A Randomized, Double-blind, Placebo-controlled, Phase 2, Six-month Study to Evaluate the Safety, Tolerability and Exploratory Efficacy of CT1812 in Participants with Mild-to-Moderate Dementia with Lewy Bodies

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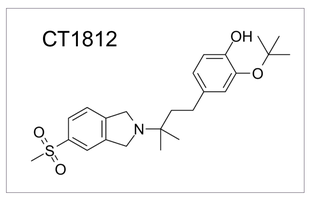
Summary: A Phase 2 proof-of-concept study in individuals with dementia with Lewy bodies (DLB), a disorder characterized by α-synuclein oligomer pathology and often concurrent Aβ pathology, is being conducted in collaboration with academic and industry organizations supported by the National Institute of Aging (R01AG071643). This study will assess whether CT1812's blockade of α-synuclein and Aβ oligomer toxicities via σ-2 receptor modulation impacts clinical endpoints in people with DLB.

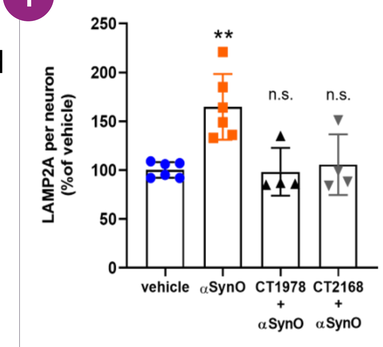
Background: CT1812 is an experimental, orally delivered, brain penetrant, small molecule therapeutic that is designed to displace toxic oligomers from neurons through modulation of the σ-2 receptor. In Alzheimer's disease clinical studies, CT1812 has been generally well tolerated with headache and nausea as the most frequent adverse events (AEs). No serious AEs have been related to CT1812 use.



CT1812 is an experimental therapeutic that is currently not approved for any indication.

Support for σ-2 Modulation in Synucleinopathies: α-synuclein oligomers have been shown to induce accumulation of LAMP2A and cause trafficking deficits in cultured neurons. Internal research has identified σ-2 receptor modulators to be effective at blocking α-synuclein oligomer-induced trafficking deficits and LAMP2A upregulation in *in vitro* models of Parkinson's and DLB (Fig 1). These results suggest that σ-2 receptor antagonists may stop α-synuclein oligomer-induced neurotoxicity.

1



σ-2 receptor antagonists rescue neuronal dysfunction induced by Parkinson's patient brain-derived α-synuclein[1].

σ-2 Interacts with Elements of the Oligomer Receptors: Prion protein is a key constituent of a receptor complex to which oligomers of α-synuclein[2,3,4] and Aβ[5,6,7] bind. These oligomer receptors interact with σ-2[8].

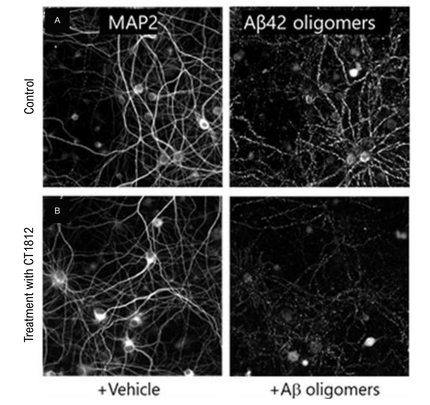
Objective: COG1201 (Fig 6) will be the first study to explore the safety, tolerability and efficacy of CT1812 in people with DLB. Exploratory biomarkers and disease pathways that may be impacted by CT1812 will also be evaluated to understand the potential of CT1812 as a novel and promising treatment approach for DLB.

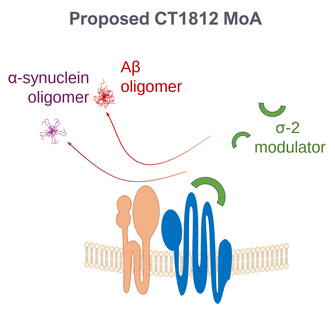
2

CT1812 Displaces Aβ / α-synuclein Oligomers *in vitro*

a

Aβ Oligomers[9]

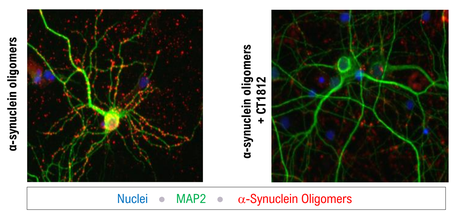




A) Aβ oligomers bind specifically & saturably to a single receptor on neurons in mature primary hippocampal and cortical neuronal cultures. B) CT1812 displaces Aβ oligomer binding when added 1hr after addition of Aβ oligomers. Scale bar = 20 microns.

b

α-synuclein Oligomers



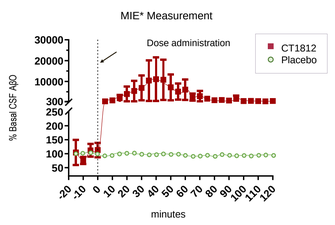
α-Synuclein oligomers (red) on primary cortical neurons in the absence (left) and presence (right) of CT1812. (data on file)

3

CT1812 Displaces Aβ Oligomers *in vivo*

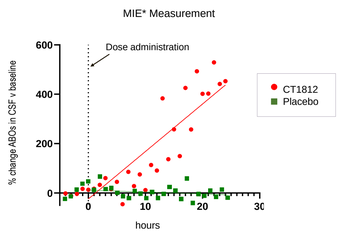
a

Alzheimer's Mice Administered CT1812 or Placebo[9]



b

Alzheimer's Subjects in SNAP Study Administered CT1812 or Placebo[10]



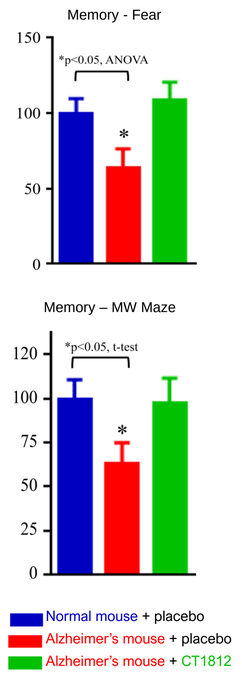
SNAP COG0104 study (NCT03522129)
funded by NIA grant 1RF1AG057780

* MIE – Microimmunoelectrode coated with oligomer-specific antibody

4

Improves Memory Function in AD Transgenic* Mice[9]

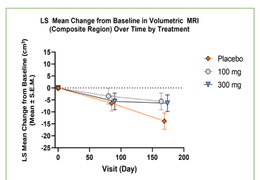
(Percent of Normal Performance)



*Thy-1 huAPPSwe/Ldn+

5

Reduces Brain Atrophy (left) and Normalizes Biomarkers[11] (right) in a Phase 2 SPARC Trial



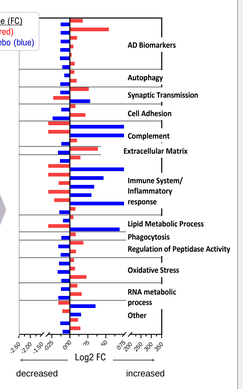
MRI Brain Volume (cm³) 6-mo change from baseline			
	CT1812 (Pooled)	Placebo	P-value vs placebo
Hippocampus	-0.09 (0.08)	-0.40 (0.11)	0.0412
Prefrontal Cortex	-0.41 (0.95)	-4.80 (1.37)	0.0125
Pericentral Cortex	0.07 (0.53)	-2.90 (0.77)	0.0032

LEFT: Trend towards preservation of brain volume (composite) in CT1812- vs placebo-treated in SPARC study.

Statistically significant ($p<0.05$) improvement in volume in three regions observed.

RIGHT: 37 proteins in CSF were significantly ($p<0.05$) normalized towards control with CT1812 compared to placebo in SPARC.

Key pathways associated with these proteins are disrupted in Alzheimer's disease, including autophagy, inflammation, synaptic function.



SPARC COG0105 study (NCT03493282)
funded by NIA grant RF1AG057553

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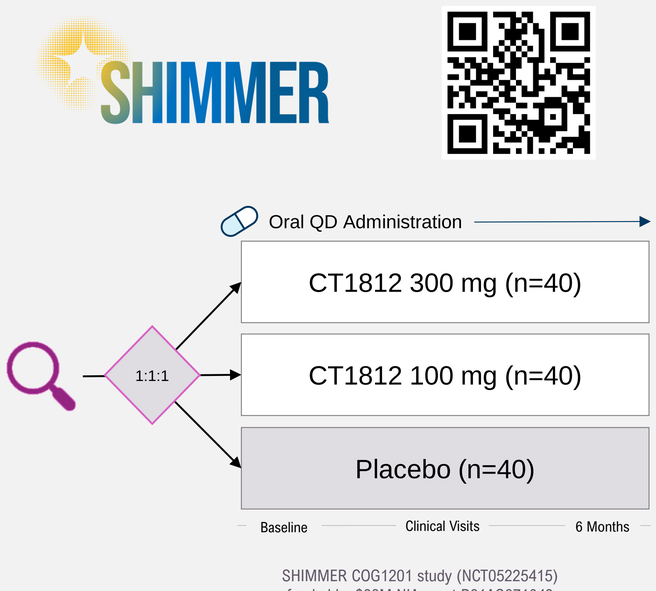

SHIMMER COG1201 study (NCT05225415)
funded by $30M NIA grant R01AG071643

FPI June 2022; enrollment ongoing with completion targeted mid-2024

Methods: This is a parallel group, randomized, double-blind, placebo-controlled study of up to 120 subjects with mild-to-moderate DLB as defined by the 4th report of the DLB Consortium. After consenting and meeting study criteria, subjects are randomized 1:1:1 to receive QD oral doses of 300 mg CT1812, 100 mg CT1812, or placebo for six months.

Key inclusion criteria:

- 50 to 85 years of age
- DLB: 4th report of DLB Consortium
- MMSE: 18-27

Key exclusion criteria:

- Comorbidities on MRI
- Parkinson's Dx or features – Hoehn Yahr stage 4 or higher

Key outcome measures:

- Montreal Cognitive Assessment (MoCA)
- Cognitive Drug Research Battery
- Clinician Assessment of Fluctuation
- Epworth Sleepiness Scale
- Unified PD Raging Scale Part III
- ADCS – Clinical Global Impression of Change (CGIC)*
- ADCS – Activities of Daily Living (ADL)
- Neuropsychiatric Inventory (NPI)
- Safety: assessed by reported adverse events, symptoms, signs and laboratory findings**

Exploratory CSF and plasma biomarkers:

- Total a-synuclein, P129
- CND alpha synuclein skin biopsy X2
- Aβ 42, Aβ 40, ptau, tTau
- Synaptic biomarkers
- Inflammatory biomarkers
- Discovery proteomics

* Modified to provide DLB-specific prompts on cognition, motor, behavioral, sleep and autonomic features[12,13]

** CT1812 has been associated with transient and mild elevations in liver enzymes without concurrent changes in bilirubin or other signs of liver injury. Liver enzymes are monitored every 4 to 6 weeks.

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