Cognition Therapeutics (CGTX): Pipeline, Trials & Analysis

By InuitionLabs.ai • 10/11/2025 • 35 min read

cognition therapeutics | ct1812 | sigma-2 receptor | alzheimer's disease | dementia with lewy bodies | cgtx | neurodegeneration | clinical trial analysis | biotechnology

Executive Summary

Cognition Therapeutics, Inc. is a clinical-stage biotechnology company developing small-molecule therapies for age-related neurodegenerative disorders. Incorporated in Delaware in 2007 and headquartered in Purchase, NY (www.sec.gov), Cognition's lead drug candidate **zervimesine (CT1812)** is an orally available sigma-2 receptor (σ-2) modulator designed to protect neuronal synapses by displacing pathogenic protein oligomers such as β-amyloid (Aβ) and α-synuclein from synaptic receptors (www.sec.gov). The company's R&D strategy leverages its proprietary **NICE** (Novel Improved Conditioned Extraction) screening platform to expand its pipeline beyond Alzheimer's disease (AD) into related indications including dementia with Lewy bodies (DLB), early AD, and dry age-related macular degeneration (AMD) (www.sec.gov) (www.sec.gov).

CT1812 has completed multiple Phase I/II trials in AD and DLB, demonstrating a favorable safety profile and encouraging "proof-of-concept" signals. In a recent Phase II SHINE trial in mild-to-moderate AD (n=153), CT1812-treated patients experienced a **39% slowing of cognitive decline** on the ADAS-Cog11 scale versus placebo (ir.cogrx.com). Similarly, an exploratory Phase II "SHIMMER" trial in mild-to-moderate DLB (n=130) reported **82% less worsening** on the Neuropsychiatric Inventory and up to **91% reduction in attentional disruptions** for CT1812 versus placebo (www.globenewswire.com). Ongoing trials include the 540-patient Phase II START study in early (prodromal) AD – uniquely permitting background use of anti-Aβ antibodies like lecanemab – and a now-discontinued Phase II MAGNIFY trial in geographic atrophy (dry AMD) (cogrx.com) (ir.cogrx.com). Early biomarker studies (cerebrospinal fluid proteomics, EEG) further support CT1812's pharmacodynamic effects on synaptic function (ir.cogrx.com) (ir.cogrx.com).

Cognition has financed its programs with public equity offerings and significant NIH/NIA grants. It raised ~$52 million in an October 2021 IPO (ir.cogrx.com) and has secured roughly **$171 million** in grant funding for its AD and DLB trials (including ~$81M for START and $30M each for SHINE and SHIMMER) (ir.cogrx.com) (ir.cogrx.com). As of end-2024, the company reported about **$25 million in cash** and ~$50 million of remaining obligated NIA grant funds (www.sec.gov), though it cautioned that "substantial doubt" exists about its ability to fund operations beyond the next year without raising additional capital (www.sec.gov) (www.sec.gov).

In sum, Cognition Therapeutics is an R&D-stage company whose platform approach targets a novel synaptic **"housekeeping" receptor** (σ-2) to address protein toxicity in neurodegeneration. Its completed trials offer intriguing early data that CT1812 may slow cognitive decline and neuropsychiatric symptoms in AD and DLB, respectively. However, all findings to date are from small Phase II cohorts lacking robust statistical power, and larger trials (Phase III) will be required to validate efficacy. Going forward, the company's success will depend on confirming these early signals, managing cash burn, and positioning CT1812 either as

a monotherapy or adjunct to emerging antibody therapies. This comprehensive report reviews Cognition's corporate history, technology platform, pipeline programs, clinical progress, and future outlook, with detailed data analyses and citations throughout.

Introduction and Company Background

Cognition Therapeutics, Inc. is a clinical-stage biopharmaceutical firm focused on **neurodegenerative diseases** and retinal disorders caused by toxic protein accumulations. Incorporated in Delaware on August 21, 2007 (www.sec.gov), Cognition operates out of Purchase, New York (2500 Westchester Ave.) and trades on the Nasdaq under ticker **CGTX** (Common Stock, $0.001 par value) (www.sec.gov) (www.sec.gov). The company's management team is led by CEO **Lisa Ricciardi** (a biotech executive formerly of Kolon Tissuegene and Onyx Therap.), with Dr. Anthony O. Caggiano as Chief Medical Officer and Head of R&D, and John Doyle as CFO (cogrx.com). The Board of Directors includes pharma executives and scientists, such as Brett Monia, Ph.D. (former Ionis CEO) and Ellen Richstone, CPA (audit committee chair) (cogrx.com). As of 2025 the company employs around 30 full-time staff (per LinkedIn) in scientific, clinical and administrative roles.

Cognition's stated **mission** is to develop "disease-modifying treatments" for patients suffering from age-related degenerative CNS and retinal disorders (ir.cogrx.com). It emphasizes small molecules that target cellular "housekeeping" pathways disrupted by toxic protein aggregates. According to its 2024 10-K, *"zervimesine (CT1812) … is an orally delivered, small molecule designed to protect neuronal synapses by preventing the binding of oligomers of pathogenic proteins including β-amyloid (Aβ) and α-synuclein. These oligomers have been linked to the progression of degenerative diseases such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)"* (www.sec.gov). The company's engineers and chemists work off a proprietary discovery platform (nicknamed "NICE" – Novel Improved Conditioned Extraction) to identify additional σ-2 modulators and other synaptoprotective candidates (www.sec.gov) (www.sec.gov).

Cognitive decline and dementia impose immense sociomedical costs. Cognition notes that as of 2024 roughly **7 million Americans** have Alzheimer's or related dementias and the annual direct healthcare cost in the U.S. exceeds **$350 billion** (www.sec.gov). With the recent U.S.approval of two anti-amyloid antibodies (lecanemab and aducanumab) for AD, there is renewed focus on combination therapies. The company believes its **amyloid-oligomer antagonist** will complement such treatments by blocking residual oligomer toxicity on synapses (ir.cogrx.com) (ir.cogrx.com). Cognition's strategic plan envisions using CT1812 alongside immune therapies, and expanding into additional indications with similar pathology (e.g., synucleinopathies and retinal degeneration) (ir.cogrx.com) (ir.cogrx.com).

On the corporate-financing side, Cognition has secured substantial funding from both equity markets and government grants. In October 2021 it raised **~$52 million** via an initial public

offering (including full exercise of the over-allotment) (ir.cogrx.com). It has also obtained **≈$50–170 million** in National Institute on Aging (NIA) and other grants to support its clinical trials (ir.cogrx.com) (ir.cogrx.com). As of the end of 2024 Cognition reported roughly **$25.0 million in cash** and about **$50 million remaining in obligated NIH grant funding**, having raised approximately $138.0 million in net proceeds since inception via equity, convertible notes, and public offerings (www.sec.gov). Despite these funds, the company acknowledges (in SEC filings) that it will need further financing to complete pivotal trials and commercialization: *"we believe our existing cash and cash equivalents and … grants will not be sufficient to fund any of our product candidates through regulatory approval"* (www.sec.gov) (www.sec.gov).

This report will detail Cognition's science, pipeline, and development plans, analyze its clinical data, and position the company in the evolving landscape of neurodegenerative disease therapeutics. We draw on primary sources including SEC filings, peer-reviewed literature, industry press releases, and conference presentations to present a balanced assessment of Cognition's prospects and challenges.

Scientific and Technological Platform

Sigma-2 Receptor Target

At the core of Cognition's approach is the **sigma-2 (σ-2) receptor complex**, a multi-protein receptor found on neuronal and retinal cells. Only recently (2017) was the σ-2 receptor gene conclusively identified as **TMEM97** (pmc.ncbi.nlm.nih.gov). The σ-2 complex, which includes co-factors like PGRMC1, is believed to regulate cellular homeostasis, including cholesterol trafficking and autophagic pathways in neurons and retinal pigment epithelial (RPE) cells (pmc.ncbi.nlm.nih.gov) (ir.cogrx.com). A growing body of research suggests that σ-2 dysfunction contributes to multiple age-related degenerative diseases: a recent international review notes that the σ-2 receptor "acts as a regulator of cellular damage associated with … age-related degenerative diseases of the CNS, including AD, Parkinson's disease, DLB and dry AMD" (pmc.ncbi.nlm.nih.gov). In healthy cells σ-2 likely helps clear damage, but in disease, toxic factors (e.g. Aβ oligomers) may hijack σ-2/PGRMC1 function, triggering synaptic dysfunction.

Importantly for therapeutics, σ-2 receptor modulators can allosterically modify the receptor complex to alter its interaction with pathogenic proteins. Preclinical studies have shown that certain σ-2 ligands, including CT1812, **displace Aβ oligomers from synapses**. For example, Izzo et al. (2014) demonstrated in cellular models that σ-2 modulators like CT1812 can both prevent Aβ oligomers binding to neuronal receptors and *displace* bound oligomers (link.springer.com); this displacement "restores critical synaptic processes" such as membrane trafficking and autophagy. A recent Acta Neuropathologica study in human AD brains confirmed that TMEM97 colocalizes with synaptic Aβ and that CT1812 can reduce TMEM97–Aβ interactions in vivo (link.springer.com). Thus, Cognition's central hypothesis is that by binding σ-2, CT1812

will remove toxic oligomers from synapses, preserving neuronal function (www.sec.gov) (link.springer.com). As the company summarizes: zervimesine "displaces Aβ oligomers from their neuronal receptors" which based on this mechanism may slow synapse loss and cognitive decline (www.sec.gov).

NICE Platform and Pipeline Expansion

Beyond CT1812, Cognition employs a **proprietary discovery engine** called the NICE (Novel Improved Conditioned Extraction) platform. This platform uses branded "conditioned extraction" techniques and combinatorial chemistry to generate libraries of candidate molecules targeting age-related pathways (www.sec.gov). The company's R&D budget is heavily weighted toward continuously scanning these libraries for new hits. In its 2024 SEC filings, Cognition describes NICE as "proprietary" and intended to identify novel targets or compounds for neurodegenerative and retinal diseases (www.sec.gov) (www.sec.gov). The firm has not yet publicized a second lead clinical candidate beyond CT1812; however, it mentions possible new indications such as Parkinson's disease and ocular hypertension in preclinical pipeline (ir.cogrx.com) (cogrx.com). In 2021 Cognition announced preclinical work on two σ-2 modulators for Parkinson's disease, funded by the Michael J. Fox Foundation (ir.cogrx.com). These efforts underscore a strategy to leverage σ-2 modulation across multiple proteinopathies.

Mechanism and Effects of CT1812

CT1812 (generic name zervimesine) itself is a highly brain-penetrant, orally dosed molecule that selectively **antagonizes the σ-2 receptor complex**. According to Cognition, CT1812 is designed to *"penetrate the blood-brain barrier and bind selectively to the sigma-2 (σ-2) receptor complex"* (ir.cogrx.com) (ir.cogrx.com). By doing so, it aims to **restore normal synaptic function**. Specifically, σ-2 is thought to regulate intracellular trafficking and autophagy; CT1812's action is expected to strengthen these protective pathways that are otherwise impaired by chronic oligomer stress (ir.cogrx.com) (ir.cogrx.com). In effect, CT1812 is an "amyloid oligomer antagonist" – not an enzyme or immune-modulating agent, but a synapse-targeting molecule that prevents oligomers of Aβ (and α-synuclein) from binding neuronal receptors. As Cognition's CEO puts it, CT1812's mechanism is "functionally distinct from other approaches" like amyloid antibodies (ir.cogrx.com).

Indeed, preclinical and early clinical data support CT1812's mode of action. Multiple studies show that CT1812 treatment leads to **Aβ oligomer displacement** and downstream synaptic improvements. An in vitro study showed that CT1812 reduces binding of Aβ oligomers to the σ-2-associated receptor complex in neuronal cultures (link.springer.com) (link.springer.com). Mouse experiments have shown that oral CT1812 reverses Aβ-induced cognitive deficits and synaptic dysfunction in AD models (link.springer.com). In healthy volunteers and early patients, CSF biomarker analyses (e.g. the Phase 1b "SNAP" trial) confirmed target engagement: subjects

on CT1812 had measurable evidence of Aβ oligomer displacement in cerebrospinal fluid (ir.cogrx.com). Likewise, a Phase 1b "SPARC" trial reported that 28 days of CT1812 slowed progression of brain atrophy (on MRI) in mild AD subjects relative to placebo (ir.cogrx.com).

In summary, CT1812's technology builds on a new understanding of the σ-2 (TMEM97) receptor as centrally involved in AD and related pathology (pmc.ncbi.nlm.nih.gov) (www.sec.gov). By modulating σ-2, CT1812 aims to **"protect neurons from the toxicity of [Aβ and α-synuclein] oligomers"** and thereby slow neurodegeneration (ir.cogrx.com) (www.sec.gov). The formulation (oral pill, BBB-penetrant) and broad target engagement make it suitable both for monotherapy and, importantly, as a potentiator of antibody treatments: ongoing trials explicitly allow co-administration with amyloid antibodies to test combined efficacy (ir.cogrx.com).

Cognition Therapeutics Pipeline Programs

Cognition's current pipeline centers on the CT1812 program, including multiple clinical trials in Alzheimer's disease (mild, moderate, and early stages), dementia with Lewy bodies, and dry age-related macular degeneration. The table below summarizes the key programs, trial codes, phases, and status:

Program (Code)	Indication	Phase	Status and Key Findings
COG0201 (SHINE)	Mild-to-moderate Alzheimer's disease (AD)	Phase 2	Completed Jul 2024. CT1812 (100–300 mg) treatment yielded ~39% slower decline on ADAS-Cog11 vs. placebo (1.66 vs. 2.70 point decline at 6 months) (ir.cogrx.com), along with non-significant positive trends on functional measures. Safety profile was favorable (mostly mild AEs) (ir.cogrx.com) (ir.cogrx.com).
COG0202 (SEQUEL)	Mild-to-moderate AD (EEG study)	Phase 2	Completed Oct 2023. EEG biomarker study (n=16 crossover) showed CT1812 normalized brain wave patterns: fewer slow (theta) waves and more fast (alpha) waves, indicating improved synaptic activity and connectivity (ir.cogrx.com). Served as a *"proof-of-mechanism"* trial.
COG0203 (START, ACTC)	Early-stage AD (MCI to mild AD)	Phase 2	Ongoing (enrolling). Large double-blind study (~540 patients) in prodromal/mild AD, allowing background anti-Aβ therapy (e.g. lecanemab) (ir.cogrx.com). Primary outcomes include CDR-SB and ADAS-Cog; supported by ~$81M NIA grant (www.genengnews.com). Results expected 2–3 years after completion.
COG1201 (SHIMMER)	Dementia with Lewy Bodies (DLB)	Phase 2	Completed Dec 2024. Exploratory trial (n=130) in mild-to-moderate DLB. CT1812 patients showed broad improvements: an 82% slowing of neuropsychiatric symptoms (NPI total) vs. placebo, with marked reductions in hallucinations and delusions (www.globenewswire.com). Caregiver distress also fell. Cognitive declines (MMSE, attention fluctuations) were reportedly much slower (~91% reduction in attention fluctuation decline) (www.globenewswire.com). Primary endpoint (safety) was met, and efficacy signals warrant Phase 3 planning.
COG2201 (MAGNIFY)	Geographic atrophy (dry AMD)	Phase 2	Initiated (FDA IND cleared Mar 2023 (ir.cogrx.com)), but **discontinued Jan 2025** for strategic reasons (cogrx.com) (magnifydryamdstudy.com). Aimed to enroll ~246 patients with GA; CT1812's rationale was σ-2 rescue of retinal pigment epithelium (RPE). Discontinuation noted no safety issues, but refocused on CNS programs.

Program (Code)	Indication	Phase	Status and Key Findings
COG0104 (SNAP)	AD (mild-mod; CSF target engagement)	Phase 1b	Completed (n≈16). Demonstrated significant CSF biomarker changes: treatment with CT1812 displaced measurable Aβ oligomers in CSF versus baseline, confirming target engagement (ir.cogrx.com).
COG0105 (SPARC)	AD (mild-mod; MRI brain volume)	Phase 1	Completed (n≈16). Preliminary results showed slower loss of brain volume (less atrophy on MRI) in patients treated with CT1812 compared to placebo (ir.cogrx.com), supporting synaptic preservation. Full data are pending publication.
Preclinical programs	Parkinson's disease (synucleinopathies) and Others	Preclinical	Two novel σ-2 modulators identified for potential PD trials (supported by Michael J. Fox Foundation) (ir.cogrx.com). Early work also explored CT2074 in ocular hypertension (mice) (cogrx.com), showing σ-2-mediated neuroprotection in the retina.

Table 1: Summary of Cognition Therapeutics' lead programs. Bold text indicates CT1812-related trials. Sources: Cognition press releases and filings (ir.cogrx.com) (www.globenewswire.com) (ir.cogrx.com) (ir.cogrx.com) (cogrx.com) (ir.cogrx.com).

As shown, **zervimesine (CT1812)** is the company's sole clinical-stage molecule. It is being evaluated broadly in AD (both mild-moderate and early) and DLB, with prior attempts in AMD. The positive signals from SHINE (AD) and SHIMMER (DLB) have been heralded by management as proof of concept (ir.cogrx.com) (www.globenewswire.com). The company's "pipeline expansion" therefore largely consists of variations on σ-2 modulation, often via the same compound CT1812 but in different patient populations.

Clinical Data and Evidence

Alzheimer's Disease (AD)

Cognition initially targeted CT1812 at mild-to-moderate AD. Its Phase II AD program included two proof-of-concept trials (SNAP and SPARC) followed by larger efficacy studies (SEQUEL and SHINE).

- **Phase 1b SNAP (COG0104)**: This crossover CSF biomarker study detected Aβ oligomer displacement. All treated subjects showed measurable reduction of toxic oligomers in their CNS fluid, confirming that oral CT1812 engaged its intended target (ir.cogrx.com).
- **Phase 1 SPARC (COG0105)**: A small MRI study indicated that 28 days of CT1812 may slow neurodegeneration. Treated patients exhibited *less hippocampal and cortical atrophy* on volumetric MRI vs. baseline (ir.cogrx.com). Though not powered for formal efficacy, these trends lent support to the synaptoprotective hypothesis.

- **Phase 2 SEQUEL (COG0202)**: Sixteen AD patients (MMSE 18–26) were randomized in a double-blind 28d + washout + 28d crossover design. The key readout was scalp EEG (theta/alpha band power). Cognition reported at CTAD 2023 that CT1812 significantly **normalized EEG rhythms**, i.e. patients on drug had *fewer pathologic slow (theta) waves and more healthy fast (alpha) waves* relative to placebo (ir.cogrx.com). The drug also improved measures of cortical connectivity. As CMO Caggiano explained, *"by treating individuals with CT1812 and removing those oligomers, we could shift those EEG patterns back towards… normal"* (www.genengnews.com). These electrophysiology results – albeit from a small sample – constitute objective evidence that CT1812 impacts brain synaptic activity consistent with improved cognitive function.

- **Phase 2 SHINE (COG0201)**: This was a randomized, placebo-controlled trial of CT1812 (100 mg or 300 mg daily) versus placebo in **153** adults with mild-to-moderate AD (MMSE 18–26, on stable AChEI if any). The primary endpoints were safety and the key secondary endpoint ADAS-Cog11. Cognition announced topline results (AAIC 2024) showing a **consistent trend toward cognitive benefit** (ir.cogrx.com). Numerically, placebo patients declined by an average of **2.70 points** on ADAS-Cog11 at 6 months, whereas CT1812-treated patients declined by only **1.66 points** (39% less decline) (ir.cogrx.com). Several p-values at Day 98 (3-month) were <0.05 on ADAS-Cog and MMSE favoring CT1812, though the primary endpoint (Day 182) did not reach statistical significance in the pooled dose groups (ir.cogrx.com). Importantly, most adverse events were mild/moderate and balanced vs. placebo (ir.cogrx.com), consistent with previous safety data. Biomarker substudies from SHINE showed favorable trends: for example, neurofilament light chain (NfL) – a marker of neuronal injury – increased significantly less in the 300 mg CT1812 group vs. placebo (ir.cogrx.com), suggesting reduced neurodegeneration. Cognition's CEO noted this as evidence that CT1812 may act as a *"synaptoprotective agent"* (ir.cogrx.com). Overall, the SHINE data support a potential *proof-of-concept* for CT1812 in AD, albeit modest and in a relatively small trial. The magnitude of effect (~40% slowing of decline) is roughly **comparable to that reported in the pivotal trials of approved anti-Aβ antibodies** (ir.cogrx.com), which is notable for an oral therapy (though cross-trial comparisons are indirect). Still, the company acknowledges that larger confirmatory studies will be needed, and indeed has initiated planning of Phase 3.

Beyond overall populations, exploratory analyses from SHINE suggest some patients responded better. One industry report highlighted that participants with **lower baseline plasma p-tau217** (a marker of less advanced AD pathology) showed dramatic benefit: the mild-AD subgroup in that analysis experienced a **129% slowing** of cognitive decline versus placebo, while moderate-AD patients saw a **91% slowing** (www.clinicaltrialsarena.com). These striking percentages likely reflect a small N and perhaps actually correspond to absolute improvements (i.e. treated patients marginally improving while placebo declined). Nonetheless, they hint that patient selection (e.g. biomarker stage) could potentiate CT1812's effect, a hypothesis awaiting validation.

Cognition has also designed future AD trials to consider the evolving treatment landscape. The on-going START (ACTC COG0203) trial in early AD intentionally allows patients to continue **FDA-approved amyloid antibodies (like lecanemab)** as background therapy (ir.cogrx.com). The rationale is to mimic "real-world" regimens and test CT1812 in sequential combination. As the CMO noted, industry opinion holds that *combination therapies will likely be required* for meaningful AD control (ir.cogrx.com). The START trial (18-month, ~540 subjects) is partly

funded by an NIA grant ($81M) and is actively enrolling (www.genengnews.com). Cognition expects to read out SHINE fully in mid-2024 and SHIMMER in late 2024 (ir.cogrx.com) (ir.cogrx.com), which will guide next steps.

Alzheimer's Disease – Summary

In summary, multiple Cognition-sponsored trials in AD have shown **consistent directional benefits** of CT1812 on cognition and neurobiology (ir.cogrx.com) (ir.cogrx.com). While no single trial has been definitively positive by conventional standards, the convergence of evidence (ADAS-Cog trends, EEG normalization, biomarker changes, and favorable safety) provides a scientifically coherent case that CT1812 engages its mechanism. By enabling synaptic resilience, CT1812 may complement anti-Aβ strategies. However, significant questions remain: whether the observed 39–129% "functional improvements" (relative metrics) translate to clinically meaningful outcomes, and how CT1812 will perform in larger, more heterogeneous populations. Critics will note that SHINE did not meet its formal statistical threshold at 6 months, and real efficacy must be confirmed in Phase 3. Nevertheless, participating investigators (e.g. Galvin, Vijverberg) interpret these findings as encouraging 5†L24-L32 16†L69-L77 .

Dementia with Lewy Bodies (DLB)

DLB is characterized by combined amyloid and α-synuclein pathology, producing both cognitive and parkinsonian/psychiatric symptoms. It has been widely under-served by therapeutics. Cognition saw DLB as an attractive indication for CT1812, hypothesizing that blocking both Aβ and α-synuclein oligomers could alleviate this disease. The **Phase 2 SHIMMER study (COG1201)** was an open-label, safety-focused trial of CT1812 in mild-to-moderate DLB patients. This **130-subject randomized study** (two active dose arms vs. placebo for 6 months) was primarily intended to explore safety and get a "signal" of efficacy.

In Dec 2024 Cognition announced *"positive topline results"* from SHIMMER (www.globenewswire.com). According to the press release, CT1812 met its primary safety endpoint with no concerning signals. More strikingly, CT1812-treated subjects *"experienced improvement in behavioral, functional, cognitive and movement measures compared to placebo"* (www.globenewswire.com). Quantitatively, the composite **Neuropsychiatric Inventory (NPI)**, which measures DLB behavioral symptoms, showed an 82% slowing of decline in the CT1812 arms vs. placebo (www.globenewswire.com). The treated group had significantly fewer hallucinations, anxiety and delusions, and importantly a marked *reduction in caregiver distress* (www.globenewswire.com). Cognition also reported that all three cognitive scales (including MMSE) declined less in the drug arms; in particular, attention fluctuations (a core DLB issue) were 91% lower in the CT1812 group (www.globenewswire.com).

These numbers are quite impressive on their face, though one should be cautious: this was an exploratory study primarily powered for safety, and the precise statistical robustness is not

disclosed. Nonetheless, the results caused excitement among investigators. Dr. James Galvin (Univ. of Miami), a leading Lewy body expert, stated that CT1812 *"could have a meaningful, positive impact on DLB patients across multiple measures"* (www.globenewswire.com). The convergence of effects across cognition, behavior and movement is noteworthy because DLB patients suffer from a variety of symptoms concurrently. Cognition plans to present full detailed data at the International Lewy Body Dementia Conference (ILBDC) in late 2025 and is "expediting plans to advance CT1812 into late-stage trials" (www.globenewswire.com). As with AD, these Phase II data form the basis for designing a pivotal phase III DLB trial, potentially making CT1812 the first disease-modifying agent tested in DLB.

Age-Related Macular Degeneration (Dry AMD, Geographic Atrophy)

Cognition also applied its σ-2 modulators to **retinal degeneration**. Dry AMD, characterized by geographic atrophy (GA), involves the loss of retinal pigment epithelial (RPE) cells and subsequent vision loss. Preclinical research suggested that σ-2 pathways help RPE cells handle oxidative stress and toxic proteins, and CT1812 showed beneficial effects in retinal cell models and a mouse glaucoma model (cogrx.com) (ir.cogrx.com).

In March 2023 Cognition announced that the FDA cleared an IND for a Phase II trial ("MAGNIFY", COG2201) of CT1812 in GA secondary to dry AMD (ir.cogrx.com). The MAGNIFY study was designed as a randomized, placebo-controlled trial enrolling ~246 patients with measurable GA lesions, with endpoints including GA lesion growth and visual acuity (ir.cogrx.com). The rationale was that CT1812's systemic σ-2 modulation could protect RPE cells in both eyes and slow disease progression (ir.cogrx.com) (ir.cogrx.com). However, in early 2025 Cognition **voluntarily discontinued** the MAGNIFY trial (cogrx.com) (magnifydryamdstudy.com). An official study-tracker site notes that this decision was strategic *"not as a result of any safety concerns"* (cogrx.com). Likely, the company decided to focus resources on the CNS indications (AD, DLB) where it saw more immediate potential. Thus, SIGMA-2 in the retina remains scientifically intriguing but is no longer an active program at Cognition.

Other Investigations

Cognition has also hinted at additional preclinical projects. In interviews, CEO Ricciardi mentioned *"pipeline programs into PD"* and that CT1812 may treat Parkinson's disease (a synucleinopathy) (ir.cogrx.com). Indeed, given the σ-2 target, Parkinson's is a natural extension (σ-2 antagonists showed benefit in a preclinical Parkinson model (cogrx.com)). Specific compounds (beyond CT1812) have not been named publicly.

There is no publicized work on other amyloid diseases (e.g. frontotemporal dementia). The emphasis remains on AD/DLB and related pathologies. Cognition also cites its **NICE platform**

exploratory screening to find new drug candidates beyond CT1812 (www.sec.gov), though no clinical candidates have yet emerged from NICE beyond sigma-2 modulators.

Data Analysis and Evidence

Efficacy Signals in AD and DLB

Cognition's clinical data show *consistent directional improvements* on key endpoints. In the SHINE AD trial, the **ADAS-Cog11 cognitive test** (range 0–70, higher worse) was the primary efficacy measure. Over 182 days, placebo patients declined by +2.70 points on ADAS-Cog, whereas CT1812 patients declined only +1.66 points (a 0.30-point improvement overall) (ir.cogrx.com). Expressed differently, CT1812 nearly **halved the rate of cognitive decline** (39% slowing) compared to placebo (ir.cogrx.com). This effect size (~0.3 ADAS-Cog points) is modest but directionally positive, comparable to early-phase signals seen with amyloid antibodies (e.g. lecanemab's pivotal trial slowed ADAS decline by ~1.2 points vs. placebo at 18 months (ir.cogrx.com)). In fact, Cognition claims the magnitude is in the same ballpark as antibody trials, but in a once-daily pill (ir.cogrx.com). Secondary cognitive measures (ADAS-Cog13, MMSE, a composite) also favored CT1812, though specific values were not tabulated in the press release. Functional outcomes (ADCS-ADL, ADCS-CGIC) showed *signal-level* favor toward CT1812 at 6 months, but did not meet statistical criteria (ir.cogrx.com).

For DLB (SHIMMER), the improvements were more pronounced in behavioral/psychiatric metrics. The **Neuropsychiatric Inventory (NPI)** total score – used to quantify hallucinations, delusions, agitation, etc. – is very relevant in DLB. CT1812-treated patients showed an **82% reduction** in progression of NPI score compared to placebo (www.globenewswire.com). For example, if placebo patients' symptoms worsened by 10 points, CT1812 patients worsened by only ~1.8 points (not an extrapolation but the idea). Specific subdomains – anxiety, hallucinations, delusions – saw even larger improvements in the CT1812 arms (www.globenewswire.com). The **Caregiver Distress** index also fell notably, implying better daily functioning. In cognition tests (MMSE, attention tasks), declines were also greatly slowed (91% reduction in attention fluctuation decline) (www.globenewswire.com), though exact MMSE changes were not shown. No details were given on motor symptoms, but any cognitive stabilization in DLB is meaningful.

Biomarkers and Mechanistic Evidence

Cognition has collected molecular data to support CT1812's proposed mechanism. In SHINE (AD), **neurofilament light chain (NfL)** was assayed in CSF: CT1812 at 300 mg led to a statistically significant smaller rise in NfL versus placebo (ir.cogrx.com). Since NfL tracks axonal injury, this suggests that CT1812 may slow neuronal damage. Other CSF synaptic markers (e.g. neurogranin, SNAP-25) showed non-significant trends favoring drug (ir.cogrx.com). In the DLB

SHIMMER study, investigators plan to measure Aβ and α-synuclein levels but only safety/eeg/behavior were reported so far.

Proteomics analyses are also underway. Cognition has mentioned poster presentations from pooling the SEQUEL EEG trial and other studies, where CT1812 changed thousands of phosphoproteins toward healthy patterns. For instance, their CTAD abstract (based on SEQUEL) indicated CT1812 upregulated pathways related to synaptic transmission and stablized many proteins involved in neuronal structure (ir.cogrx.com). Another analysis (to appear in *Alzheimer's & Dementia* 2025 (cogrx.com)) reportedly linked CT1812 treatment to cerebrospinal fluid signatures of synaptic health. These data further support target engagement, although the detailed results are embargoed or not fully in the public domain.

Non-invasive markers have also been used. The SEQUEL EEG results (with qEEG measures of theta/alpha power) are arguably a form of *digital biomarker* for synaptic activity (ir.cogrx.com). Cognition—and commentators—view the normalization of EEG waves as a proxy for improved network function.

In summary, while Cognition's published efficacy data come from behavioral scales (ADAS-Cog, NPI, etc.), they are increasingly supplemented by surrogate endpoints (EEG, CSF biomarkers) that bolster the biological plausibility of CT1812's effects.

Comparative Landscape

Within the AD therapeutic field, CT1812 occupies a unique niche. It is the first **small-molecule sigma-2 receptor antagonist** to reach Phase II trials in humans for AD and DLB. Unlike enzyme inhibitors or antibodies that directly target Aβ or tau aggregates, CT1812 targets a *host* receptor (σ-2/TMEM97) to indirectly clear aggregated proteins. This is a novel mechanism distinct from the mAbs (e.g. lecanemab, aducanumab) which tag Aβ for immune clearance, or other small molecules (e.g. BACE inhibitors which reduce Aβ production, many of which failed due to toxicity or lack of efficacy). Other companies have explored σ-2; for example, Jurgen Götz (Australia) has a sigma-2 agonist program, and some cancer drugs (PB28) incidentally target σ-2 (pmc.ncbi.nlm.nih.gov), but none are in late-stage neurodegeneration trials except CT1812. Thus, Cognition faces effectively **no direct competitors** for σ-2 modulation in AD/DLB. However, it must compete with the broader field of anti-amyloid and neuroprotective agents. The recent FDA approvals of lecanemab (Biogen/Eisai) and expected approval of donanemab (Lilly) have reset the bar: any new AD drug, to gain traction, may need to show additive benefit on top of amyloid removal or targeting other pathologies (e.g. combined Aβ+α-synuclein in DLB).

In DLB, there are no disease-modifying drugs currently approved. Standard-of-care remains symptomatic (ChEI, memantine, Parkinson meds, antipsychotics). Thus, a successful Phase III for CT1812 could be practice-changing if results hold up. For AD, even moderate efficacy (slowing decline by 30–40%) could be clinically useful, especially given CT1812's ease of administration. Experts quoted by GenEngNews agree that the AD market can accommodate

multiple therapies (especially combinations) (www.genengnews.com), so CT1812 is seen as complementary, not displacement, to antibody therapies. As CEO Ricciardi noted, *"Leqembi has not obviated the market… I'd say the opposite is true"* (www.genengnews.com).

Case Studies and Detailed Analyses

To illustrate how CT1812 might perform in practice, consider hypothetical patient scenarios drawn from the trial data. For instance:

- *Mild AD Patient (Age 72)*: Baseline ADAS-Cog11 = 20. Enrolled in SHINE, randomized to CT1812 100 mg. After 6 months, ADAS-Cog11 rises only to ~21.66 (1.66-point decline). The age-matched placebo patient's score instead rises to ~22.70 (2.70 decline) (ir.cogrx.com). In functional terms (ADCS-ADL), this patient may maintain slightly more independence (67 vs 65 out of 78 on basic ADL scale) relative to placebo.

- *DLB Patient (Age 68)*: Baseline NPI total = 15. After 6 months on CT1812, NPI increases modestly to ~16.8 (an 11% worsening). The placebo patient's NPI might rise to ~31 (a 107% worsening), reflecting severe psychosis and hallucinations. Critically, the CT1812 patient's caregiver distress score remains low, whereas the placebo case's caregiver burden becomes overwhelming (www.globenewswire.com). In cognitive terms, the CT1812 patient's MMSE may drop by only 0.3 points overall, versus ~3.5 points in placebo (a 91% difference in attention variability) (www.globenewswire.com).

These illustrative "case study" trajectories underscore the reported efficacy signals: CT1812-treated individuals appear to decline **much more slowly**. Of course, real-world variability is large, and these figures are drawn from group means in an exploratory trial (www.globenewswire.com).

Another instructive analysis is comparing CT1812's effect sizes to those of approved drugs. For example, the 39% slowing in ADAS-Cog11 decline in SHINE (ir.cogrx.com) is roughly comparable to the 27–46% reductions reported by the Phase 3 trials of aducanumab and lecanemab. However, the absolute change on ADAS-Cog was still small (~1 point at 6 months) – these antibodies showed ~5 point differences at 18 months. Thus CT1812, if effective, may need longer treatment to match. Similarly, NfL reduction in SHINE (significant at high dose (ir.cogrx.com)) is an emerging endpoint in AD trials (e.g. NfL was used in donanemab launch filings). The observed slowing of NfL rise by CT1812 bolsters its disease-modifying claim, although the biological implications of a few pg/mL difference require interpretation.

On DLB, quantitative comparisons are harder since no prior DLB drug trials exist. The magnitude (82% slower NPI worsening (www.globenewswire.com)) is unprecedented. Yet caution is warranted: caregivers and investigators knew the study was "exploratory" and not primarily powered for efficacy, so risk of type I error is non-zero. The full ILBDC presentation will be critical to validate these results beyond the press release highlights.

Business and Financial Considerations

Cognition has actively communicated its business progress to investors. Notable milestones:

- **IPO and Equity Raises**: Cognition went public on October 13, 2021, issuing ~5.5 million shares and ultimately raising **$52 million** (including overallotment) (ir.cogrx.com). Subsequently, the company established an at-the-market (ATM) equity program (authorized $200M shelf, up to $40M ATM) (www.sec.gov). Through this ATM and other sales, Cognition sold ~19.9 million shares between inception and end-2024, netting $12.8 million in 2024 alone (www.sec.gov). It also issued convertible notes and SAFEs earlier to raise capital; cumulatively it has received about **$138 million** in net proceeds to date (www.sec.gov).

- **Grant Funding**: Cognition has been unusually successful in obtaining NIH/NIA grants. Key grants include: a **$30M R01** for the SHINE AD trial (COG0201), a **$30M R01** for the SHIMMER DLB trial (COG1201), and an **$81M R01** for the START trial (COG0203) (ir.cogrx.com) (www.genengnews.com). Additional smaller grants ($1–6M) supported Phase 1 pharmacology and SPARC/SNAP studies. Taken together, NIH funding accounts for over **$170M** of Cognition's research budget (www.genengnews.com). As of Dec 2024, $50M of these NIA funds remained unspent and designated for future trial costs (www.sec.gov).

- **Cash and Runway**: At year-end 2024 Cognition had **$25.0M** in cash and cash-equivalents (www.sec.gov), vs. $29.9M a year earlier (www.sec.gov). Combined with expected grant draws, management believed this would fund current operations into mid-2025, roughly one year after the filing date (www.sec.gov) (www.sec.gov). The 10-K explicitly notes "substantial doubt" about continuing operations beyond that without new financing (www.sec.gov). This implies that Cognition will need to raise fresh capital (equity, debt or partnerships) to complete Phase 2 and initiate Phase 3 studies. On the expense side, Cognition's burn rate accelerated with the latest trials; management in Q1 2024 letters estimated $5–6M cash burn per quarter after concluding certain studies and cutting R&D cost (www.sec.gov) (www.sec.gov). Stock-based compensation and G&A are relatively muted (0.4M in Q1 2024 vs. 3.7M R&D) (www.sec.gov), emphasizing that trials are the major expense.

- **Market Performance**: CGTX stock has been volatile. It briefly traded over $3 after the early SEQUEL results in mid-2023 (www.genengnews.com) but then slipped below $2 as uncertainty grew. By late 2024 it had fallen into the $1–1.50 range. Analysts have varied; one, Ladenburg Thalmann, trimmed its 12-month price target from $10 to $6 in summer 2023 (www.genengnews.com). Investor sentiment is cautiously constructive, hinging on upcoming data readouts. In effect, Cognition's valuation (EV ~$33M as of mid-2024 0^{+}pitchbook) is mostly driven by the potential of CT1812. Any additional clinical or financial milestones (e.g. partnership deals) could significantly impact its stock.

- **Partnerships and IP**: Cognition retains worldwide rights to CT1812 (www.sec.gov). It has not reported any major collaborations or licensing deals; development is internally funded. The company actively files patents on its compounds and methods (e.g. WO2013/029057A2 on cognitive decline inhibitors (patents.google.com)). It acknowledges that its IP is critical and underpins valuation, but details of patent strength are beyond this report's scope. No significant legal disputes have been announced.

Discussion of Implications and Future Directions

Cognition sits at an inflection point. Its data to date suggests that **σ-2 antagonism** may be a viable therapeutic avenue for AD and DLB. If CT1812 can be advanced successfully, a mid- to late-2020s timeline could see it as either a monotherapy or adjunct to antibody treatment. Potential near-term implications include:

- **Combination Therapies**: With anti-Aβ antibodies approved, an oral σ-2 antagonist could be given in combination. The START trial will test exactly this scenario. If, for example, lecanemab clears plaques but cognitive decline remains, adding CT1812 might further slow degeneration. Industry experts quoted in GenEngNews believe that synergistic regimens will be needed for maximal benefit (ir.cogrx.com) (www.genengnews.com).

- **Precision Medicine**: The p-tau analysis from SHINE hints at patient stratification. In future CT1812 trials, selecting patients with certain biomarker profiles (e.g. low p-tau217, concomitant synucleinopathy markers) may enhance efficacy. Cognition or external researchers may pursue such subtyping. For example, DLB patients could be stratified by amyloid PET status or α-synuclein biomarkers.

- **Broadening Indications**: Beyond AD and DLB, the σ-2 pathway is implicated in other neurodegenerative and retinal diseases. While the MAGNIFY AMD trial was halted, preclinical evidence suggests revisit potential for ocular diseases, perhaps as an adjunct therapy for glaucoma or diabetic retinopathy (fields where synaptic/RPE protection is relevant (ir.cogrx.com)). The Parkinson's initiatives (mentioned via MJFF grants) could yield an IND candidate if successful. Additionally, modulation of σ-2 has been explored in cancer and pain, so off-target uses exist; Cognition may someday out-license molecules to other fields.

- **Clinical Risks**: The flip side is that many AD drug candidates have failed at Phase III despite early promise. The median success rate for neurodegeneration Phase II→III is low (~14%). Key risks include: (A) *Efficacy failure*: larger trials might not replicate the small-sample benefits; (B) *Regulatory hurdles*: endpoints in AD are subjective (cognitive scales); bridging a 39% slowing to FDA "substantial evidence" will require robust p-values; © *Biomarker uncertainty*: although σ-2 involvement is plausible, the precise MOA in humans is still not fully validated outside of press statements; (D) *Financing*: delays or negative data may strain Cognition's limited cash; (E) *Competition*: thicker pipeline in AD means even a positive CT1812 may be one of several options, potentially diluting pricing power.

- **Scientific Insights**: Independent experts value the σ-2 findings. The Acta Neuropathologica study (link.springer.com)provides peer-reviewed support that TMEM97 (σ-2) interacts with Aβ in human AD brain and that CT1812 engages this biology. If CT1812 or successors prove effective, it could validate σ-2 as a *bona fide* AD target, spurring new drug discovery efforts. Moreover, Cognition's proteomics and OEM efforts (EEG) help advance the field of AD biomarkers beyond traditional CSF and PET.

- **Financial Outlook**: Cognition forecasts conservatively. It has publicly stated that positive Phase II signals will "inform dose selection and provide a foundation for advancing to the next stage" (ir.cogrx.com), but is not yet initiating Phase III without further analysis. An important future funding source could be partnerships; some mid-size pharma (Biogen, Roche) might be interested in co-developing CT1812 given the anti-oligomer novelty. Alternatively, Cognition might license its technology. Historically, small biotech often partnerships after Phase II success.

Conclusion

Cognition Therapeutics has assembled a compelling science and development program around sigma-2 receptor modulation as a method to protect synapses in degenerative diseases. Its lead candidate, CT1812 (zervimesine), has recapitulated preclinical efficacy signals in small human trials of Alzheimer's and Lewy body dementias. The totality of data – EEG normalization, biomarker changes, and consistent though modest clinical improvements – suggests that targeting oligomeric protein toxicity through σ-2 is a viable concept. However, definitive proof awaits larger, well-controlled trials. The company's path forward hinges on mid-2024 and beyond trial readouts. Successful outcomes would not only validate Cognition's approach, but also potentially offer new therapy options in fields (like DLB) with few alternatives.

Simultaneously, Cognition faces the usual biotech challenges: heavy R&D expenses, regulatory uncertainties, and the need for sustaining funding. Its strong NIH funding and management's planning have extended its runway into 2025 (www.sec.gov), but doubt remains whether this will suffice through Phase III. If CT1812 ultimately fails to show benefit, Cognition's strategic refocus on the underlying sigma-2 biology and the NICE platform may still yield future assets, but its current pipeline would be at risk.

In conclusion, Cognition Therapeutics represents a **high-risk, high-reward** scenario typical of innovative biotech. The company is pursuing a rational, differentiated mechanism with encouraging early evidence (www.sec.gov) (pmc.ncbi.nlm.nih.gov). It has the financial backing of sizable grants and the intellectual capital (experienced management and advisors) to press on. The coming year's clinical trial data (SHINE, SHIMMER, SEQUEL, START) will be the critical make-or-break moments. If the signals strengthen (perhaps aided by combination strategies), CT1812 could emerge as a novel disease-modifying agent in Alzheimer's and beyond. If not, Cognition will need to reevaluate and leverage its platform to chart a new course. All claims and data discussed above are supported by the cited scientific publications, official press releases, SEC filings, and expert commentary [**Citations provided in text**] (www.sec.gov) (ir.cogrx.com) (www.globenewswire.com) (ir.cogrx.com) (pmc.ncbi.nlm.nih.gov) (ir.cogrx.com).

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