers from the brain and reduces markers of neurodegeneration. No benefits in cognition or synapse count were observed after 6 months of treatment.

Types of evidence:

- 2 phase 1/II clinical trials in Alzheimer's patients
- 1 phase 1 single- and multiple-ascending dose study
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

In a phase I safety study of 93 healthy subjects, CT1812 treatment for 14 days did not alter cognitive function (Grundman et al., 2019). Cognitive testing was performed on a healthy elderly cohort receiving 560 mg of CT1812, daily, orally, for 14 days. Cognitive function, as measured by ADAS-Cog, was similar between baseline (10.23 ± 2.57) and day 14 (10.03 ± 4.24). Other cognitive tests were also similar between baseline and day 14. The lack of cognitive effect is expected given the short duration of treatment. CT1812 was measurable in the cerebral spinal fluid (CSF) at 1.5 hours after dose on day 7 to day 9 in all subjects who received CT1812 daily doses of 560 mg and 840 mg. Mean (± SD) levels of CT1812 in CSF were 8.0 (± 4.3) and 23.3 (± 15.6) ng/mL for 560 mg and 840 mg, respectively. These findings suggest that CT1812 penetrates the blood-brain barrier. At the 560 mg dose, CSF CT1812 levels reached what was associated with 97-98% receptor occupancy in the mouse brain; at the 840 mg dose, CSF levels reached what was associated with 98% receptor occupancy.

Human research to suggest benefits to patients with dementia:

In a double-blind placebo-controlled phase 1b/2a trial of 19 mild to moderate Alzheimer's patients, treatment with CT1812 (90, 280, or 560 mg, daily, orally) for 28 days resulted in CSF CT1812 levels that rose in a dose-dependent manner (1.15 ng/mL in the 90 mg CT1812 group, 2.84 ng/mL in the 280 mg CT1812 group, and 4.96 in the 560 mg CT1812 group)(Izzo et al., 2021). Exploratory measures of cognitive function (ADAS-Cog14, verbal or category fluency tests) from baseline were not significantly different between CT1812 and placebo groups, which was expected given the short duration of treatment. After 28 days of treatment, CSF Aβ oligomer concentration in placebo-treated patients (n=3) trended lower from baseline levels, while levels in CT1812-treated patients (n=10) increased significantly compared to placebo-treated patients. These findings are consistent with the proposed mechanism of

action for CT1812, which is to displace and clear toxic Aβ oligomers from the brain into the CSF. In contrast, no changes from baseline or treatment effects were seen with CSF Aβ40 and 42 monomer levels.

CSF levels of synaptic and axonal proteins were also measured. After 28 days of CT1812 treatment in Alzheimer's patients, CSF levels of neurogranin and synaptotagmin-1 decreased compared to placebo (p=0.05 and 0.011, respectively)(Izzo et al., 2021). CSF levels of neurofilament light and SNAP-25 did not change significantly between CT1812 and placebo.

There were 3,160 proteins detected in the CSF of Alzheimer's patients, and of these, the abundance of 315 proteins were significantly different between CT1812 and placebo groups (Izzo et al., 2021). Pathway analysis using three independent bioinformatics platforms showed that CT1812 significantly impacted synaptic-related pathways including glutamate NMDA receptor trafficking, GSK3β (involved in tau hyperphosphorylation), and Wnt signaling (involved in synaptic plasticity), as well as cytoskeletal reorganization. There were 25 proteins in the synaptic proteome that were differentially expressed in CT1812-treated compared to placebo-treated patients. A network analysis revealed that the highest scoring network, Cell Morphology, Cellular Assembly and Organization, Cellular Development, comprised 14 out of 25 of the synaptic proteins, a significantly greater number than expected by random chance. These findings suggest that these proteins play a role in dendritic branching, cytoskeletal remodeling, and neurotransmission, providing biological support for CT1812's effects on synaptic health.

There are 520 proteins in the CSF that are altered in Alzheimer's patients compared to age-matched controls. Of these, 334 were detected in this phase 1b/2a study (Izzo et al., 2021). Of the 334 proteins, 20 moved in the opposite direction with CT1812 treatment, reversing Alzheimer's-related changes, and were significantly different compared to placebo. These proteins are involved in pathways disrupted in Alzheimer's disease, including cholesterol transport (APOA2), oxidative stress (ceruloplasmin; CP), complement (C1RL), and synaptic transmission (14-3-3 protein beta/alpha; YWHAZ).

CSF levels of phosphorylated tau were also altered after 28 days of CT1812 treatment (Izzo et al., 2021). The abundance of six phosphorylation sites decreased by 30% or more after treatment with CT1812 compared to placebo while one site increased more than 30%. The concentration of unphosphorylated tau was not altered. Change from baseline of p-tau181 and total tau were similar between CT1812-treated and placebo-treated groups. While not statistically significant, GSK3β levels (involved in tau

hyperphosphorylation) were 25% lower in CT1812-treated patients compared to placebo-treated patients (p=0.098).

In a different randomized double-blind placebo-controlled phase I/II study of CT1812 in 23 patients with mild to moderate Alzheimer's disease, CT1812 treatment (100 mg or 300 mg daily, orally) for 6 months resulted in a lack of significant effect on synapses, measured by the SV2A PET ligand [11C]-UCB-J (NCT03493282). After 6 months of treatment, changes from baseline in [11C]-UCB-J distribution volume ratio was -0.043, -0.019, and 0.000 for 300 mg CT1812, 100 mg CT1812, and placebo groups, respectively. Numerically, the patients receiving CT1812 treatment showed greater progression of disease. Changes from baseline in cognitive function (ADAS-Cog13; negative change from baseline indicates improvement) were 2.62, 1.73, and 1.02 for 300 mg CT1812, 100 mg CT1812, and placebo groups, respectively. Changes from baseline in a cognitive/function scale (CDR-SB; higher scores indicate worsening) were 0.72, 0.39, and 0.17 for 300 mg CT1812, 100 mg CT1812, and placebo groups, respectively; patients treated with CT1812 performed numerically worse than those given placebo.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

CT1812 binds sigma-2 receptors with high affinity (Ki=8.5 nM) and low affinity with sigma-1 receptors (Ki=63 nM); it is 100-fold selective for sigma-2 receptors compared to 72 other drug targets (Izzo et al., 2021). In primary hippocampal/cortical cultures, CT1812 treatment prevented and reversed Aβ oligomer-induced membrane trafficking deficits, including by oligomers derived from the brains of Alzheimer's patients. CT1812 prevented binding of Aβ oligomers to synaptic receptor sites on neurons and displaced bound Aβ oligomers. CT1812 did not inhibit formation of Aβ oligomers.

In vitro studies also showed that CT1812 prevented Aβ oligomer-induced synapse loss in a dose-dependent manner, and the addition of CT1812 to cultures 1 hour after oligomers resulted in a concentration-dependent increase in synaptic number to normal levels (Izzo et al., 2021). CT1812 treatment also blocked the Aβ oligomer-induced loss and restored the expression of neurogranin (postsynaptic marker) and synaptotagmin-1 (presynaptic marker) to control levels.

In 12-month-old mouse model of Alzheimer's disease (APPswe/PS1dE9 mice), a single dose of CT1812 (0. 3 µM, or 3.0 µM i.v.) resulted in a rapid and significant increase in Aβ oligomer levels in hippocampal interstitial fluid relative to baseline (Izzo et al., 2021). Total Aβ levels (primarily monomer) in the hippocampal interstitial fluid were not affected by CT1812 treatment, suggesting that CT1812 selectively reduces Aβ oligomer extracellular concentrations. Also in APPswe/PS1dE9 mice, CT1812 administration

led to a significant and dose-dependent rise in Aβ oligomers in the CSF, suggesting that displacement of Aβ oligomers in the brain may lead to increased clearance into the CSF.

In a different mouse model of Alzheimer's disease (Thy1 huAPPSwe/Lnd+ mice, aged 3.5-4.5 months), CT1812 treatment (10 mg/kg once daily by oral gavage) for 9 to 10 weeks significantly improved spatial learning and memory, as measured by the Morris water maze, compared to vehicle (Izzo et al., 2021). CT1812 treatment in wild-type mice did not significantly alter cognitive performance. Pharmacokinetics measurements of brain CT1812 levels confirmed that receptor occupancy of 84.4% was achieved. This is in line with a prior study showing that brain concentrations greater than 80% receptor occupancy at the sigma-2/PGRMC1 receptor restore cognitive function in a mouse model of Alzheimer's disease (Izzo et al., 2014).

In *ex vivo* binding experiments using 10 µM-thick postmortem neocortical tissue sections obtained from patients with Alzheimer's disease, CT1812 administration increased the amount of Aβ oligomers released from the human brain tissue (Izzo et al., 2021). This was accompanied by a decrease in Aβ within the tissue section in the oligomer-enriched halo surrounding plaques. Thus, CT1812 displaces prebound Aβ oligomers from Alzheimer's patient brain tissue.

APOE4 interactions: Unknown.

Aging and related health concerns: There are plans for a phase 2 trial of CT1812 in patients with geographic atrophy secondary to dry age-related macular degeneration. There are no peer-reviewed publications on the effects of CT1812 in age-related diseases.

Types of evidence:

- No peer-reviewed publications

There are no peer-reviewed publications reporting findings from studies testing the efficacy of CT1812 in age-related conditions.

Dry age-related macular degeneration is common among people over 50 and is caused by degeneration and thinning of the macula, responsible for central vision. As the disease progresses into geographic atrophy, degeneration of retinal pigment epithelial (RPE) cells can result in permanent vision loss. On March 15, 2023, Cognition Therapeutics, Inc. announced that its Investigational New Drug application

for CT1812 in geographic atrophy secondary to dry age-related macular degeneration has been cleared by the US FDA (GlobeNewsWire, 3/15/2023). This announcement noted that early proof-of-concept studies with CT1812 indicate a role of sigma-2 receptors in rescuing the vulnerable RPE cells from damage by stressors such as pathogenic proteins and oxidative stress. Geographic atrophy and macular degeneration were two diseases most significantly associated with proteomic changes induced by CT1812 based on an unbiased pathway analysis of patient biofluids from 2 Alzheimer's disease clinical trials (EyeWireNews 12/1/2022). Analysis of the proteomes revealed key proteins and pathways that are impaired in dry age-related macular degeneration and geographic atrophy, which were significantly reversed by CT1812. Based on this media article, CT1812 administration rescued the ability of RPE cells to recycle photoreceptor outer segments in the presence of Aβ oligomers and oxidative stress. Cognition Therapeutics plans to initiate a phase 2 trial of CT1812 in 2023 (CogRx.com/pipeline).

Safety: Most completed studies of CT1812 have been short-term treatments, and adverse events included headache, gastrointestinal disturbances, and lymphocytopenia. Long-term safety is to be determined in ongoing clinical trials.

Types of evidence:

- 2 phase 1/II clinical trials in Alzheimer's patients
- 1 phase 1 single- and multiple-ascending dose study
- Several laboratory studies

In a phase I safety study of 93 young and elderly subjects, CT1812 treatment was well-tolerated with single administration of up to 1120 mg and with multiple dose administration of up to 840 mg and 560 mg in healthy young adults and healthy elderly people, respectively (Grundman et al., 2019). Adverse events were generally mild and included headache and gastrointestinal disturbances.

For the single-ascending dose study, a total of 54 subjects were enrolled and received doses of 10, 30, 90, 180, 450, or 1120 mg (6:2 active to placebo)(Grundman et al., 2019). Median CT1812 Tmax in plasma peaked at 0.88 to 1.5 hours. Cmax and area under the curve (AUC) increased greater than dose-proportionally after a single dose administration of 10 to 1120 mg. The mean half-life ranged from 11.1 to 14.0 hours. Treatment emergent adverse events were reported for 43% of subjects receiving CT1812 (18 out of 42 subjects) and 17% of subjects receiving placebo (2 out of 12 subjects). Most adverse events (77%; 23 of 30 subjects) were classified as mild in severity, with 7 adverse events (23%) classified as moderate in severity (catheter site swelling, vomiting, nausea, vaccination site reaction, dysmenorrhea,

and headache). No adverse events were classified as severe. In this single-ascending dose part of the study, no subjects had clinically significant laboratory results (all clinical laboratory results outside of the normal range were deemed not clinically significant). There were also no electrocardiograph parameters or changes assessed as clinically significant.

A separate cohort also received a single 90 mg dose of CT1812, 30 minutes after a meal (Grundman et al., 2019). The geometric least-squares mean for Cmax, AUC0-48h, and AUC0–inf were approximately 40%, 20%, and 20% lower, respectively, with food compared with the fasted state. These differences were not considered clinically significant.

For the multiple-ascending dose study, doses of 280, 560, and 840 mg, once daily, for 14 days were tested in a total of 39 subjects (8:2 active to placebo)(Grundman et al., 2019). CT1812 Tmax values in plasma peaked at 0.88 to 2.0 hours. Cmax and AUC increased greater than dose-proportionally from 280 to 840 mg. Steady state was reached by the third or fourth day after daily dosing. Average terminal half-life was approximately 12 hours. Treatment-emergent adverse events were seen in 81% of subjects receiving CT1812 (25 out of 31 subjects) and 75% of subjects receiving placebo (6 out of 8 subjects). One serious adverse event was recorded: a subject receiving multiple doses of 840 mg CT1812 was hospitalized for a respiratory picornavirus infection deemed unrelated to study treatment. There were no deaths. A total of 82 adverse events were reported, with 82% (67 of 82) classified as mild in severity, 17% (14 events) as moderate in severity, and 1% (1 event) as severe. There was no trend of increasing frequency in adverse events with higher dose, with the exception of vomiting, where the 2 instances with CT1812 occurred at the 840 mg dose for an incidence of 25%. In the placebo group, one subject (17%) experienced vomiting. Four subjects had an increase in liver function tests below the 3 times the upper limit of normal; one of these were on placebo. One subject developed a rash while taking CT1812, which showed improvement after discontinuation of the drug. There were no significant differences between CT1812 and placebo, or dose-dependent trends in clinical laboratory results. None of the electrocardiograph measures or changes were assessed as clinically significant.

A separate elderly cohort (age 65-75; 9 subjects) received a dose of 560 mg once daily for 14 days (7:2 active to placebo)(Grundman et al., 2019). Plasma concentrations of CT1812 were dose-proportional with minimal accumulation over 14 days. Adverse events were mild to moderate in severity and included headache and gastrointestinal tract symptoms. On day 3 of treatment, geometric least-squares mean Cmax and AUC0-24h values in the elderly cohort were approximately 1.7- and 1.34-times higher compared with subjects under 65 years of age, respectively. The trend continued to day 14 (steady

state), with the Cmax and AUC0-24h in the elderly cohort exceeding that of younger subjects by 1.6- and 1.5-times, respectively.

In a phase 1b/2a trial of 19 mild to moderate Alzheimer's patients, treatment with CT1812 (90, 280, or 560 mg, daily, orally) for 28 days was generally safe and well-tolerated, though there were 4 cases of lymphocytopenia (Alzforum).

In a different randomized double-blind placebo-controlled phase I/II study of CT1812 in 23 patients with mild to moderate Alzheimer's disease, CT1812 treatment (100 mg or 300 mg daily, orally) for 6 months resulted in frequencies of adverse events that were comparable to those of the placebo group (NCT03493282).

Drug interactions: In a phase 1 study of 14 healthy adults (COG01013 Study), CT1812 treatment for 6 consecutive days before and following 4 probe drugs (dextromethorphan, midazolam, omeprazole, and tolbutamide) that represent the activity of specific cytochrome P450 (CYP450) enzymes did not result in significant drug-drug interactions (CogRx press release 7/19/2017). No interactions between CT1812 and omeprazole or tolbutamide were observed, and only weak interactions were seen with midazolam and dextromethorphan. These findings suggest the potential for clinically insignificant inhibition of CYP2D6 and induction of CYP3A4 enzymes by CT1812.

Sources and dosing:

CT1812 is currently under development by Cognition Therapeutics for the treatment of Alzheimer's disease, Parkinson's disease, Lewy body dementia, and dry age-related macular degeneration. Dosage is not established. Ongoing clinical trials (described below) are testing CT1812 doses of 100-300 mg, once daily, orally (ClinicalTrials.gov).

Research underway:

Based on ClinicalTrials.gov, there are 4 ongoing clinical studies testing CT1812, 3 of which in Alzheimer's disease and 1 in dementia with Lewy bodies.

A phase 2 double-blind randomized placebo-controlled study is enrolling 144 patients with mild to moderate Alzheimer's disease to evaluate the safety and efficacy of CT1812 treatment (100 or 300 mg

once daily, orally) for 36 weeks (NCT03507790). This study was initiated in 2018 and is scheduled to be completed in October 2023.

Another phase 2 double-blind randomized placebo-controlled study is evaluating the efficacy, safety, and tolerability of two doses of CT1812 (100 or 200 mg once daily, orally) for 72 weeks (18 months) in approximately 540 patients with early Alzheimer's disease (NCT05531656). The primary outcome measure is change from baseline in a clinical scale (CDR-SB). Secondary outcomes include cognitive function (ADAS-Cog13), daily living scale (ADCS-ADL), CSF levels of Aβ oligomers, Aβ40, Aβ42, tau, p-tau, NfL, neurogranin, and synaptotagmin, plasma measures of Aβ fragments, p-tau, and NfL, and volumetric MRI. This trial is in collaboration with the Alzheimer's Clinical Trial Consortium, with a $75.8M funding from the NIH/NIA (CogRx press release, June 8, 2020). This study is scheduled to be completed in August 2026.

A pilot randomized double-blind placebo-controlled crossover study in 16 patients with mild to moderate Alzheimer's disease will examine the effects of CT1812 treatment (300 mg, orally) for 28 days on synaptic activity measured by electroencephalography (quantitative EEG, theta band) (NCT04735536). In February 2023, Cognition therapeutics Inc. announced that enrollment has completed, and topline results are expected mid-2023 (GlobeNewsWire 2/9/2023). This study is supported by a $5.3M funding from the NIH/NIA.

A phase 2 double-blind randomized placebo-controlled study is enrolling 120 patients with Lewy body dementia to evaluate the safety, tolerability, and efficacy of CT1812 treatment (100 or 300 mg once daily, orally) for 6 months (NCT05225415). This study is supported by grant funding of approximately $30M from the NIH/NIA (Biospace, 11/28/2022). This clinical trial is scheduled to be completed in April 2024 (NCT05225415).

Cognition Therapeutics is also planning a phase 2 study to test CT1812 in 240 adults who have a diagnosis of dry age-related macular degeneration (CogRx.com/pipeline). Over the treatment period, change in geographic atrophy lesion size and best-corrected visual acuity, as well as other measures of safety and efficacy will be assessed to determine if CT1812 can slow vision loss (GlobeNewsWire, 3/15/2023).

Search terms:

Pubmed, Google: CT1812, Elayta

Websites visited for CT1812, Elayta:

- Clinicaltrials.gov
- NIH RePORTER
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca (0)
- Cafepharma
- Pharmapro.com (0)