

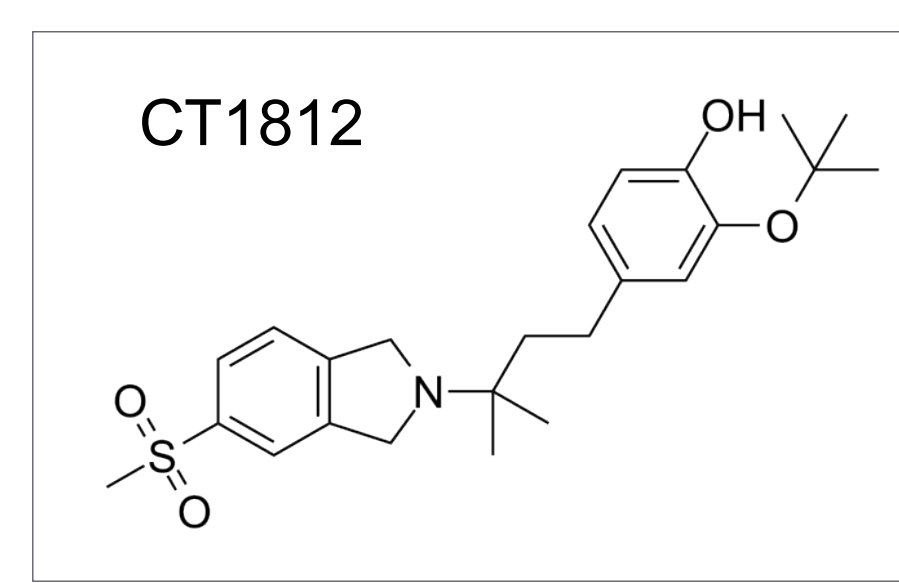
A Randomized, Double-blind, Placebo-controlled, Phase 2, Six-month Study to Evaluate the Safety, Tolerability and Exploratory Efficacy of CT1812 in Participants with Mild-to-Moderate Dementia with Lewy Bodies

Galvin JE^a, Tolea MP^a, Hamby ME^b, Grundman M^c, Caggiano AO^b

^aComprehensive Center for Brain Health, Dept of Neurology, University of Miami Miller School of Medicine, Miami, FL; ^bCognition Therapeutics Inc., Purchase, NY; ^cGlobal R&D Partners, San Diego, CA

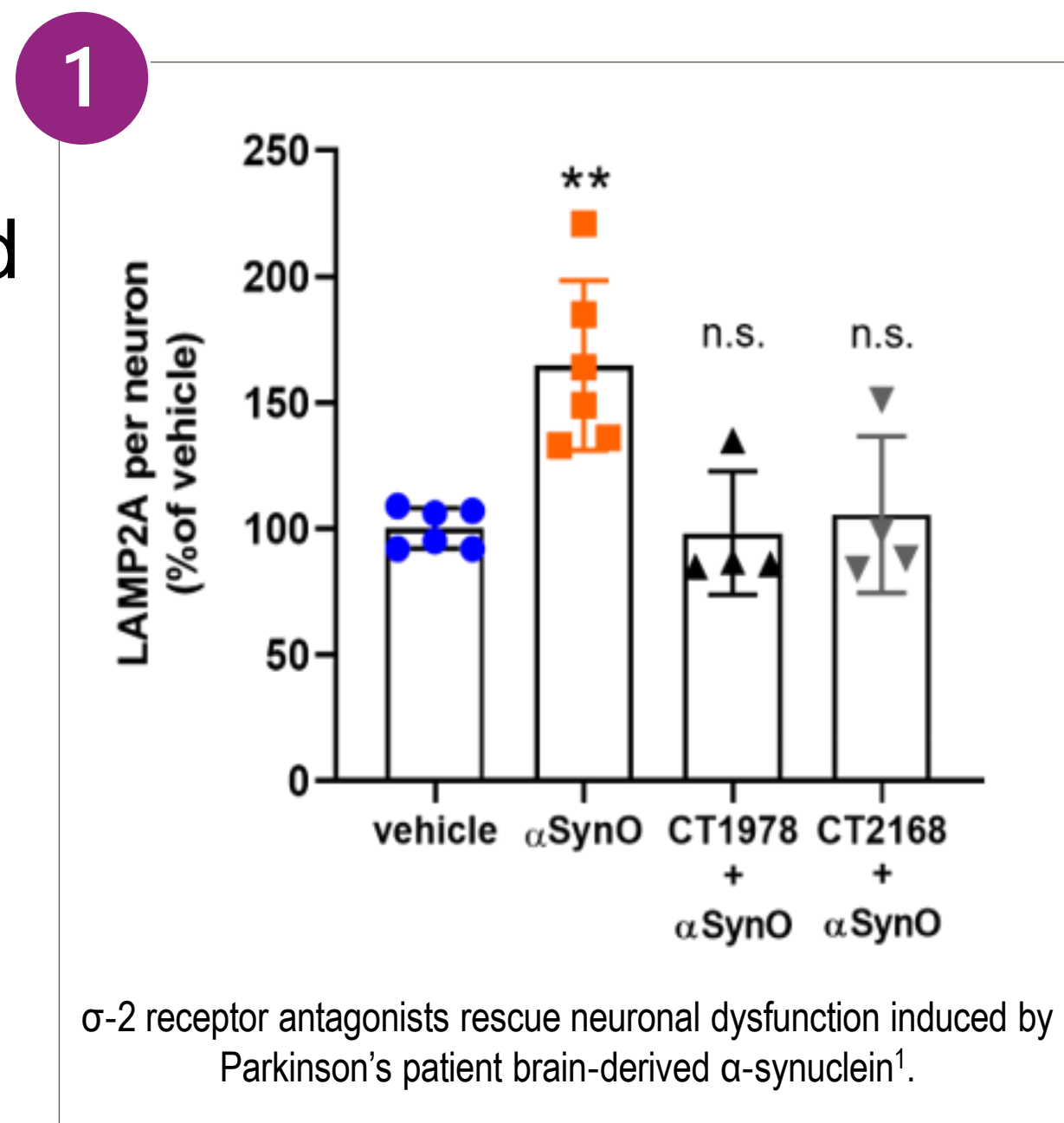
Summary: A Phase 2 proof-of-concept study in individuals with dementia with Lewy bodies (DLB), a disorder characterized by α -synuclein oligomer pathology and often concurrent A β pathology, is being conducted in collaboration with academic and industry organizations supported by the National Institute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



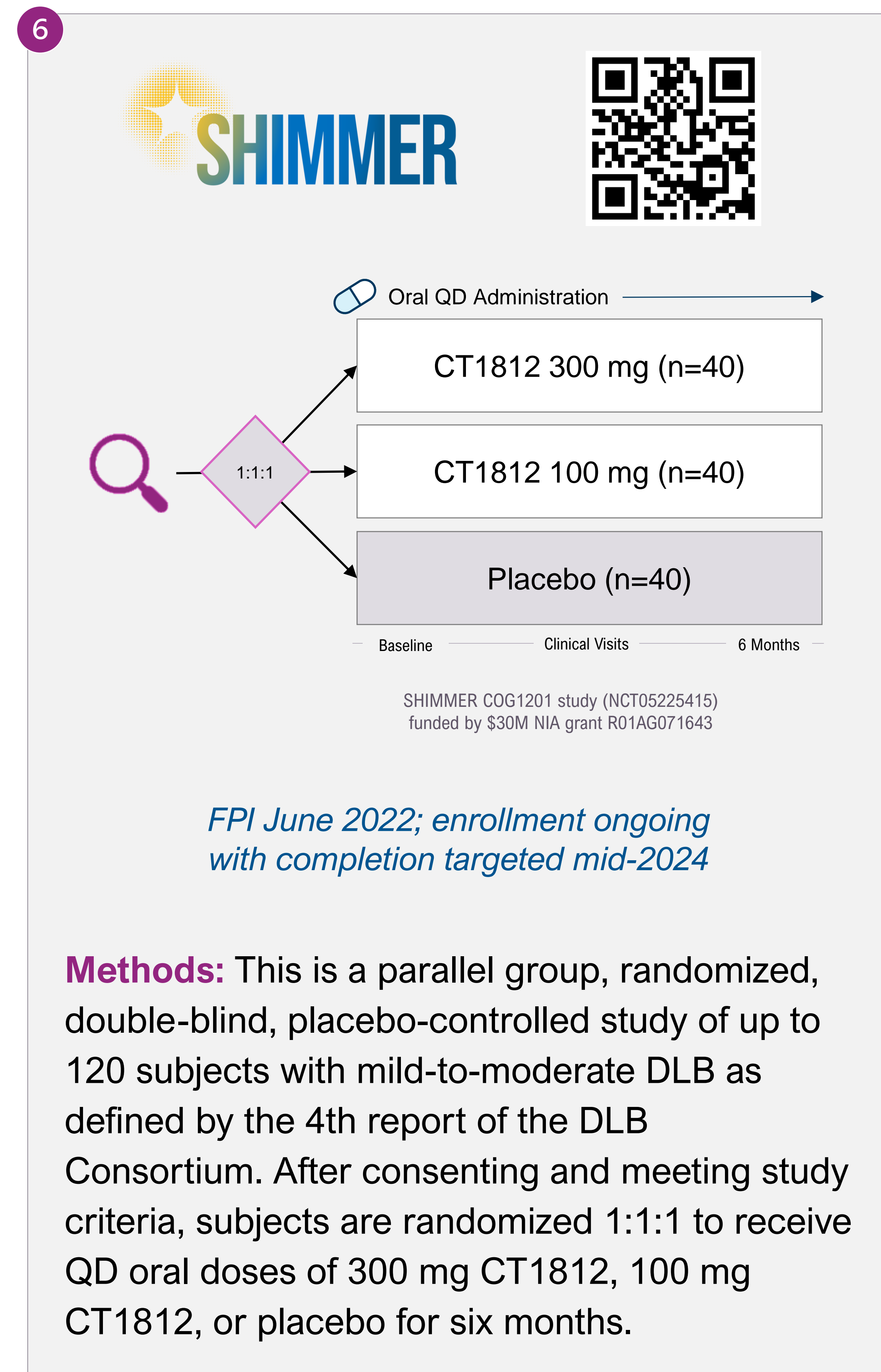
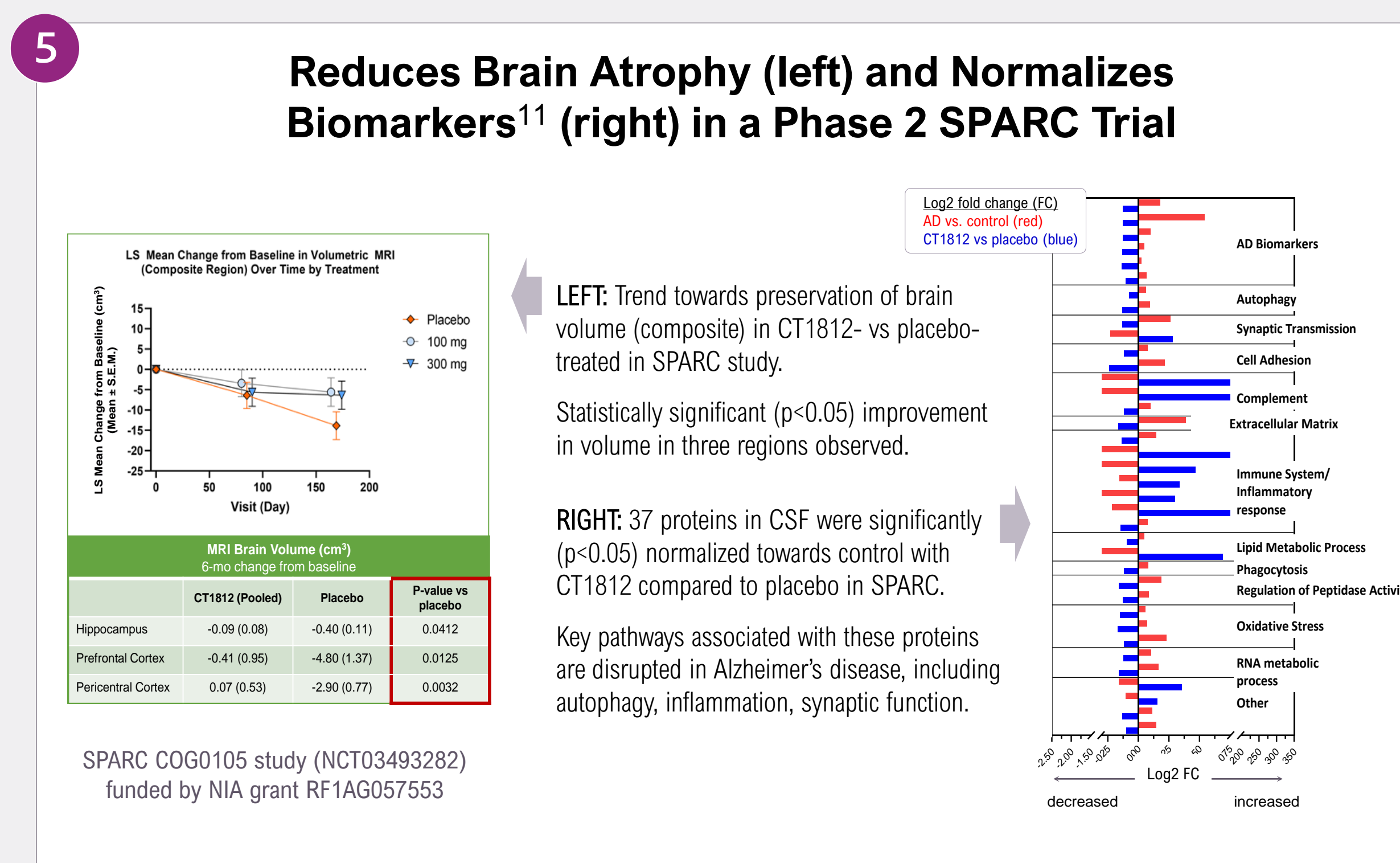
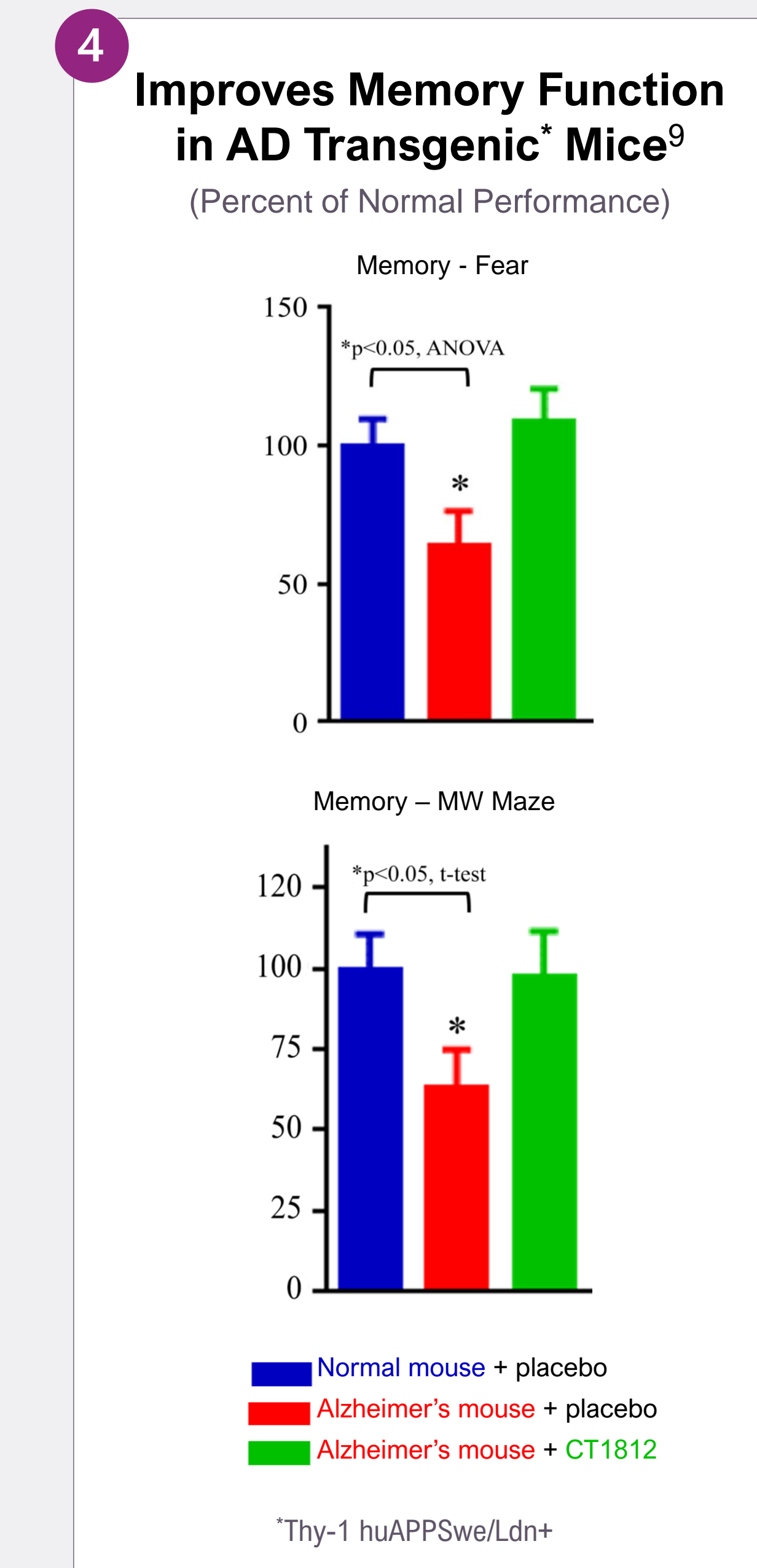
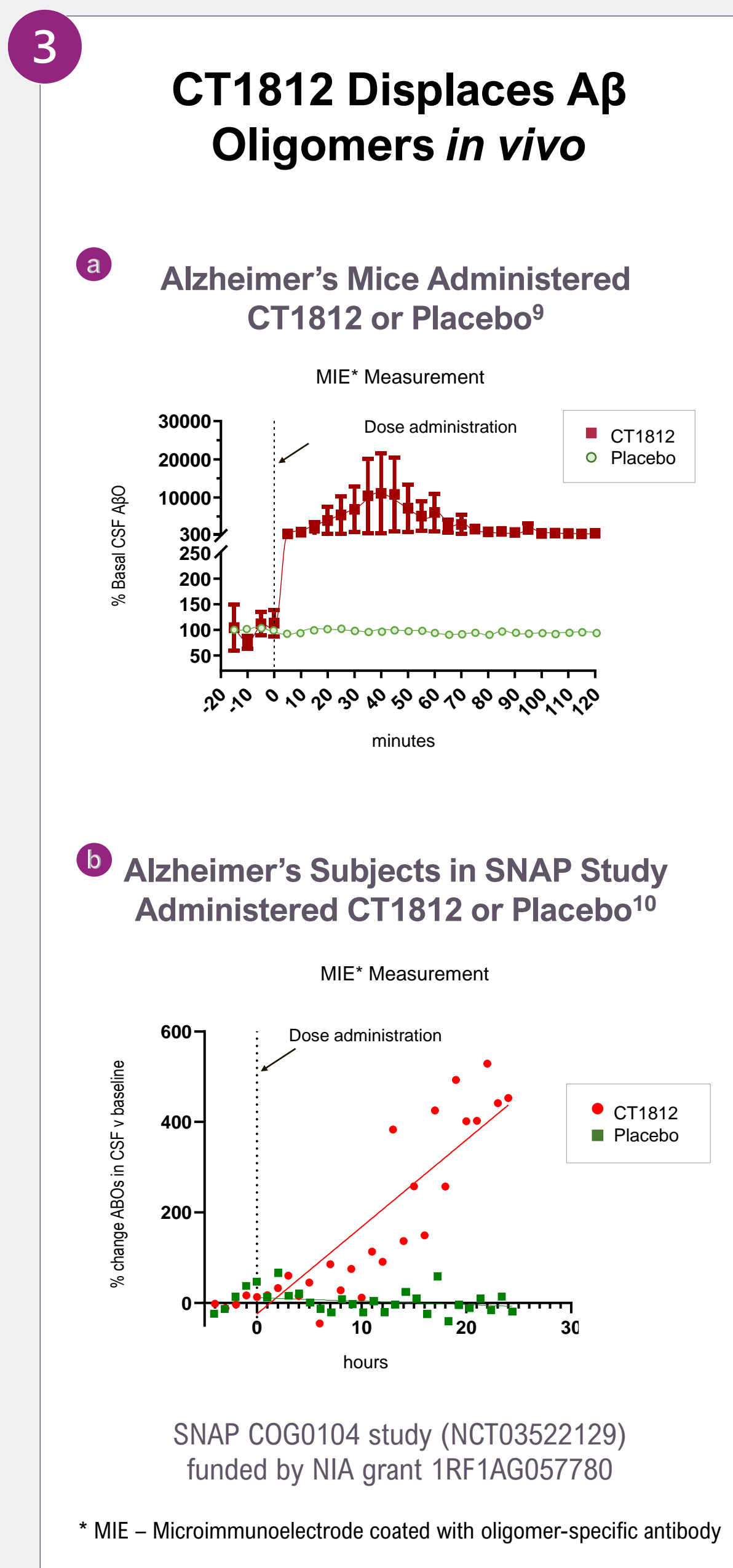
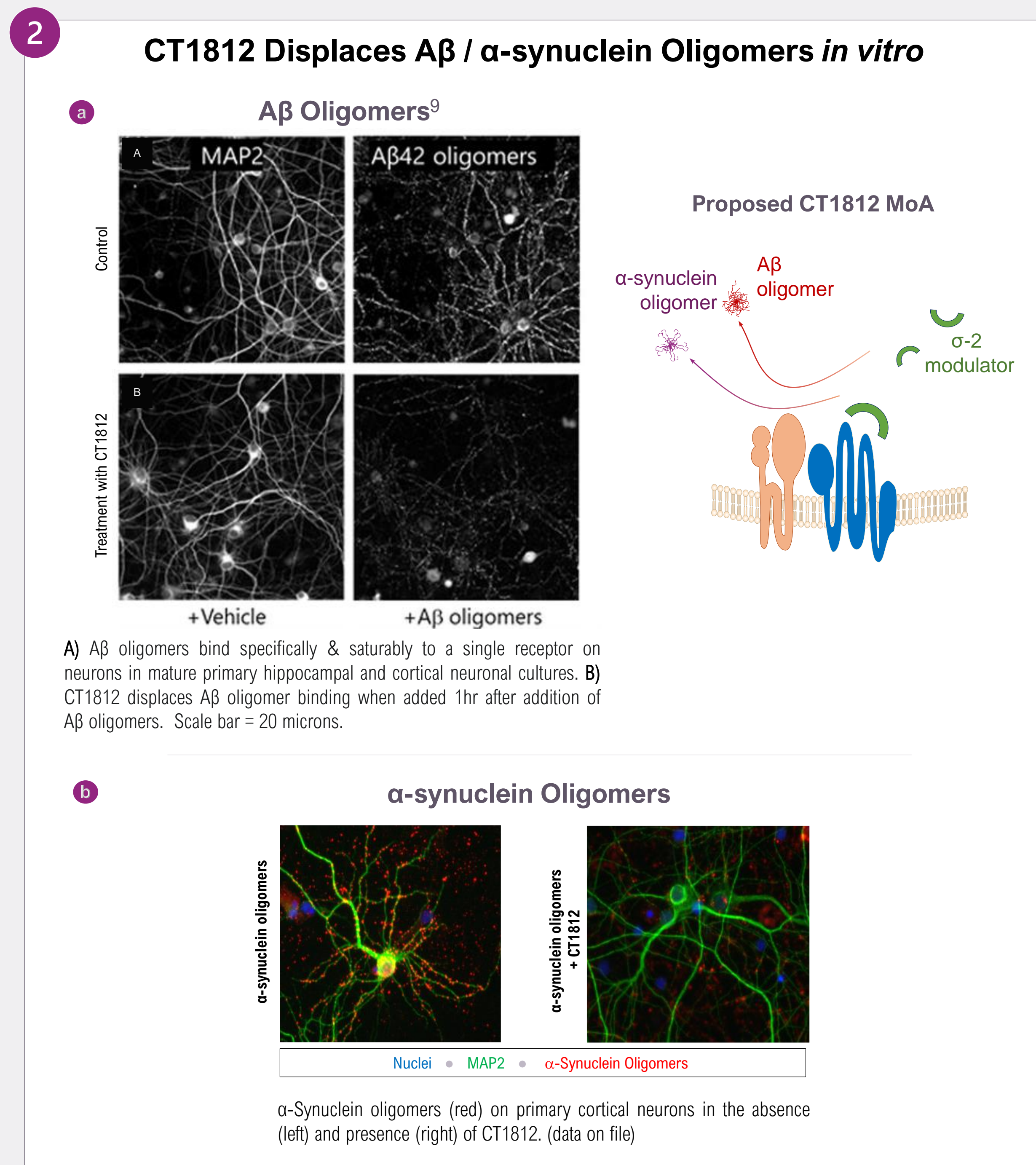
CT1812 is an experimental therapeutic that is currently not approved for any indication.

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.



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 A β ^{5,6,7} bind. These oligomer receptors interact with σ -2⁸.

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.



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 α -synuclein, P129
- Synaptic biomarkers
- CND α synuclein skin biopsy X2
- Inflammatory biomarkers
- A β 42, A β 40, ptau, tTau
- 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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