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)

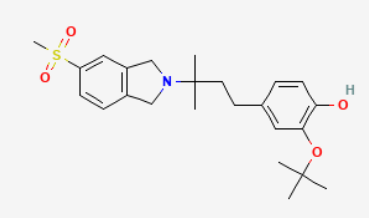
Evidence Summary

CT1812 treatment has shown trends in slowing cognitive decline and preserving brain volume, along with improvements in some CSF biomarkers in AD. A larger trial in AD is ongoing.

Neuroprotective Benefit: In a phase 2 trial, CT1812 treatment showed a trend for slowing of cognitive decline. A small earlier phase trial reported a trend towards brain tissue preservation. A larger, longer phase 2 trial in Alzheimer's disease is ongoing.

Aging and related health concerns: A CSF proteomics study suggests CT1812 impacts pathways related to age-related macular degeneration (AMD). A phase 2 trial of CT1812 is ongoing in geographic atrophy secondary to dry AMD.

Safety: The most common adverse events include headache, gastrointestinal disturbances, and infections. Higher doses have resulted in increased liver enzymes. Long-term safety will be evaluated in the ongoing 18-month trial in Alzheimer's disease.

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: A phase 2 trial in Alzheimer's patients included a total of 153 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, Lewy body dementia, and dry age-related macular degeneration.

Neuroprotective Benefit: In a phase 2 trial, CT1812 treatment showed a trend for slowing of cognitive decline. A small earlier phase trial reported a trend towards brain tissue preservation. A larger, longer phase 2 trial in Alzheimer's disease is ongoing.

Types of evidence:

- 7 phase 1 or 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 phase 1b double-blind randomized controlled trial of 3 patients with mild to moderate Alzheimer's disease, a single oral dose of CT1812 (560 mg) led to a significant rise in CSF Aβ oligomers by > 250%–500% above baseline, consistent with Aβ oligomer displacement from neurons and clearance into CSF (LaBarbera et al., 2023). CT1812 exposure level in one of the patients (AUC0-last = 120 h*ng/ml, Cmax = 24.9 ng/ml) was more than two-fold higher than that of the other patient (AUC0-last = 46.4 h*ng/ml, Cmax = 7.27 ng/ml), and CSF Aβ oligomer levels were higher in the former compared to the latter patient. In the placebo-treated patient, there was no increase in CSF Aβ oligomer levels. No changes in Aβ monomer levels were observed in the two patients receiving CT1812 or the patient receiving placebo.

In a phase 1b double-blind randomized controlled trial of 23 mild to moderate Alzheimer's patients, CT1812 treatment (100 mg or 300 mg, daily, orally) for 24 weeks did not significantly alter synaptic density (measured by the SV2A PET ligand [11C]UCB-J), brain metabolism (measured by FDG-PET), cognitive clinical rating scales (ADAS-Cog11, ADAS-Cog13, MMSE, ADCS-ADL, CDR-SB), or CSF biomarkers (Aβ40, Aβ42, total tau, p-tau, neurogranin, SNAP-25, synaptotagmin, and NfL)(van Dyck et al., 2024). There was a nonsignificant trend towards tissue preservation in patients treated with either dose of CT1812, measured by volumetric MRI (composite of Alzheimer's disease-associated brain regions). The least squared mean difference compared to placebo in the composite of brain regions for the pooled CT1812 treatment groups was 7.86±4.07 (95% CI, -0.50 to 16.21; p=0.06). In an exploratory analysis of 16 brain regions, nominally significant differences (p≤0.05) with both doses of CT1812 compared to placebo were observed in the pericentral, prefrontal, and hippocampal cortices.

Changes from baseline in cognitive function (ADAS-Cog11; negative change from baseline indicates improvement) were 1.78, 1.28, and 1.37 for 300 mg CT1812, 100 mg CT1812, and placebo groups, respectively (NCT03493282). 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.

In a pilot qEEG study, CT1812 treatment for 4 weeks in 15 mild to moderate Alzheimer's patients showed a non-significant but numerical reduction in global relative theta power (p=0.123) and in relative theta power in the frontal, temporal, parietal, occipital, and central brain regions (Vijverberg et al., 2024). A nominally significant improvement was observed with CT1812 treatment in global alpha

amplitude envelope correlation (AEC-c; p=0.034)(Vijverberg et al., 2024). Global alpha AEC-c reflects the ability of the brain to communicate and exchange information between brain regions and this ability is reduced in people with Alzheimer's disease (Briels et al., 2020).

CSF samples from the interim SHINE cohort (SHINE-A) and SPARC cohort were used to study the proteomics signature of CT1812 treatment (Lizama et al., Alzheimers Dement 2024). Both cohorts were from phase 2 double-blind randomized placebo-controlled trials in mild to moderate Alzheimer's patients that tested the effects of CT1812 treatment for 6 months. For the SPARC cohort (n=17), an unbiased analysis of tandem-mass tag mass spectrometry (TMT-MS) quantitative proteomics, pathway analysis, and correlation analyses with volumetric MRI were performed. The TMT-MS can measure levels of more than 2000 proteins from a single CSF sample. For the interim SHINE-A cohort (n=18, part of a larger SHINE study), comparative analyses and a meta-analysis, followed by network analysis were used to study the biological effects of CT1812.

Unbiased proteomics analysis from the SPARC cohort found that CT1812 treatment promoted pathways related to synapses, amyloid biology, and immune response (Lizama et al., Alzheimers Dement 2024). Select proteins that were altered with CT1812 treatment versus placebo included those involved in amyloid biology or lipid binding/lipid handling, such as apolipoproteins apolipoprotein C-IV and apolipoprotein J (also known as clusterin; plays a key role in lipid transport, immune modulation, and Aβ binding and clearance; a SNP in the clusterin gene confers increased risk for late-onset Alzheimer's disease), spondin 1 (binds amyloid precursor protein, associated with dementia risk), low-density lipoprotein receptor-related protein 1 (LRP1; receptor of Aβ, interacts with PrPc, regulates amyloid clearance and cholesterol uptake), and Niemann-Pick protein type C1 (NPC1), a sigma 2 receptor-interacting protein. Other impacted proteins include the neurodegeneration-associated GPR37, carboxypeptidase E, the macrophage-related interferon-gamma receptor 1 (IFNGR1) and complement C1q tumor necrosis factor-related protein 4 (C1QTNF4), the Alzheimer's disease-related biomarker tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta (YWHAB), tyrosine-protein kinase receptor (TIE1), immunoglobulin lambda variable 1-44 (IGLV1-44), and arginase-1.

A meta-analysis of the CSF proteomes from SPARC and SHINE-A cohorts identified biomarkers impacted by CT1812 treatment, including Alzheimer's disease-related biomarkers (clusterin, amyloid beta precursor protein, amyloid beta precursor-like protein 2, and sphingosin-1-phosphate phosphatase 1) and synaptic proteins (synaptotagmin-7, NRXN1 and NRXN2, and integrin beta-2)(Lizama et al., Alzheimers Dement 2024). Weighted gene co-expression network analysis of the differential expression (change from baseline, CT1812 versus placebo) identified networks of proteins that correlate with

CT1812 treatment, highly enriched in biological pathways related to synapses, amyloid biology, lipid homeostasis, or immune response. The MetaCore pathway analysis revealed that the most significantly impacted pathways included amyloid-related biological processes ("gamma-secretase proteolytic targets" and "gamma-secretase regulation of neuronal cell development and function"), immune response ("lectin-induced complement pathway," "classical complement pathway," "alternative complement pathway," and "alternative complement cascade disruption in age-related macular degeneration"), and trafficking-related processes ("dynein-dynactin motor complex in axonal transport in neurons" and "aberrant lipid trafficking and metabolism in age-related macular degeneration pathogenesis").

Also in the meta-analysis of SPARC and SHINE-A CSF proteomes, 144 proteins that were significantly disrupted in Alzheimer's disease versus control (using reference standards) were differentially affected by CT1812 treatment ($p<0.05$)(Lizama et al., Alzheimers Dement 2024). Proteins normalized by CT1812 treatment included synaptic signaling proteins calbindin 2 and semaphorin 4B, lipid homeostasis protein apolipoprotein L1 (APOL1), and several Alzheimer's disease or Aβ-related proteins that were found previously to be normalized by CT1812 in SHINE-A (spondin 1, HTRA1, clusterin). The meta-analysis identified sigma 2 receptor-interacting (PRNP; PrPc, an Aβ oligomer receptor) and amyloid-related (APP, APLP2, clusterin) proteins as drivers of biological processes correlated with CT1812 treatment. The meta-analysis further identified a genetic risk factor for Alzheimer's disease, olfactomedin-like 3 (OLFML3), that was normalized by CT1812 treatment.

In an interim analysis of a subcohort of the phase 2 trial (SHINE-A, n=18) in mild to moderate Alzheimer's disease, CT1812 treatment (100 mg or 300 mg, daily, orally) for 6 months significantly altered a set of proteins in the CSF, including pathway engagement biomarkers (those tied to sigma 2 receptor biology) and Alzheimer's disease-related biomarkers (Lizama et al., Neurobiol Dis 2024). Changes were observed in proteins associated with synapse, immune, secretion, and lipoprotein-related biological processes. Notable proteins include fatty acid binding protein 1 (FABP1), the intracellular cholesterol transporter NPC1 (higher in CT1812 vs placebo CSF), as well as neurexin 2 (NRXN2), amyloid precursor protein (APP; its mutations lead to autosomal dominant familial Alzheimer's disease), and clusterin (lower in CT1812 vs placebo CSF). Brain mapping of these proteins to modules showed that proteins changing in response to CT1812 treatment were represented in the "synapse/neuron", "oligodendrocytes/myelination", and "MHC complex/immune function" modules. There were 21 proteins that were significantly disrupted in Alzheimer's disease and normalized towards healthy control levels by CT1812. Clusterin was abundant in the Alzheimer's cohort compared to healthy control CSF, but CT1812-treated patient CSF had significantly lower CSF clusterin levels than placebo-treated patients

(p=0.02). Additionally, CSF levels of HLA class II histocompatibility antigen DRB1 beta chain (HLA-DRB1; the SNP, rs9271192, is associated with late-onset Alzheimer's disease [Lu et al., 2017]) were higher in the pooled Alzheimer's cohort than healthy control CSF, but CT1812-treated patient CSF had significantly lower levels than placebo-treated patient CSF (p=0.036). Because of the exploratory nature of the analyses and the small interim cohort size, unadjusted p-values were used and the analyses did not control for multiple comparisons. There were no significant CT1812 treatment effects on CSF Aβ42/40 ratio compared to placebo.

In a proof-of-concept phase 2 trial (SHINE study) of 153 mild to moderate Alzheimer's patients, CT1812 treatment (100 mg or 300 mg, daily orally) for 6 months showed a trend in slowing of cognitive decline compared to placebo (CogRx AAIC poster, July 2024). The primary endpoint was safety and tolerability. The key secondary endpoint was ADAS-Cog11. Participants in the placebo arm worsened approximately 2.70 points as measured by ADAS-Cog11 after 6 months, while CT1812-treated participants declined by an average of 1.66 points, a 39% slowing of decline favoring CT1812. Other cognitive measures, including ADAS-Cog13 and MMSE, showed a similar trend of improvement. Exploratory measures of function, ADCS-ADL and CGIC, showed a numerical slowing of decline with CT1812 after 6 months of treatment, but not at earlier time points. With regards to CSF biomarkers, the neurodegeneration marker, NfL, was significantly reduced with the 300 mg dose of CT1812 compared to placebo. There were no significant changes in the Aβ42/40 ratio with CT1812 treatment.

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: A CSF proteomics study suggests CT1812 impacts pathways related to age-related macular degeneration (AMD). A phase 2 trial of CT1812 is ongoing in geographic atrophy secondary to dry AMD.

Types of evidence:

- 1 phase 2 study in Alzheimer's disease that evaluated CSF proteomics

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. Based on a CSF proteomics study in Alzheimer's patients, one biological process impacted by CT1812 treatment by MetaCore pathway analysis was "Aberrant lipid trafficking and metabolism in age-related macular degeneration (AMD) pathogenesis", and two disease ontology associations identified by STRING were "Age related macular degeneration" and "Degeneration of macula and posterior pole (Lizama et al., Neurobiol Dis 2024).

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 (EyeWireNews 12/1/2022). 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. A phase 2 double-blind randomized placebo-controlled study (MAGNIFY trial) is enrolling 240 adults with geographic atrophy secondary to dry age-related macular degeneration to evaluate the safety and efficacy of CT1812 treatment (NCT05893537).

Safety: The most common adverse events include headache, gastrointestinal disturbances, and infections. Higher doses have resulted in increased liver enzymes. Long-term safety will be evaluated in the ongoing 18-month trial in Alzheimer's disease.

Types of evidence:

- 7 phase 1 or 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 proof-of-concept phase 2 trial (SHINE study) of 153 mild to moderate Alzheimer's patients, CT1812 treatment (100 mg or 300 mg, daily orally) for 6 months achieved its primary objective of demonstrating safety and tolerability (CogRx AAIC poster, July 2024). The percentage of participants experiencing any adverse event was similar between the pooled CT1812 treatment arms (76.5%) and the placebo group (78%). The majority of adverse events were mild or moderate in severity. The most commonly reported treatment-emergent adverse events were infections and infestations (urinary tract infection), injury, poisoning and procedural complications (falls and skin lacerations), gastrointestinal disorders, and headache. Serious adverse events were observed in 10% of participants in the placebo arm and 6% of subjects in the CT1812 treatment arms. Of CT1812-treated participants, 2 experienced treatment-emergent serious adverse events in the 100 mg arm, including stomatitis, chronic constipation, and hip fracture (all deemed not related to treatment), and 3 experienced treatment-emergent serious adverse events in the 300 mg arm, including hematuria, abdominal pain, and infection (all deemed not related to treatment) and recurrent presyncope (lightheadedness upon rising from a seated or lying position; deemed related to treatment). At the CT1812 300 mg dose, 9 patients experienced treatment-emergent liver function test increases (AST or ALT increase greater than 3 times the upper limit of normal), which subsided after cessation of drug without evidence of serious liver injury. There were no liver function test elevations observed with the 100 mg dose.

In a phase 1b double-blind randomized controlled trial of 23 mild to moderate Alzheimer's patients, CT1812 treatment (100 mg or 300 mg, daily, orally) for 24 weeks led to early treatment discontinuations in 1 participant in the placebo group, 2 in the CT1812 100 mg group, and 3 in the CT1812 300 mg group (van Dyck et al., 2024). There were no deaths in the study. A total of 5 serious adverse events occurred, 4 in the CT1812 groups and 1 in the placebo group: psychotic disorder (moderate), seizure (severe), thalamic infarct (severe) encephalitis (severe; in placebo group), and ureterolithiasis (moderate, occurred in the extension period), all deemed unrelated or unlikely related to study treatment. Two participants in the CT1812 300 mg dose group were withdrawn from the primary study due to treatment emergent adverse events of liver function test increases (mild, probably related to study treatment); in both cases, the adverse event was considered resolved on the day of withdrawal, there were no associated bilirubin abnormalities, and the participants were asymptomatic. Treatment emergent adverse events were reported for 18 of 23 participants (78%) across the 3 treatment groups, for a total of 52 events. In this period, the most common treatment emergent adverse event in the CT1812 treatment arms was headache, reported in 5 total participants who received CT1812 (2 of 8 subjects [25%] receiving 100 mg and 3 of 8 participants [38%] receiving 300 mg CT1812) and 1 of 8 participants (14%) receiving placebo. Thirteen treatment emergent adverse events were deemed possibly or probably related to study treatment in a total of 10 of 23 participants (43%). Most (12 out of 13) treatment emergent adverse events were considered mild in severity, but one was of moderate severity (dizziness, in the CT1812 300 mg treatment group, deemed possibly related). Two participants (both in the CT1812 100 mg group) had post-dose neurological examination findings assessed as clinically significant, one related to coordination (bilateral ideomotor apraxia, or inability to imitate hand gestures) and one related to mental state (presence of delusions), both of which were deemed unrelated to study drug. Two CT1812-treated participants developed transient suicidal ideation (assessed by the C-SSRS). In both participants, the suicidal ideation occurred at only a single clinical visit with no recurrences. No other safety differences were observed between CT1812 and placebo treatment, as assessed by clinical laboratory tests, vital signs, ECG assessments, or physical or neurological examination findings, and no dose-related trends were observed among participants who received CT1812. There were no treatment-emergent amyloid related imaging abnormalities (ARIA). Compliance assessed by remaining pill counts was 95%, 88.7%, and 92.2% for the CT1812 100 mg group, CT1812 300 mg group, and placebo groups, respectively.

Safety data of the 13 subjects who entered the optional 6-month extension period were similar to the to those of the primary study period (van Dyck et al., 2024). In the extension period, there were no deaths, no additional discontinuations due to adverse events, and no serious adverse events attributed to the

study drug. There was one additional treatment-related treatment emergent adverse event in the placebo group (headache) and one additional serious adverse event (ureterolithiasis) in the CT1812 100 mg group.

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, 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 3 ongoing clinical studies testing CT1812.

A phase 2 double-blind randomized placebo-controlled study (START trial) 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 April 2027.

A phase 2 double-blind randomized placebo-controlled study (SHIMMER trial) is enrolling 130 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 November 2024 (NCT05225415).

A phase 2 double-blind randomized placebo-controlled study (MAGNIFY trial) is enrolling 240 adults with geographic atrophy secondary to dry age-related macular degeneration to evaluate the safety and efficacy of CT1812 treatment (200 mg once daily, orally) for 104 weeks (NCT05893537). The primary outcome is change from baseline in geographic atrophy lesion area over 104 weeks in the study eye. Secondary outcomes include safety and tolerability and plasma concentration of CT1812. This clinical trial is scheduled to be completed in August 2027.

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)

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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.