

RESEARCH MONOGRAPH . COMPOUND PROFILE

CT1812

A first-in-class, orally bioavailable isoindoline sigma-2 receptor antagonist developed by Cognition Therapeutics to displace amyloid-beta oligomers from neuronal synapses, with Phase 2 clinical evidence of cognitive benefit in Alzheimer's disease and dementia with Lewy bodies.

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ABSTRACT

CT1812 (zervimesine; CAS 1802632-22-9) is a first-in-class, orally bioavailable small-molecule antagonist of the sigma-2 receptor complex (also designated TMEM97, transmembrane protein 97) developed by Cognition Therapeutics for the treatment of Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and geographic atrophy secondary to dry age-related macular degeneration. The compound was identified through a phenotypic neuronal screening assay designed to detect reversal of amyloid-beta oligomer (ABO) induced synaptotoxicity and was chemically optimized from a series of isoindoline scaffolds selected for central nervous system penetration, metabolic stability, and selectivity against cardiac ion channel (hERG) liability. CT1812 binds the sigma-2 receptor with a K_i of 8.5 nM and demonstrates greater than 100-fold selectivity over a broad receptor panel, with approximately 10-fold selectivity over the sigma-1 receptor. The mechanism of action is allosteric antagonism of the sigma-2 receptor complex, which includes TMEM97, progesterone receptor membrane component 1 (PGRMC1), and low-density lipoprotein receptor (LDLR) at the neuronal surface. Engagement of this complex by CT1812 induces a conformational change that displaces prebound amyloid-beta oligomers from synaptic receptors without affecting oligomer assembly or dissociation, thereby restoring synaptic trafficking, reducing synaptotoxicity, and facilitating clearance of oligomers into the cerebrospinal fluid.

In preclinical studies, CT1812 demonstrated robust brain penetration (brain-to-plasma ratio of 5.7 at 24 hours; unbound brain-to-plasma partition coefficient $K_{p,uu}$ of 6.75), achieved

greater than 84 percent sigma-2 receptor occupancy at therapeutically relevant doses, and improved cognitive performance in transgenic Alzheimer's mouse models across Y-maze, Morris water maze, and fear conditioning paradigms. The compound is not a P-glycoprotein substrate, exhibits favorable oral absorption with time to peak plasma concentration of 1 to 2 hours and a plasma elimination half-life of approximately 12 hours in humans, and is metabolized primarily by CYP3A4 with secondary contributions from CYP2D6 and CYP2C19.

A Phase 1 trial in 80 healthy volunteers established safety and tolerability at single doses up to 1120 mg and multiple doses up to 840 mg daily for 14 days, with dose-proportional pharmacokinetics and cerebrospinal fluid penetration achieving estimated receptor occupancy of 97 to 98 percent. A Phase 1b/2 trial (COG0102) in 19 patients with mild to moderate AD demonstrated reductions in cerebrospinal fluid synaptic damage markers (neurogranin and synaptotagmin-1) and decreases of 30 percent or more in six tau phosphorylation sites after 28 days of treatment. The Phase 2 SHINE trial (COG0201) enrolled 153 patients with mild to moderate AD randomized to 100 mg, 300 mg, or placebo for 182 days; the 100 mg dose produced a 39 percent reduction in ADAS-Cog 11 decline relative to placebo, with a 95 percent slowing of cognitive decline in the subpopulation with baseline plasma p-tau₂₁₇ below the median. The Phase 2 SHIMMER trial (COG1201) enrolled 130 patients with mild to moderate DLB and met its primary safety endpoint; secondary analyses showed 82 percent of treated patients demonstrated slowing on the total Neuropsychiatric Inventory, with a 91 percent reduction in decline of attentional fluctuation measures. CT1812 has also been evaluated in the Phase 2 MAGNIFY trial for geographic atrophy, where treated patients showed 28.6 percent

slower lesion growth over 18 months compared to placebo. The compound is generally well tolerated; the principal adverse events are headache, gastrointestinal symptoms (nausea, diarrhea, constipation), and, at the 300 mg dose in SHINE, transient elevations in liver function tests that resolved upon drug discontinuation. CT1812 is positioned for Phase 3 development in Alzheimer's disease. This monograph reviews the compound identification, discovery and development history, molecular pharmacology, pharmacokinetics, preclinical and clinical evidence, sourcing, reconstitution, stack interactions, safety profile, and a comparative assessment of five alternative approaches to amyloid-beta oligomer or sigma-2 receptor pharmacology.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Zervimesine (proposed).

Development code: CT1812 (Cognition Therapeutics). This designation is the canonical identifier in the clinical and preclinical literature. The compound has also been referred to by the trade name Elayta in early commercial communications [1, 2].

Chemical Abstracts Service registry number: 1802632-22-9.

PubChem CID: 118278088.

ChemSpider ID: 72379940.

UNII: 0661V34NTV.

KEGG ID: D13086.

ChEMBL ID: ChEMBL4846092.

International Union of Pure and Applied Chemistry name: 4-[3-methyl-3-(5-methylsulfonyl-1,3-dihydroisoindol-2-yl)butyl]-2-[(2-methylpropan-2-yl)oxy]phenol.

1.2 Structural class and chemistry

CT1812 is a substituted isoindoline bearing a methylsulfonyl group at the 5-position of the isoindoline ring, a gem-dimethyl substituent adjacent to the nitrogen, and a 4-hydroxyphenyl moiety with a tert-butoxy ether at the 2-position. The structural class places CT1812 within a medicinal chemistry series developed from natural-product-derived screening hits, optimized for central nervous system druglikeness, oral bioavailability, and sigma-2 receptor selectivity [1].

Molecular formula: C₂₄H₃₃NO₄S.

Molecular weight: 431.59 g/mol.

Physical properties: CT1812 is a small, lipophilic molecule with physicochemical properties consistent with blood-brain barrier penetration. The compound exhibits high oral bioavailability in rodent species, is not a P-glycoprotein substrate (CACO-2 efflux ratio 0.95), and demonstrates a free fraction of approximately 13 percent in brain tissue and 5 percent in plasma [1, 3].

1.3 Synthesis

The published manufacturing process for CT1812 has been described by Bhatt et al. (2025) in a commercial-scale synthesis report [4]. The synthesis proceeds through construction of the 5-methylsulfonyl-isoindoline core, introduction of the gem-dimethyl aminoalkyl side chain, and coupling to the tert-butoxyphenol moiety. The compound was originally identified through optimization of a hit series discovered in a phenotypic screen of a CNS-druglike chemical library derived from natural materials using supercritical fluid extraction. Early hits (benzylic amines) demonstrated anti-amyloid-beta oligomer activity but carried metabolic instability and hERG liability. Structural evolution through isoindoline scaffolds with increased polar surface area achieved submicromolar neuronal activity with improved metabolic stability and reduced cardiac ion channel risk. The final gem-dimethyl substitution adjacent to nitrogen and the methyl sulfone group on the isoindoline ring yielded CT1812 with the desired pharmacokinetic and selectivity profile [1].

2. Abstract

CT1812 (zervimesine) is a first-in-class, orally bioavailable antagonist of the sigma-2 receptor complex (TMEM97/PGRMC1/LDLR) developed by Cognition Therapeutics for the treatment of neurodegenerative diseases characterized by amyloid-beta oligomer driven synaptotoxicity [1, 2]. The compound was identified through a phenotypic neuronal assay measuring the synaptotoxic effects of soluble amyloid-beta oligomers and was optimized from isoindoline scaffolds for brain penetration, metabolic stability, and receptor selectivity. CT1812 binds the sigma-2 receptor with a K_i of 8.5 nM and achieves greater than 100-fold selectivity over a broad receptor panel [1].

The molecular mechanism involves allosteric antagonism of the sigma-2 receptor complex at the neuronal surface. This engagement induces a conformational change in the oligomer receptor complex, displacing prebound amyloid-beta oligomers from synaptic sites and facilitating their clearance into the cerebrospinal fluid, without affecting oligomer aggregation or dissociation kinetics [1, 5]. In pre-clinical transgenic Alzheimer's disease mouse models, CT1812 improved cognitive performance across multiple behavioral paradigms and achieved robust brain penetration with a brain-to-plasma ratio of 5.7 and receptor occupancy exceeding 84 percent [1, 3].

Clinical development has progressed through Phase 1 safety and pharmacokinetic characterization in 80 healthy volunteers [3], a Phase 1b/2 biomarker study (COG0102) in 19 AD patients demonstrating reductions in CSF synaptic damage proteins and tau phosphorylation [5, 6], the Phase 2 SHINE trial (COG0201) in 153 mild to moderate AD patients showing a 39 percent reduction in cognitive decline on ADAS-Cog 11 at 182 days [7, 8], the Phase 2 SHIMMER trial (COG1201) in 130 DLB patients meeting its primary safety endpoint with favorable secondary cognitive and behavioral signals [9, 10], and the Phase 2 MAGNIFY trial in geographic atrophy secondary to dry age-related macular degeneration showing 28.6 percent slower lesion growth [11]. The compound is generally well tolerated, with headache and gastrointestinal symptoms as the principal adverse events, and transient liver function test elevations observed at the 300 mg dose in SHINE that resolved upon discontinua-

tion [7, 8]. CT1812 is positioned for Phase 3 advancement in Alzheimer's disease and represents the first sigma-2 receptor antagonist to achieve proof-of-concept clinical efficacy in neurodegenerative disease.

3. Discovery and Development History

3.1 Origin and rationale

CT1812 was developed by Cognition Therapeutics, Inc. (Pittsburgh, Pennsylvania), a clinical-stage biotechnology company founded on the hypothesis that soluble amyloid-beta oligomers, rather than insoluble amyloid plaques, are the proximate drivers of synaptic dysfunction and cognitive decline in Alzheimer's disease [1]. This "oligomer hypothesis" distinguishes the CT1812 program from anti-amyloid monoclonal antibody programs (aducanumab, lecanemab, donanemab) that target plaque clearance. The rationale held that a small molecule capable of displacing oligomers from their synaptic binding sites would protect synapses and restore cognitive function without requiring intravenous infusion or carrying the amyloid-related imaging abnormalities (ARIA) risk associated with antibody therapies.

3.2 Phenotypic screening and hit identification

The discovery program employed an unbiased phenotypic neuronal assay measuring the synaptotoxic effects of soluble amyloid-beta oligomers on cultured neurons [1]. A CNS-druglike chemical library derived from natural materials using supercritical fluid and conditioned extraction techniques was screened for compounds that prevented and reversed oligomer-induced synaptic damage. Early hit compounds (designated compounds 1 through 3 in the published medicinal chemistry series) were benzylic amines that demonstrated anti-amyloid-beta oligomer activity but were limited by metabolic instability and cardiac ion channel (hERG) liability.

3.3 Medicinal chemistry optimization

Structural optimization through the isoindoline scaffold class (compounds 4 through 7) achieved submicromolar neuronal activity with improved metabolic stability and reduced off-target effects through increased polar surface area [1]. CT1812 (compound 7 in the series) incorporated gem-dimethyl substitution adjacent to the isoindoline nitrogen and a methyl sulfone group at the 5-position of the isoindoline ring, yielding the combination of high sigma-2 receptor affinity (Ki 8.5 nM), favor-

able brain penetration (brain-to-plasma ratio 5.7), metabolic stability, and selectivity against hERG and a broad receptor panel (greater than 100-fold selectivity, with approximately 10-fold selectivity over sigma-1) [1].

3.4 Target identification

The molecular target of CT1812 was identified as the sigma-2 receptor, subsequently characterized at the gene level as transmembrane protein 97 (TMEM97) [1, 12]. Further studies established that the sigma-2 receptor forms a multiprotein complex with progesterone receptor membrane component 1 (PGRMC1) and low-density lipoprotein receptor (LDLR) at the cell surface, and that amyloid-beta oligomer binding to neuronal surfaces involves this complex along with cellular prion protein (PrPC), Nogo receptor 1 (NgR1), and leukocyte immunoglobulin-like receptor B2 (LILRB2). CT1812 engagement of the sigma-2 receptor complex induces a conformational change that reduces the affinity of the oligomer for its receptor complex, effectively displacing prebound oligomers without affecting oligomer assembly or dissociation [1].

3.5 Preclinical advancement

Preclinical pharmacology studies demonstrated cognitive improvement in transgenic Alzheimer's disease mouse models, displacement of amyloid-beta oligomers from human postmortem AD brain tissue, and favorable pharmacokinetic properties including oral bioavailability, brain penetration exceeding plasma levels, and absence of P-glycoprotein efflux [1, 3]. These findings supported advancement to first-in-human studies.

3.6 Clinical development timeline

Phase 1 studies were conducted from September 2015 to May 2016 in Melbourne, Australia, in 80 healthy volunteers [3]. The Phase 1b/2 COG0102 trial in mild to moderate AD patients was completed with 28-day dosing at 90, 280, and 560 mg/day [5, 6]. Subsequently, Cognition Therapeutics initiated four Phase 2 programs: SNAP (COG0105, synaptic density PET), SHINE (COG0201, AD efficacy), SHIMMER (COG1201, DLB), and MAGNIFY (COG2201, geographic atrophy). The SHINE trial completed enrollment of 153 patients in November 2023 and reported topline results in July 2024 [7, 8]. The SHIMMER trial reported positive results in January 2025

[9, 10]. The MAGNIFY trial reported topline results in May 2025 [11]. Cognition Therapeutics is preparing for Phase 3 development in AD based on the SHINE results, with a preferred dose of 100 mg once daily.

3.7 Regulatory and commercial status

CT1812 is an investigational compound. It has not been approved by any regulatory authority for any indication. The compound received Fast Track designation from the United States Food and Drug Administration for Alzheimer's disease and Orphan Drug designation for DLB. Cognition Therapeutics is a publicly traded company (NASDAQ: CGTX).

4. Mechanism of Action

4.1 The sigma-2 receptor complex

The sigma-2 receptor (S2R) was originally characterized as a pharmacological binding site distinct from the sigma-1 receptor, with preferential binding of the radioligand [3H]-DTG (1,3-di-o-tolylguanidine) in the presence of (+)-pentazocine to mask sigma-1 sites [12, 13]. The molecular identity of the sigma-2 receptor was established by Alon et al. (2017) as TMEM97 (transmembrane protein 97), an endoplasmic reticulum resident protein that traffics to the cell surface in complex with other proteins [12]. At the neuronal surface, the sigma-2 receptor forms a multiprotein complex with PGRMC1 (progesterone receptor membrane component 1) and LDLR (low-density lipoprotein receptor). This complex serves as a binding site for amyloid-beta oligomers and is implicated in cholesterol homeostasis, intracellular calcium signaling, and synaptic plasticity [1, 13].

Evidence for increased synaptic levels of TMEM97 in Alzheimer's disease brain tissue supports the hypothesis that sigma-2 receptor upregulation contributes to oligomer-mediated synaptotoxicity and that pharmacological modulation of this receptor may be therapeutically relevant [1, 14].

4.2 Amyloid-beta oligomer displacement

The principal pharmacological action of CT1812 is allosteric antagonism of the sigma-2 receptor complex, resulting in displacement of prebound amyloid-beta oligomers from neuronal synaptic sites [1, 5]. The mechanism operates through conformational modulation rather than direct competition at the oligomer binding site. CT1812 binds the canonical sigma-2 receptor site on TMEM97 with a K_i of 8.5 nM, inducing a conformational change in the multiprotein complex that reduces the affinity of the complex for amyloid-beta oligomers. This results in release of oligomers from the synapse into the extracellular space and, subsequently, into the cerebrospinal fluid.

Importantly, CT1812 does not affect oligomer assembly, dissociation, or aggregation kinetics [1]. The compound acts specifically on the receptor-oligomer interaction at the synapse, distinguishing it mechanistically from anti-amyloid antibodies

(which bind and clear oligomers and plaques directly), from beta-secretase inhibitors (which reduce amyloid-beta production), and from gamma-secretase modulators.

In preclinical assays, CT1812 prevented and reversed trafficking deficits caused by amyloid-beta oligomers in cultured neurons with a treatment EC₅₀ of 358 nM and 88 percent recovery of normal synaptic trafficking [1].

4.3 Synaptic protection and restoration

The downstream consequence of oligomer displacement is synaptic protection. Amyloid-beta oligomers bound to neuronal surfaces impair synaptic vesicle trafficking, disrupt long-term potentiation, reduce dendritic spine density, and trigger excitotoxic calcium influx through NMDA receptor dysregulation [1, 5]. By displacing oligomers, CT1812 restores normal synaptic vesicle trafficking, preserves dendritic spine morphology, and normalizes synaptic calcium dynamics in preclinical models. The synaptic protection hypothesis is supported by clinical biomarker evidence: in the COG0102 trial, CT1812 treatment reduced cerebrospinal fluid concentrations of neurogranin and synaptotagmin-1, proteins released during synaptic damage, relative to placebo [5, 6].

4.4 Tau phosphorylation modulation

An additional pharmacodynamic effect observed in clinical studies is modulation of tau phosphorylation. In the COG0102 trial, 28 days of CT1812 treatment produced reductions of 30 percent or more in six tau phosphorylation sites (T52, T205, S262, S263, S285, S305) relative to placebo, while one site (S191) increased more than 30 percent [5, 6]. Unphosphorylated tau concentrations were unchanged. The reduction in tau phosphorylation is consistent with reduced oligomer-driven kinase activation (particularly glycogen synthase kinase 3-beta and cyclin-dependent kinase 5) downstream of synaptic protection, although a direct effect of sigma-2 receptor modulation on tau biology has not been excluded.

4.5 Sigma-2 receptor modulation in non-neuronal tissues

The sigma-2 receptor is expressed beyond the central nervous system, including in retinal pigment epithelium, immune cells, and various peripheral tissues [11, 15]. In the retinal pigment epithelium, CT1812 has demonstrated neuroprotective activ-

ity and modulation of key pathways associated with geographic atrophy, supporting the MAGNIFY trial in dry age-related macular degeneration [11]. The broader tissue expression of the sigma-2 receptor suggests potential applications beyond neurodegenerative disease, although CT1812 development has been focused on CNS and retinal indications.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

CT1812 is rapidly absorbed after oral administration. In the Phase 1 trial in healthy volunteers, peak plasma concentrations (T_{max}) were reached within 0.88 to 1.5 hours (median values) after single ascending doses of 10 to 1120 mg and within 0.88 to 2.0 hours after multiple doses [3]. Plasma exposure increased in a slightly greater than dose-proportional manner across two orders of magnitude. Food had a minimal effect on absorption, with approximately a 20 percent reduction in AUC observed at the 90 mg dose when administered in the fed versus fasted state [3]. The compound demonstrates high oral bioavailability in rodent species, and the Phase 1 human data are consistent with efficient gastrointestinal absorption.

5.2 Distribution

CT1812 is highly lipophilic with robust central nervous system penetration. In pre-clinical studies, the brain-to-plasma ratio was 5.7 at 24 hours post-dose, with an unbound brain-to-plasma partition coefficient ($K_{p,uu}$) of 6.75 [1]. The free fraction is approximately 13 percent in brain tissue and 5 percent in plasma, indicating substantially greater unbound drug concentrations in the brain relative to plasma. The compound is not a P-glycoprotein substrate (CACO-2 efflux ratio 0.95), which contributes to the favorable brain penetration [1, 3].

In human cerebrospinal fluid, CT1812 was detectable at therapeutically relevant concentrations: 8.0 (plus or minus 4.3) ng/mL at the 560 mg dose and 23.3 (plus or minus 15.6) ng/mL at the 840 mg dose in the Phase 1 multiple ascending dose study [3]. These CSF concentrations corresponded to estimated receptor occupancy of 97 to 98 percent based on preclinical receptor occupancy models, confirming target engagement at clinically feasible doses.

The compound is highly protein-bound in plasma from rat, mouse, dog, and human, but is only weakly bound to blood cells [1, 3].

5.3 Metabolism

CT1812 undergoes extensive first-pass metabolism, primarily via oxidation and direct glucuronidation [1, 3]. Studies with human recombinant cytochrome P450 isoforms demonstrate rapid metabolism by CYP3A4, with slower metabolism by CYP2D6 and CYP2C19. A direct glucuronide conjugate has been observed in human hepatocyte incubations in vitro [1]. The metabolic profile indicates that CYP3A4 is the principal determinant of CT1812 clearance, with implications for drug-drug interactions with CYP3A4 inhibitors and inducers.

5.4 Elimination

The plasma elimination half-life of CT1812 is approximately 11 to 14 hours after single doses and approximately 12 hours at steady state in the multiple ascending dose study [3]. Steady-state plasma concentrations were achieved by day 3 to 4 of once-daily dosing, consistent with the half-life. Accumulation was minimal with repeated dosing [3]. A dedicated absorption, metabolism, excretion, and mass balance study (NCT05225389) has been conducted to fully characterize the elimination pathways.

5.5 Special populations

In the Phase 1 trial, elderly subjects (65 to 75 years) receiving 560 mg once daily for 14 days showed 1.6- to 1.7-fold higher C_{max} and 1.3- to 1.5-fold higher AUC compared to younger subjects at the equivalent dose [3]. This age-related increase in exposure is consistent with reduced hepatic metabolic capacity in the elderly and has been considered in dose selection for Phase 2 trials, which enrolled patients with Alzheimer's disease (typically aged 55 to 85 years) at 100 mg and 300 mg doses.

5.6 Route of administration

CT1812 is administered as a once-daily oral capsule. The oral route, the favorable pharmacokinetics (rapid absorption, 12-hour half-life supporting once-daily dosing, robust brain penetration), and the absence of infusion-related adverse events distinguish CT1812 operationally from anti-amyloid monoclonal antibodies, which require intravenous infusion and MRI monitoring for ARIA.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

CT1812 binds the sigma-2 receptor with a K_i of 8.5 nM in radioligand displacement assays [1]. The compound demonstrates greater than 100-fold selectivity across a broad receptor panel, with approximately 10-fold selectivity over the sigma-1 receptor [1]. In cultured neurons exposed to synthetic amyloid-beta oligomers, CT1812 prevented and reversed oligomer-induced trafficking deficits with a treatment EC_{50} of 358 nM and achieved 88 percent recovery of normal synaptic function [1]. The compound displaced prebound oligomers from neuronal surfaces without affecting oligomer assembly or dissociation kinetics.

In human postmortem Alzheimer's disease brain tissue, CT1812 displaced amyloid-beta oligomers from synaptosomes, supporting the relevance of the preclinical mechanism to human disease biology [1].

6.2 Cognitive efficacy in transgenic mouse models

CT1812 was evaluated in transgenic mouse models expressing familial Alzheimer's disease mutations. Drug-treated animals demonstrated significant cognitive improvement across multiple behavioral paradigms [1]:

Y-maze spontaneous alternation: CT1812-treated mice showed significantly improved alternation behavior relative to vehicle-treated controls, indicating enhanced spatial working memory.

Morris water maze: Drug-treated mice demonstrated significantly improved swim lengths (shorter escape latencies), consistent with improved spatial learning and memory consolidation.

Fear conditioning: CT1812-treated animals showed significant enhancements in both spatial (contextual) and cue-dependent (auditory) learning and memory compared to vehicle-treated controls.

6.3 Brain penetration and receptor occupancy

Pharmacokinetic studies in mice confirmed that brain concentrations of CT1812 exceeded plasma concentrations, with a brain-to-plasma ratio of 5.7 at 24 hours post-dose [1]. The unbound brain-to-plasma partition coefficient ($K_{p,uu}$) of 6.75 indicates active accumulation in the CNS rather than simple partitioning. At therapeutically relevant doses, receptor occupancy of 84.4 percent was achieved, as measured by ex vivo receptor binding [1]. The compound is not a P-glycoprotein substrate, consistent with the absence of active efflux at the blood-brain barrier.

6.4 Retinal pharmacology

CT1812 has demonstrated neuroprotective activity in retinal pigment epithelium models relevant to dry age-related macular degeneration [15]. The compound modulated key pathways associated with RPE dysfunction, including oxidative stress response and complement activation, providing the preclinical basis for the Phase 2 MAGNIFY trial in geographic atrophy.

7. Clinical Evidence Base

7.1 Phase 1 in healthy volunteers (COG0101)

The first-in-human Phase 1 trial was a randomized, double-blind, placebo-controlled study in 80 healthy volunteers conducted at a single center in Melbourne, Australia, from September 2015 to May 2016 [3]. The study comprised two parts:

Part A (single ascending dose): 54 healthy young subjects (under 65 years) received single doses of CT1812 from 10 mg to 1120 mg or placebo (6:2 active-to-placebo ratio per cohort).

Part B (multiple ascending dose): 24 young adults received 280, 560, or 840 mg once daily for 14 days (8:2 active-to-placebo ratio), and 9 elderly subjects (65 to 75 years) received 560 mg once daily for 14 days (7:2 ratio).

CT1812 was well tolerated at all dose levels. Adverse events were predominantly mild (77 to 82 percent of events) and included headache, nausea, vomiting, dyspepsia, diarrhea, constipation, and dizziness [3]. No serious drug-related adverse events occurred. No clinically significant laboratory abnormalities or electrocardiographic changes were observed. Pharmacokinetic parameters demonstrated rapid absorption (T_{max} 0.88 to 1.5 hours), dose-proportional exposure, and a half-life of 11 to 14 hours supporting once-daily dosing. CSF concentrations at 560 and 840 mg confirmed brain penetration at levels consistent with 97 to 98 percent receptor occupancy [3].

7.2 Phase 1b/2 biomarker study in AD (COG0102)

The Phase 1b/2 trial (COG0102, NCT02907567) was a randomized, double-blind, placebo-controlled study in 19 subjects with mild to moderate AD who received CT1812 at 90, 280, or 560 mg/day or placebo for 28 days [5, 6]. The primary endpoint was safety; secondary endpoints included cerebrospinal fluid biomarker analysis.

CT1812 was safe and well tolerated in this patient population. CSF biomarker analysis demonstrated that concentrations of the synaptic damage markers neurogranin (Nrgn) and synaptotagmin-1 (Sytn1) decreased in CT1812-treated patients relative to placebo, while remaining unchanged in placebo recipients [5, 6].

Additionally, the abundance of six tau phosphorylation peptides decreased by 30 percent or more relative to placebo (T52, T205, S262, S263, S285, S305), while unphosphorylated tau concentrations did not change [6]. These findings provided the first clinical evidence that CT1812 engages its target and modulates downstream synaptic and tau biology in Alzheimer's disease patients, supporting advancement to larger efficacy trials.

The 28-day treatment duration was not sufficient to detect changes in cognitive measures, which is expected given the slow trajectory of cognitive decline in AD.

7.3 Phase 2 SHINE trial in Alzheimer's disease (COG0201)

The SHINE trial (COG0201) was a randomized, double-blind, placebo-controlled, parallel-group Phase 2 study evaluating the safety and efficacy of CT1812 in 153 adults with mild to moderate Alzheimer's disease over 182 days [7, 8]. Participants were randomized to CT1812 100 mg, CT1812 300 mg, or placebo administered as a once-daily oral capsule. The primary endpoint was safety and tolerability; secondary endpoints included ADAS-Cog 11, ADAS-Cog 13, cognitive composite, and MMSE.

The trial met its primary safety endpoint. CT1812 was generally well tolerated; serious adverse events occurred less frequently in the CT1812 groups (6 percent) than in the placebo group (10 percent) [7, 8]. At the 300 mg dose, nine patients experienced treatment-emergent liver function test elevations (greater than 3 times the upper limit of normal), which resolved upon drug discontinuation without progressing to serious liver injury. No liver function test elevations were observed at the 100 mg dose [8].

On the ADAS-Cog 11 secondary endpoint, participants on placebo experienced a 2.70-point decline over 182 days, while CT1812-treated participants (pooled 100 and 300 mg) showed a decline of 1.66 points, representing a 39 percent reduction in cognitive decline favoring treatment [7, 8]. A pre-specified biomarker analysis demonstrated that participants with baseline plasma p-tau₂₁₇ levels below the median experienced a 95 percent slowing of cognitive decline on ADAS-Cog 11 when treated with CT1812 [8]. Consistent trends favoring CT1812 were observed across all cognitive measures including ADAS-Cog 13, cognitive composite, and MMSE [7].

These results supported advancement of the 100 mg dose for further clinical development. Cognition Therapeutics has characterized the cognitive improvement as comparable in magnitude to approved anti-amyloid antibodies, with the advantage of once-daily oral administration and lower patient burden [7].

7.4 Phase 2 SHIMMER trial in dementia with Lewy bodies (COG1201)

The SHIMMER trial (COG1201) was an exploratory, randomized, double-blind, placebo-controlled Phase 2 trial enrolling 130 adults with mild to moderate dementia with Lewy bodies randomized to CT1812 100 mg, 300 mg, or placebo for 6 months [9, 10]. The primary endpoint was safety and tolerability.

The trial met its primary safety endpoint; CT1812 demonstrated a favorable safety and tolerability profile consistent with previous clinical experience [9, 10]. On secondary efficacy measures, 82 percent of patients in the CT1812 treatment arms showed slowing on the total Neuropsychiatric Inventory (NPI), a composite measure tracking behavioral and neuropsychiatric symptom progression [10]. Participants treated with CT1812 demonstrated slowing of decline across all three cognitive measures relative to placebo, with a 91 percent reduction in decline of attentional fluctuation measures, which represent a core clinical feature of DLB [10].

Results were presented at the International Lewy Body Dementia Conference in Amsterdam in January 2025 and published in *Alzheimer's and Dementia* [9, 10].

7.5 Synaptic density PET study (COG0105 SNAP)

A pilot study (COG0105) evaluated the effect of CT1812 on brain synaptic density using [11C]UCB-J positron emission tomography (SV2A PET) in patients with mild to moderate AD [16]. This imaging biomarker study was designed to provide direct evidence of synaptic preservation. The study design and protocol have been published; full results are pending.

7.6 Phase 2 MAGNIFY trial in geographic atrophy (COG2201)

The MAGNIFY trial (COG2201, NCT05893537) was a Phase 2 study of CT1812 in adults with geographic atrophy secondary to dry age-related macular degeneration [11]. Approximately 100 of a planned 246 participants were enrolled before the study was voluntarily concluded to focus resources on the AD and DLB programs. Topline results reported in May 2025 showed that CT1812-treated participants had 28.6 percent slower geographic atrophy lesion growth on average, with lesions 28.2 percent smaller compared to placebo at 18 months [11]. As a once-daily oral therapy, CT1812 would represent a potential alternative to the intravitreal injections currently used for complement-targeting therapies in geographic atrophy (pegcetacoplan, avacincaptad pegol).

7.7 EEG biomarker study (COG0104)

A pilot electroencephalography study evaluated the effect of CT1812 on synaptic activity in patients with mild to moderate Alzheimer's disease [17]. The study used quantitative EEG as a pharmacodynamic biomarker of synaptic function. Published results demonstrated that CT1812 treatment was associated with changes in EEG spectral power consistent with improved synaptic activity relative to placebo.

8. Sourcing and Quality Verification

CT1812 (zervimesine) is an investigational compound not yet approved for any clinical indication. Research-grade CT1812 is available from select chemical suppliers, including MedChemExpress (catalog number HY-109182), for in vitro and preclinical research applications.

Purity: Research-grade material is typically supplied at greater than 98 percent purity by HPLC.

Supply form: The compound is supplied as a solid powder, typically in milligram quantities.

CAS verification: Investigators should confirm compound identity against CAS 1802632-22-9.

Analytical verification: For research applications requiring dose-response precision, investigators should confirm:

- HPLC purity (area-percent, ideally greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (431.59 g/mol for the free base; $[M+H]^+$ at m/z 432.22)
- Nuclear magnetic resonance spectroscopy for structural confirmation
- Residual solvent analysis

Clinical supply of CT1812 is manufactured under current Good Manufacturing Practice (cGMP) by Cognition Therapeutics for use in clinical trials. The commercial manufacturing process has been published by Bhatt et al. (2025) [4]. Clinical-grade material is not available for independent research procurement.

Investigators should note that CT1812 is a proprietary compound protected by patents assigned to Cognition Therapeutics. Use in research should comply with applicable intellectual property considerations.

9. Reconstitution and Handling

CT1812 is a lipophilic small molecule supplied as a solid powder. For in vitro research applications, the compound may be reconstituted in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (typically 10 to 50 mM), which can then be diluted into aqueous assay media at the desired final concentration. The DMSO concentration in the final assay should be maintained below 0.1 percent to avoid solvent cytotoxicity.

Storage: The solid compound should be stored desiccated at minus 20 degrees Celsius, protected from light and moisture. DMSO stock solutions should be aliquoted for single use and stored at minus 20 degrees Celsius; repeated freeze-thaw cycles should be minimized.

Aqueous solubility: As a lipophilic compound, CT1812 has limited aqueous solubility. For in vivo preclinical studies, formulation vehicles such as methylcellulose suspensions, cyclodextrin-based solutions, or PEG-based vehicles have been used in published preclinical work [1].

Clinical formulation: In clinical trials, CT1812 is administered as an oral capsule formulation at 100 mg and 300 mg strengths, taken once daily with or without food [7, 8].

Handling precautions: Standard laboratory safety precautions for investigational pharmaceutical compounds apply. The compound should be handled with appropriate personal protective equipment. Material Safety Data Sheets are available from research chemical suppliers.

10. Stack Interaction Considerations

CT1812 is metabolized primarily by CYP3A4, with secondary contributions from CYP2D6 and CYP2C19 [1, 3]. Investigators conducting research with CT1812 in combination with other compounds should consider:

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, grapefruit juice) may substantially increase CT1812 plasma exposure and brain concentrations. Dose adjustment or avoidance of concurrent strong CYP3A4 inhibitors should be considered. A dedicated drug interaction study (NCT03716427) was conducted in healthy volunteers to characterize this interaction [18].

CYP3A4 inducers: Strong inducers (rifampin, carbamazepine, phenytoin, St. John's wort) may substantially reduce CT1812 exposure and compromise therapeutic efficacy.

CYP2D6 interactions: CT1812 is a secondary CYP2D6 substrate. Concurrent strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) may modestly increase exposure, although the contribution of CYP2D6 to overall clearance is less than that of CYP3A4.

Acetylcholinesterase inhibitors: Many AD patients in CT1812 clinical trials were receiving stable background therapy with donepezil, rivastigmine, or galantamine. No clinically significant pharmacokinetic interactions have been reported, and CT1812 clinical trials permitted concurrent cholinesterase inhibitor therapy [7, 8, 9].

Memantine: Concurrent memantine therapy was permitted in CT1812 clinical trials. No characterized pharmacokinetic interaction has been reported.

Anti-amyloid antibodies: CT1812 acts through a mechanistically distinct pathway from anti-amyloid monoclonal antibodies (lecanemab, donanemab). The combination has not been studied clinically but represents a plausible research direction given the complementary mechanisms (oligomer displacement at the synapse versus oligomer and plaque clearance by antibody).

QT-prolonging agents: No clinically significant QT prolongation was observed in the Phase 1 study at doses up to 1120 mg [3]. However, standard precautions regarding concurrent use with known QT-prolonging agents should be maintained.

Hepatotoxic agents: Given the observation of transient liver function test elevations at the 300 mg dose in the SHINE trial, concurrent use of known hepatotoxic agents should be approached with caution, and liver function monitoring may be warranted.

11. Adverse Events and Safety

11.1 Phase 1 safety profile

In the Phase 1 study of 80 healthy volunteers, CT1812 was well tolerated at single doses up to 1120 mg and multiple doses up to 840 mg daily for 14 days [3]. Adverse events were predominantly mild (77 to 82 percent of events). The incidence of treatment-emergent adverse events was 43 percent in active drug recipients versus 17 percent in placebo recipients after single doses, and 81 percent versus 75 percent after multiple doses [3].

Common adverse events included:

- Headache
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Abdominal pain
- Dyspepsia
- Dizziness
- Myalgia
- Rash (mild)
- Pain at lumbar puncture site (in participants undergoing CSF sampling)

No serious drug-related adverse events occurred. No clinically significant laboratory abnormalities, vital sign changes, or electrocardiographic changes were observed [3].

11.2 Phase 1b/2 safety in AD patients (COG0102)

In the 28-day study in 19 AD patients at doses of 90, 280, and 560 mg/day, CT1812 was safe and well tolerated [5, 6]. The adverse event profile was consistent with that observed in healthy volunteers.

11.3 Phase 2 SHINE trial safety

In the 182-day SHINE trial of 153 AD patients, the overall safety profile was favorable [7, 8]. Serious adverse events occurred less frequently in the CT1812 groups (6 percent) than in the placebo group (10 percent). The most common treatment-emergent adverse events included infections, injury and procedural complications (such as falls and skin lacerations), gastrointestinal symptoms, and headache [7, 8].

The principal safety finding was dose-dependent hepatotoxicity at the 300 mg dose: nine patients experienced treatment-emergent liver function test elevations greater than 3 times the upper limit of normal [8]. These elevations were transient and resolved upon drug discontinuation. No cases of serious liver injury, Hy's law cases, or liver failure occurred. No liver function test elevations were observed at the 100 mg dose, supporting the selection of 100 mg for further development [8].

Serious adverse events in the 100 mg group included stomatitis, chronic constipation, and hip fracture, all assessed as unrelated to study drug. In the 300 mg group, serious adverse events included hematuria, abdominal pain, infection (unrelated), and recurrent presyncope (assessed as possibly related to treatment) [7, 8].

11.4 Phase 2 SHIMMER trial safety

In the 6-month SHIMMER trial of 130 DLB patients, CT1812 demonstrated a favorable safety and tolerability profile consistent with previous clinical experience [9, 10]. Most treatment-related adverse events were mild or moderate.

11.5 Hepatic considerations

The transient liver function test elevations observed at 300 mg in SHINE represent the most notable safety signal identified to date. The dose-dependent pattern (absent at 100 mg, present at 300 mg) suggests a dose-related hepatic effect that is manageable through dose selection. The mechanism of the hepatic effect has not been fully characterized but may relate to the CYP3A4-mediated metabolic pathway or to a direct pharmacological effect of sigma-2 receptor modulation in hepatocytes. Liver function monitoring is recommended in ongoing and future clinical studies [8].

11.6 Cardiovascular safety

No clinically significant electrocardiographic changes, QT prolongation, or cardiovascular adverse events have been reported across the clinical development program at doses up to 1120 mg (single dose) and 840 mg (14-day multiple dose) [3].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative approaches to amyloid-beta oligomer or sigma-2 receptor pharmacology against CT1812, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected to represent the principal therapeutic strategies competing with or complementary to CT1812 in the Alzheimer's disease treatment landscape.

12.1 Lecanemab (Leqembi)

Mechanism: Humanized IgG1 monoclonal antibody targeting soluble amyloid-beta protofibrils. Binds large soluble aggregated forms of amyloid-beta with high affinity and promotes their clearance through Fc-mediated phagocytosis [19].

Development trajectory: Developed by Eisai and Biogen. Approved by the FDA in January 2023 under accelerated approval and converted to traditional approval in July 2023 based on the Phase 3 CLARITY-AD trial in 1795 patients with early AD, which demonstrated a statistically significant 27 percent slowing of cognitive decline on CDR-SB at 18 months [19].

Novelty: Moderate. Lecanemab is the second anti-amyloid antibody to achieve FDA approval (after aducanumab) and represents an incremental advance in the anti-amyloid antibody class rather than a novel mechanism.

Effect size: The CLARITY-AD trial reported a Cohen's d effect size of approximately 0.21 on CDR-SB, representing a small but statistically significant clinical effect [19]. The 27 percent slowing of decline has been debated regarding its clinical meaningfulness.

Promising potential: High. Lecanemab is an approved, commercially available treatment with growing clinical adoption. It serves as the benchmark for novel AD therapeutics.

Side-effect profile: The principal safety concern is amyloid-related imaging abnormalities (ARIA), occurring in approximately 21 percent of treated patients as ARIA-E (edema/effusion) and 17 percent as ARIA-H (hemorrhage/hemosiderin deposition) [19]. Most ARIA cases were asymptomatic, but approximately 3 percent were symptomatic. Infusion-related reactions occurred in approximately 26 percent of patients. The requirement for regular MRI monitoring and intravenous infusion contributes to patient burden.

Overall validation: High. Phase 3 positive, FDA-approved, commercially launched.

Comparison to CT1812: Lecanemab and CT1812 target different aspects of amyloid-beta biology: lecanemab clears protofibrils from the brain, while CT1812 displaces oligomers from synapses. The mechanisms are complementary and could theoretically be combined. CT1812 offers the operational advantages of once-daily oral dosing, absence of ARIA, and no requirement for MRI monitoring. Lecanemab has the advantage of a completed Phase 3 trial and FDA approval. The SHINE trial 39 percent slowing of ADAS-Cog 11 decline with CT1812 is numerically comparable to the 27 percent slowing of CDR-SB decline with lecanemab, though different cognitive scales and patient populations preclude direct comparison.

12.2 Donanemab (Kisunla)

Mechanism: Humanized IgG1 monoclonal antibody targeting a modified, pyroglutamatated form of amyloid-beta (N3pG-Abeta) present in established amyloid plaques [20].

Development trajectory: Developed by Eli Lilly. Approved by the FDA in July 2024 based on the Phase 3 TRAILBLAZER-ALZ 2 trial in 1736 early symptomatic AD patients, which demonstrated a 35 percent slowing of cognitive decline on iADRS at 76 weeks [20].

Novelty: Low to moderate. Donanemab targets plaque-associated amyloid-beta, a well-validated but extensively explored target.

Effect size: The TRAILBLAZER-ALZ 2 trial reported a 35 percent slowing of decline on the integrated Alzheimer's Disease Rating Scale (iADRS) in the combined population, with a larger effect (36 percent) in participants with low/medium tau burden at baseline [20].

Promising potential: High. FDA-approved with commercial launch.

Side-effect profile: ARIA rates were higher than lecanemab: ARIA-E in approximately 24 percent, ARIA-H in approximately 31 percent. Three deaths potentially related to ARIA occurred in the trial [20]. Infusion reactions occurred in approximately 9 percent. The ARIA burden is the most significant safety limitation.

Overall validation: High. Phase 3 positive, FDA-approved.

Comparison to CT1812: Similar to lecanemab, donanemab addresses amyloid plaque clearance while CT1812 addresses oligomer-synapse interaction. CT1812 avoids the ARIA risk entirely and offers oral administration. The effect sizes on cognitive decline are in a comparable range when cross-referenced across different instruments.

12.3 SAS-0132

Mechanism: Selective sigma-2 receptor antagonist. Modulates intracellular calcium levels in neuroblastoma cells and demonstrates neuroprotective activity in *C. elegans* models of APP-mediated neurodegeneration [13, 21].

Development trajectory: SAS-0132 was developed as a research tool compound and demonstrated cognitive improvement in both the Thy-1 hAPPLond/Swe+ transgenic mouse model of AD and in healthy wild-type mice [21]. The compound has not advanced to human clinical trials.

Novelty: Moderate. SAS-0132 shares the sigma-2 receptor antagonist mechanism with CT1812 but was not optimized for clinical development.

Effect size: Preclinical only. Improved cognitive performance in transgenic AD mice and wild-type mice.

Promising potential: Low. The compound is a preclinical research tool without a clinical development program.

Side-effect profile: Preclinical only. No human safety data available.

Overall validation: Low. Preclinical research tool that validates the sigma-2 receptor target but has no clinical evidence.

Comparison to CT1812: SAS-0132 provides target validation for the sigma-2 receptor mechanism but is not a clinical competitor. CT1812 is the optimized clinical candidate from the same mechanistic class, with substantially more advanced development including Phase 2 clinical efficacy data.

12.4 Roluperidone (MIN-101)

Mechanism: Non-selective ligand of sigma-2, serotonin, and adrenergic receptors, developed for negative symptoms and cognitive impairment in schizophrenia [22].

Development trajectory: Developed by Minerva Neurosciences. Advanced through Phase 2b in schizophrenia, where it showed promising effects on negative symptoms and cognitive function. The compound received a Complete Response Letter from the FDA in 2023 for negative symptoms of schizophrenia, requesting additional data [22].

Novelty: Low. The non-selective receptor profile makes it difficult to attribute effects specifically to sigma-2 receptor modulation.

Effect size: Phase 2b data showed significant improvement in negative symptoms of schizophrenia (PANSS negative symptom factor score). Cognitive effects were observed but it is unclear whether they reflect sigma-2, serotonergic, or adrenergic mechanisms [22].

Promising potential: Low to moderate. Development for schizophrenia has encountered regulatory obstacles. The compound has not been developed for Alzheimer's disease.

Side-effect profile: Generally well tolerated in clinical trials. Principal adverse events included headache, insomnia, and somnolence. No significant hepatic or ARIA-like signals.

Overall validation: Moderate. Positive Phase 2b data in schizophrenia; regulatory setback; limited relevance to AD.

Comparison to CT1812: Roluperidone and CT1812 both bind the sigma-2 receptor, but roluperidone lacks sigma-2 selectivity and has not been developed for AD. CT1812 is substantially more advanced as an AD therapeutic with selective sigma-2 antagonism and clinical proof of concept.

12.5 Aducanumab (Aduhelm)

Mechanism: Human IgG1 monoclonal antibody targeting aggregated forms of amyloid-beta (oligomers and fibrils). Promotes amyloid plaque clearance through Fc-mediated phagocytosis [23].

Development trajectory: Developed by Biogen and Eisai. Approved by the FDA in June 2021 under accelerated approval based on amyloid plaque reduction as a surrogate endpoint. The approval was controversial owing to conflicting Phase 3 trial results (EMERGE positive, ENGAGE negative after futility analysis). Biogen discontinued commercial sale of aducanumab in January 2024 [23].

Novelty: Moderate at the time of approval. First anti-amyloid antibody to receive FDA approval.

Effect size: Conflicting. The EMERGE trial reported a 22 percent slowing of CDR-SB decline at the high dose; the ENGAGE trial showed no benefit. The discordance led to the controversial approval decision [23].

Promising potential: Very low. Commercially discontinued. No longer available for clinical use.

Side-effect profile: ARIA rates were high: ARIA-E in approximately 35 percent and ARIA-H in approximately 19 percent of high-dose recipients. Symptomatic ARIA occurred in approximately 6 percent [23].

Overall validation: Low. Conflicting Phase 3 data, controversial approval, commercial discontinuation.

Comparison to CT1812: Aducanumab's commercial failure underscores the limitations of the anti-amyloid antibody approach and highlights the potential value of alternative mechanisms such as CT1812's sigma-2 receptor antagonism. CT1812 avoids ARIA entirely, offers oral dosing, and has produced consistent (though earlier-stage) clinical evidence of cognitive benefit.

12.6 Comparator summary

The five comparators span two mechanistic classes: anti-amyloid monoclonal antibodies (lecanemab, donanemab, aducanumab) and sigma-2 receptor ligands (SAS-0132, roluperidone). **Lecanemab** and **donanemab** represent the current standard of care with FDA approvals and demonstrated clinical efficacy, but carry the burdens

of intravenous infusion, ARIA risk, and MRI monitoring. **Aducanumab** has been commercially discontinued following conflicting efficacy data and represents a cautionary example for the antibody class. **SAS-0132** validates the sigma-2 receptor target preclinically but has no clinical development trajectory. **Roluperidone** engages the sigma-2 receptor non-selectively and has not been developed for AD.

CT1812 occupies a unique position: it is the only selective sigma-2 receptor antagonist with Phase 2 clinical proof of concept in AD and DLB, the only orally administered candidate in this comparison with evidence of cognitive benefit in AD clinical trials, and the only compound that acts through synaptic oligomer displacement rather than amyloid clearance. The 100 mg dose demonstrated cognitive benefit comparable in magnitude to approved antibodies while avoiding ARIA and offering once-daily oral administration. The principal limitation relative to the approved antibodies is that CT1812 has not completed Phase 3 development; the SHINE and SHIMMER results support advancement but do not constitute registration-level evidence. The transient hepatic signal at 300 mg, absent at 100 mg, is a manageable dose-selection consideration rather than a fundamental safety liability.

The practical question for the research and clinical positioning of CT1812 is whether sigma-2 receptor mediated oligomer displacement at the synapse will produce durable, clinically meaningful cognitive benefit in larger, longer Phase 3 trials. The consistency of the cognitive signal across SHINE and SHIMMER, the supportive biomarker evidence from COG0102, and the favorable safety profile at 100 mg provide a credible foundation for Phase 3 advancement. The complementary mechanism relative to anti-amyloid antibodies also raises the possibility of combination therapy, which represents a high-value research direction that has not yet been clinically tested.

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