COGNITION™ Therapeutics

Targeting Amyloid Beta Oligomers:

A Disruptive Approach to the Treatment of CNS Disorders

November 2024

Forward-looking Statements

FORWARD-LOOKING STATEMENTS

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Cognition Snapshot

Successful Phase 2 AD trial read out plus studies ongoing in other indications

Alzheimer's Disease

- Pursuing 2 populations: mild-to-moderate; and early / MCI
  - ✓ Achieved goals of Phase 2 SHINE study in mild-moderate AD
  - Phase 2 START ongoing in early AD with ACTC
- Oral QD drug with no added ARIA-risk, important differentiator
- Extensive preclinical/clinical foundation supports oligomer antagonism approach

Dementia with Lewy Bodies (DLB)

- Phase 2 signal-finding SHIMMER study in mild-to-moderate DLB completed enrollment; data year-end 2024
  - Will determine CT1812's impact on constellation of symptoms
- No approved d-m treatments
- CT1812 protects against oligomers of both amyloid beta (Aβ) and alpha-synuclein (α-syn)

Geographic Atrophy Secondary to dry AMD

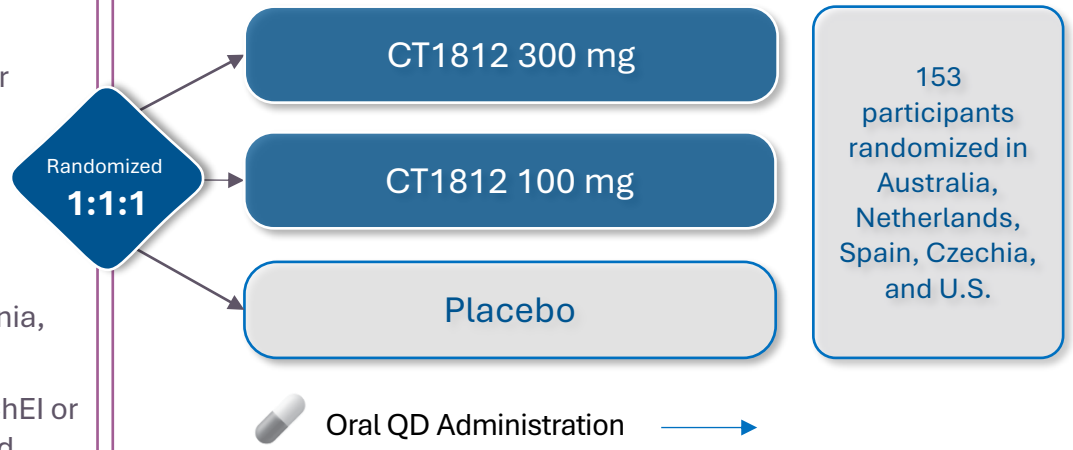
- Phase 2 signal-finding MAGNIFY study in geographic atrophy (GA) ongoing
  - Will determine to what extent CT1812 protection of RPE cells preserves vision
- Oral QD drug important differentiator from IVT therapies

SHINE Phase 2 Study in Amyloid-positive Adults with Mild-to-Moderate Alzheimer's Disease

Enrollment Criteria

- AD diagnosis
- PET or CSF biomarker definition of AD
- MMSE 18-26
- MRI w/o significant abnormality
- No MDD, schizophrenia, bipolar disorder
- Stable regimen of AChEI or memantine permitted

Treatment Period
6 months



153 participants randomized in Australia, Netherlands, Spain, Czechia, and U.S.

Assessments

- Safety/tolerability
- Principal cognitive measure: ADAS-Cog 11
- Exploratory including:
  - ADAS-Cog 13
  - ADCS-ADL & CGIC
  - NTB
  - MMSE
- Biomarkers (CSF/Plasma)
- Plasma CT1812 exposure

Program Objectives

- ✓ Identify efficacy signal(s)
- ✓ Confirm safety and tolerability profile
- ✓ Identify dose(s) for Phase 3

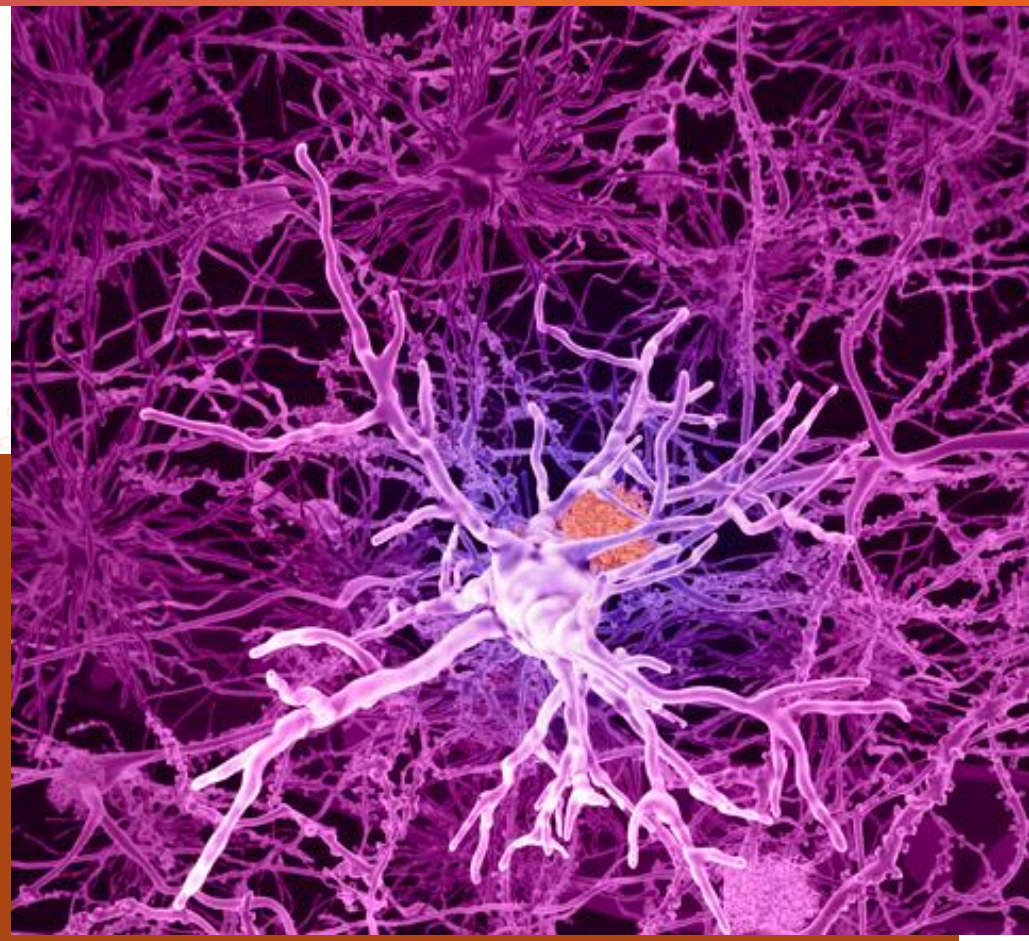
SHINE COG0201 study (NCT03507790) partially funded by $31M NIA grant R01AG058660

MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PET, positive emission tomography; QD, daily; CSF, cerebrospinal fluid

SHINE Patient Population

- PET- or biomarker-confirmed Alzheimer's disease
- Majority of participants were female (60%), Caucasian (96%), approximately 72 years of age
- Mean MMSE score upon entry: 21.37
- ~60% of patients were carriers of the ApoE4 gene
- Characteristics well-balanced between all 3 arms

Phase 2 *Topline* Results in Alzheimer's Disease



39% slowing of cognitive decline in CT1812-treated 'SHINE' participants

Amyloid positivity confirmed for all participants by CSF or PET

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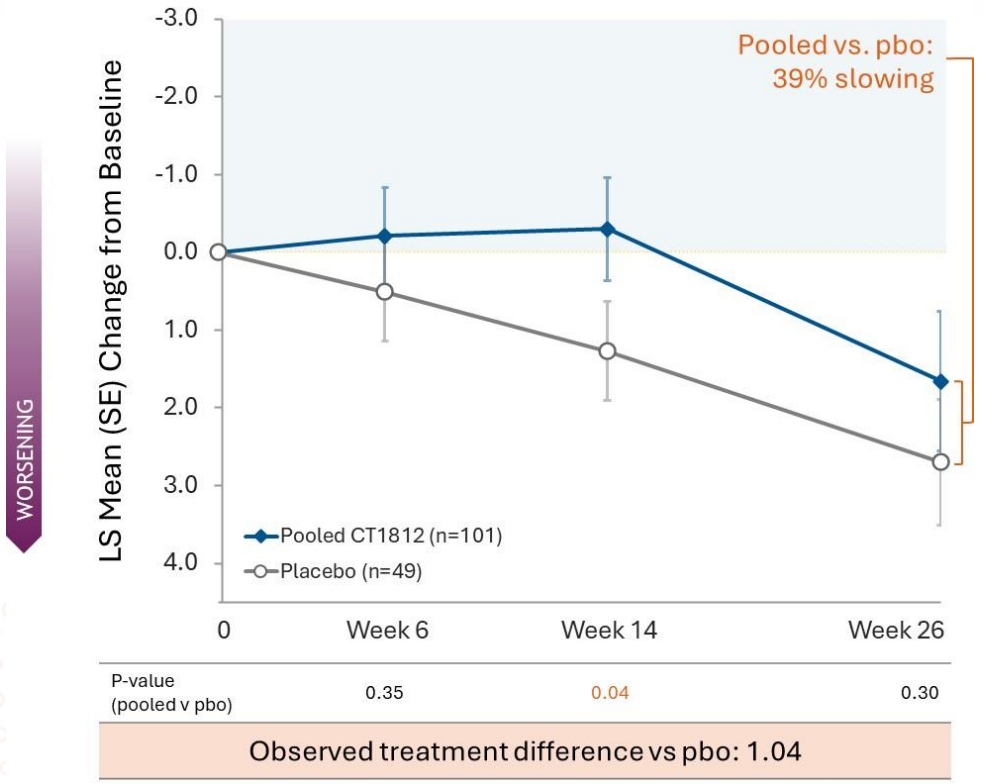
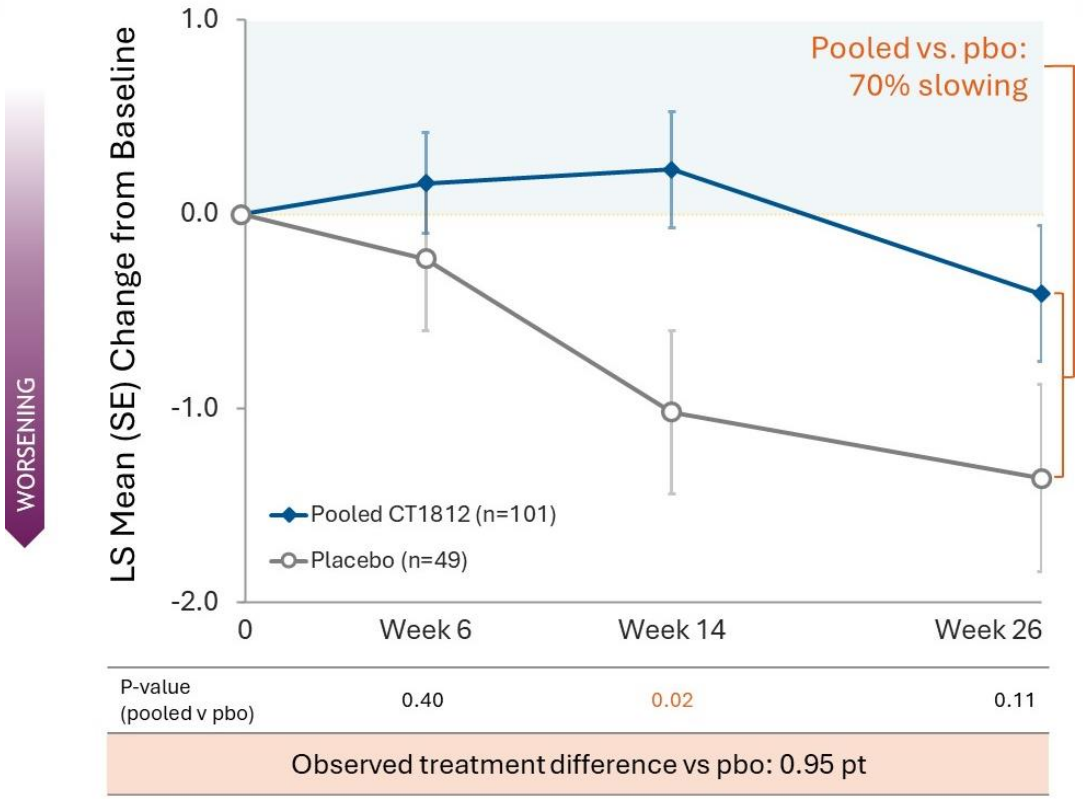
SHINE Cognitive Endpoints: ADAS-Cog 11 and MMSE

Magnitude of ADAS-Cog 11 decline at 6 months similar to approved MAbs

ADAS-Cog 11* mITT population (n=150)



MMSE mITT population (n=150)



** ADAS-Cog 11 mITT in the pooled dose group vs placebo was the first of the ordered secondary efficacy endpoints*

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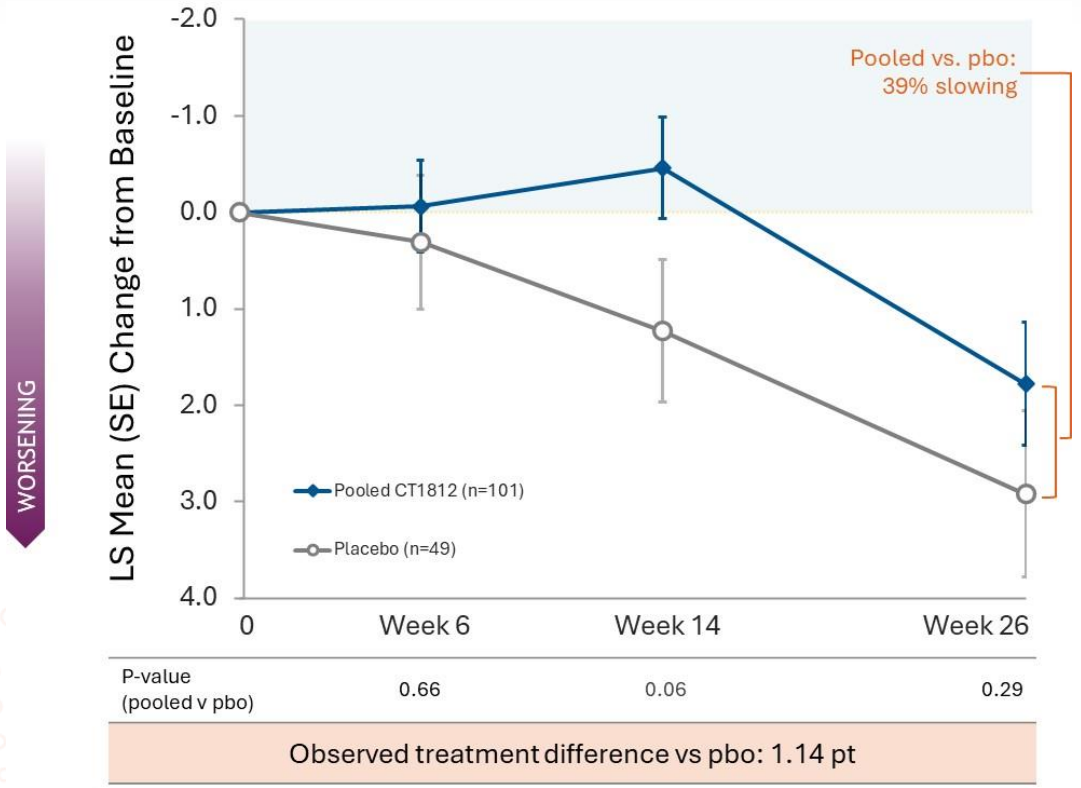
SHINE Cognitive Endpoints: ADAS-Cog 13, Cognitive Composite

Consistent results across multiple cognitive endpoints

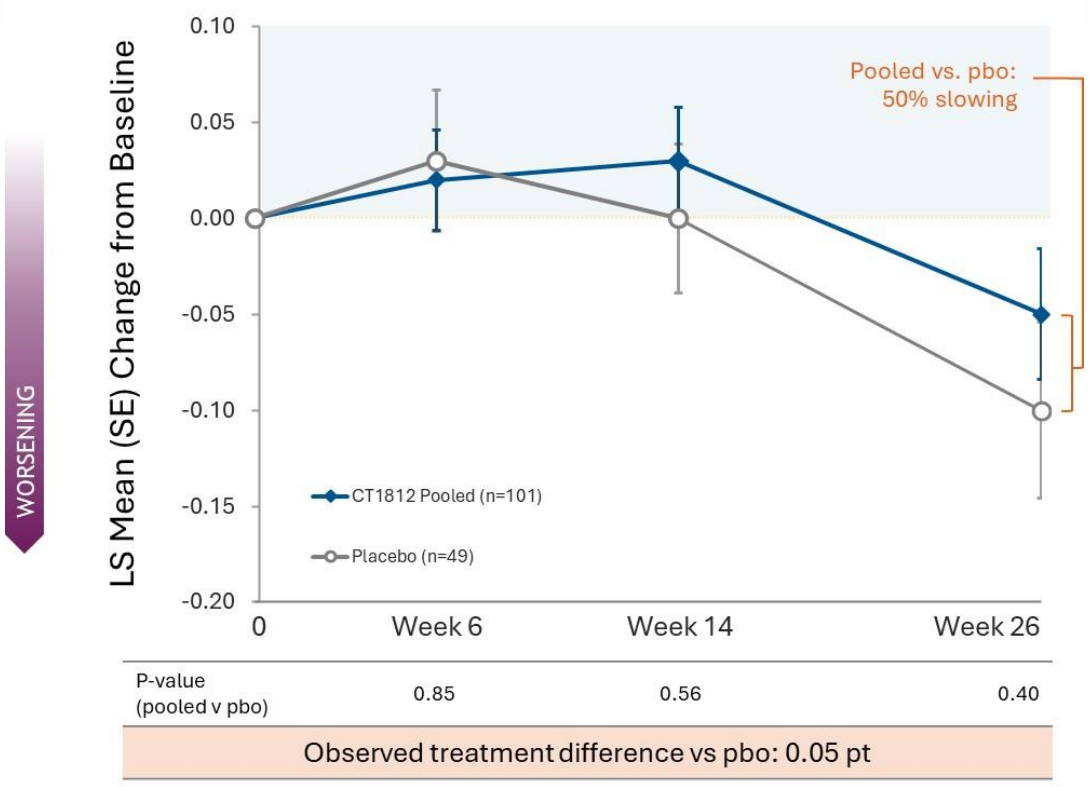
ADAS-Cog 13



P-value (pooled v pbo)	0.66	0.06	0.29

Observed treatment difference vs pbo: 1.14 pt

Cognitive Composite



P-value (pooled v pbo)	0.85	0.56	0.40

Observed treatment difference vs pbo: 0.05 pt

Note: n's are at Day 182

CT1812 Market Opportunity

Insights from a Survey of Neurologists

Survey Design:

- 51 neurologists from academic, community or private settings who treat over 13,000 Alzheimer's patients annually were surveyed
- None were involved in CT1812 clinical trials

Current Options for Alzheimer's Disease:

- Two recently approved monoclonal antibodies: lecanemab and donanemab
- Acetylcholinesterase (AChE) inhibitors: donepezil, galantamine, and rivastigmine
- NMDA receptor antagonist: memantine

Market Opportunity:

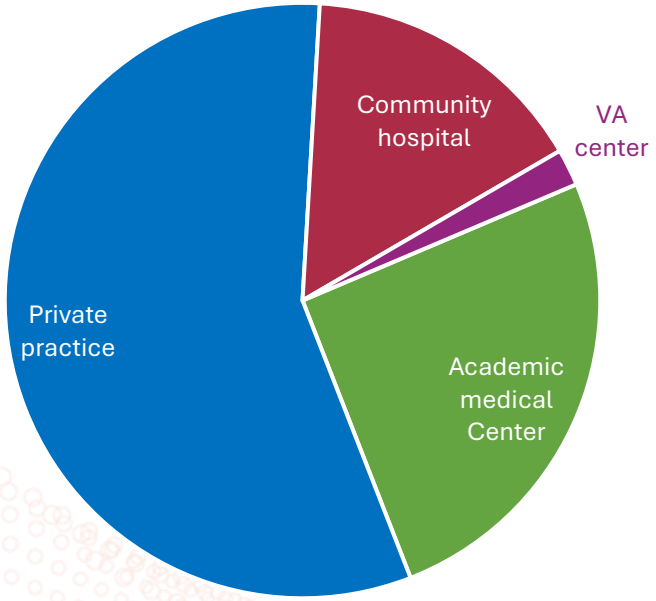
- 7 M in the U.S. & 55 M worldwide have Alzheimer's*

** Alzheimer's Disease Facts and Figures 2024*

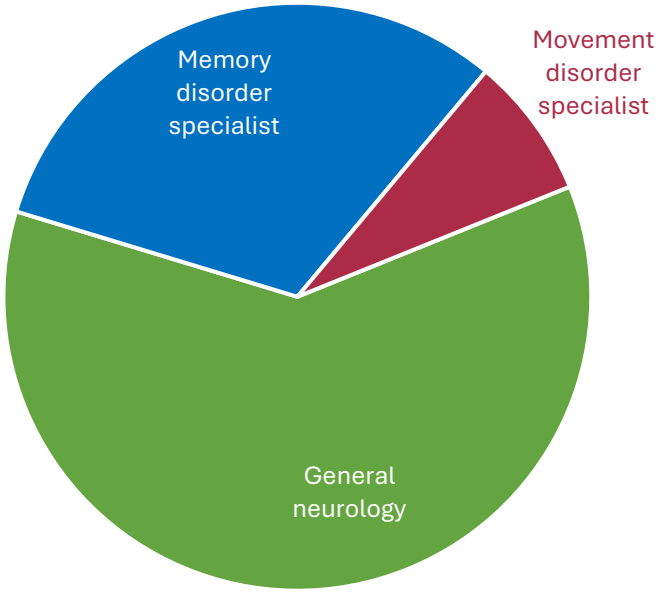
SHINE Data Feedback from Neurologists

Surveyed diverse group of 51 neurologists who treat over 13,000 AD patients annually

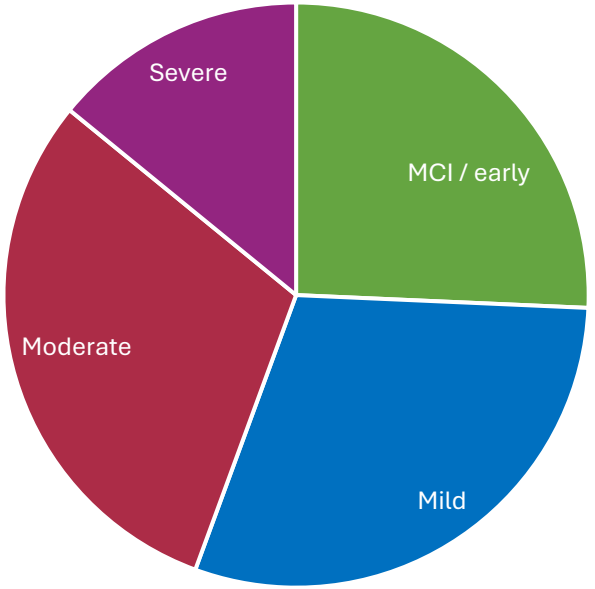
Cross Section of Practice Setting



Cross Section of Specialties



Cross Section of Patients (MMSE)



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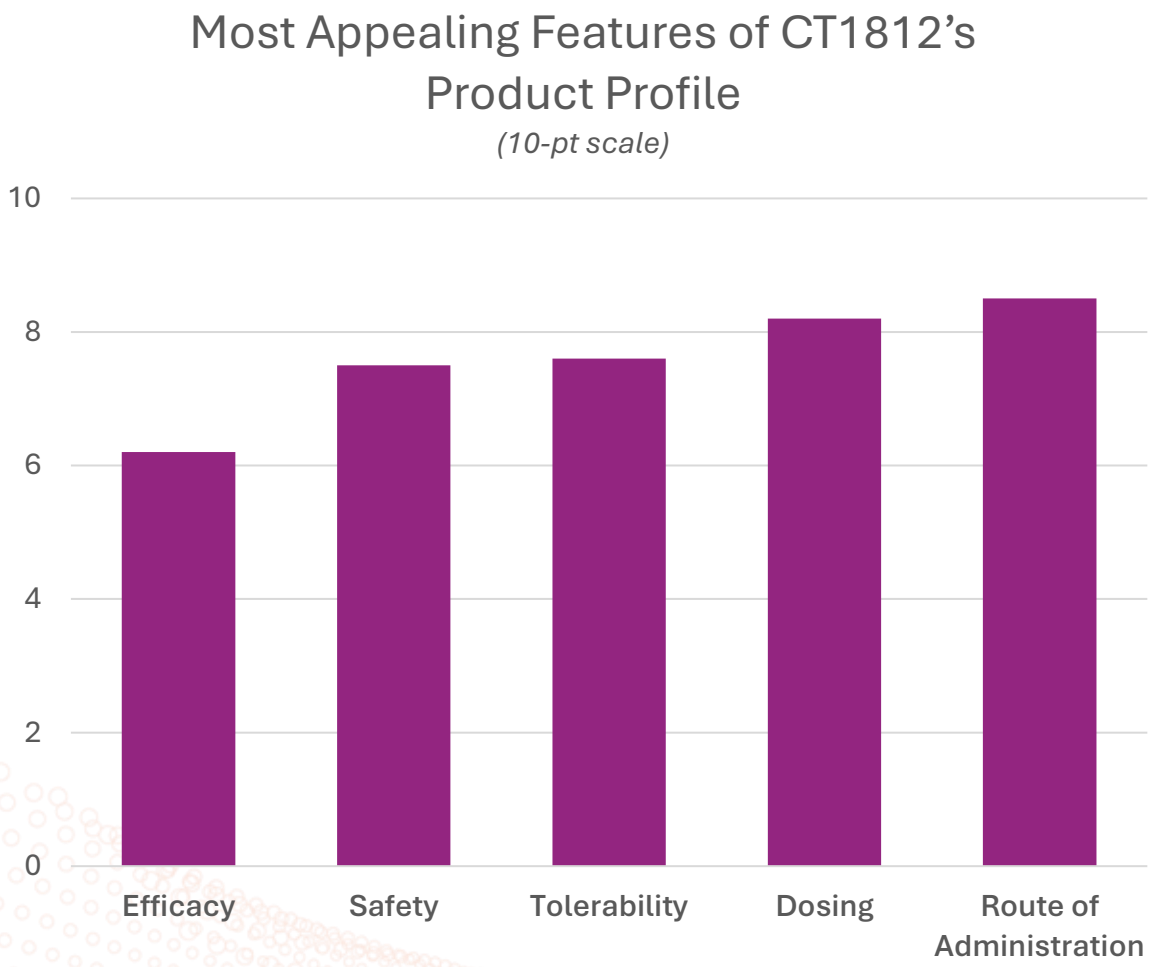
CT1812's Safety and Oral Delivery Appealed to Neurologists



"Ease of dosing as oral medication"

"Oral medication without ARIA risks"

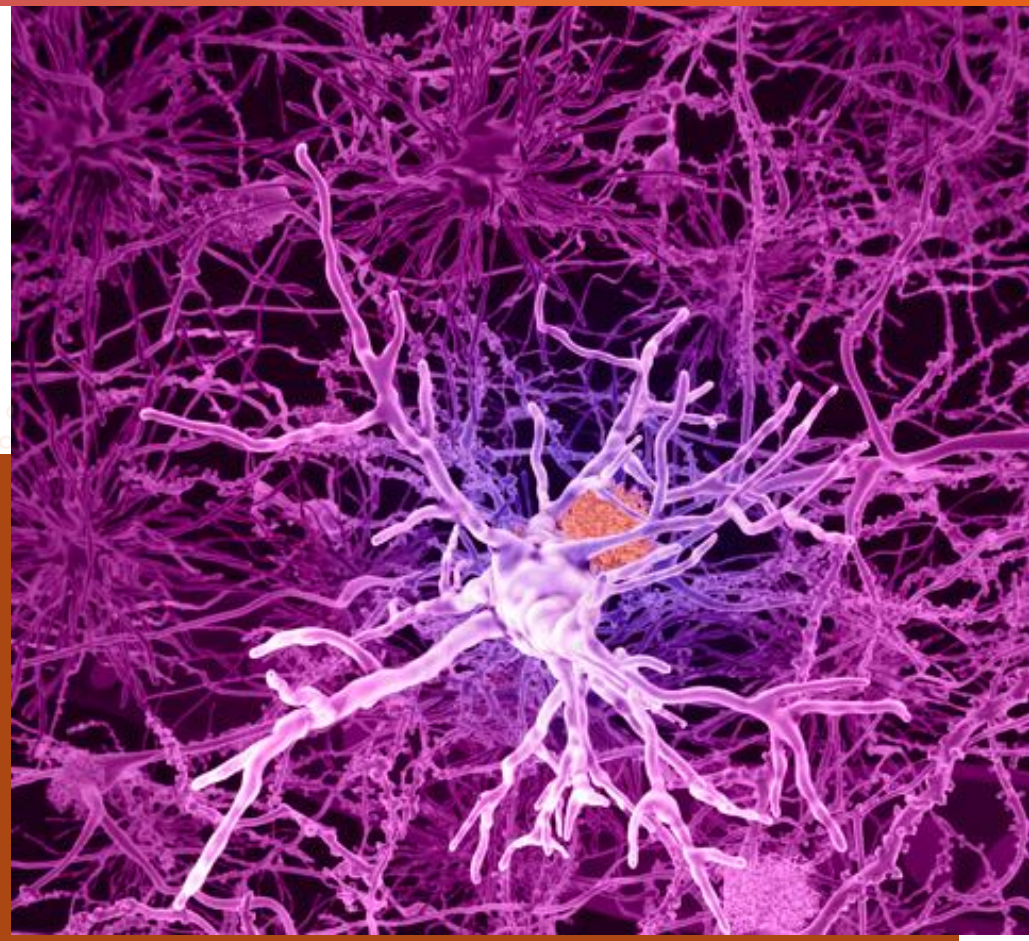
"Pill form is always welcome over an IV infusion"

"Does not require infusion or intensive monitoring"

Prespecified Subgroup Analysis from Phase 2

95% slowing of cognitive decline in lower-p-tau217 'SHINE' participants

Amyloid positivity confirmed for all participants by CSF or PET



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Tau Burden in Amyloid-related AD Clinical Trials

Baseline plasma p-tau217: a predictive biomarker of response to therapy

- Plasma p-tau217 reflects brain amyloid and tau burden
- Prior data indicate that individuals with lower AD pathology at baseline, as reflected by lower levels of plasma p-tau217, have greater response to amyloid-based therapies, eg:
  - Donanemab TRAILBLAZER 2*
    - iADRS: 36% slowing in low tau tercile
    - iADRS: 21% slowing in high tau tercile
- Given CT1812's MoA of displacing Aβ oligomers, we hypothesized that larger treatment effect may be observed in participants with lower plasma p-tau217
- Prespecified subgroup analysis defined by median baseline plasma p-tau217 within study population

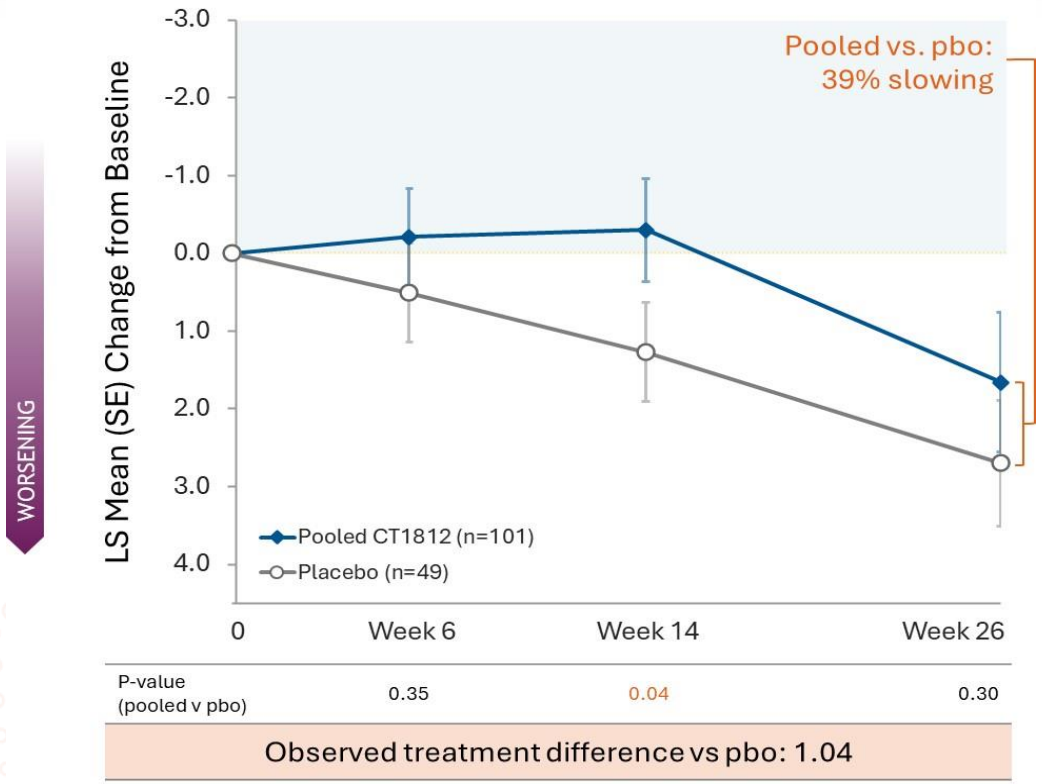
** Mintun MA et al. Predicting Efficacy in Donanemab-Treated Participants. slides presented at CTAD 2023*

iARDS, Integrated Alzheimer's Disease Rating Scale

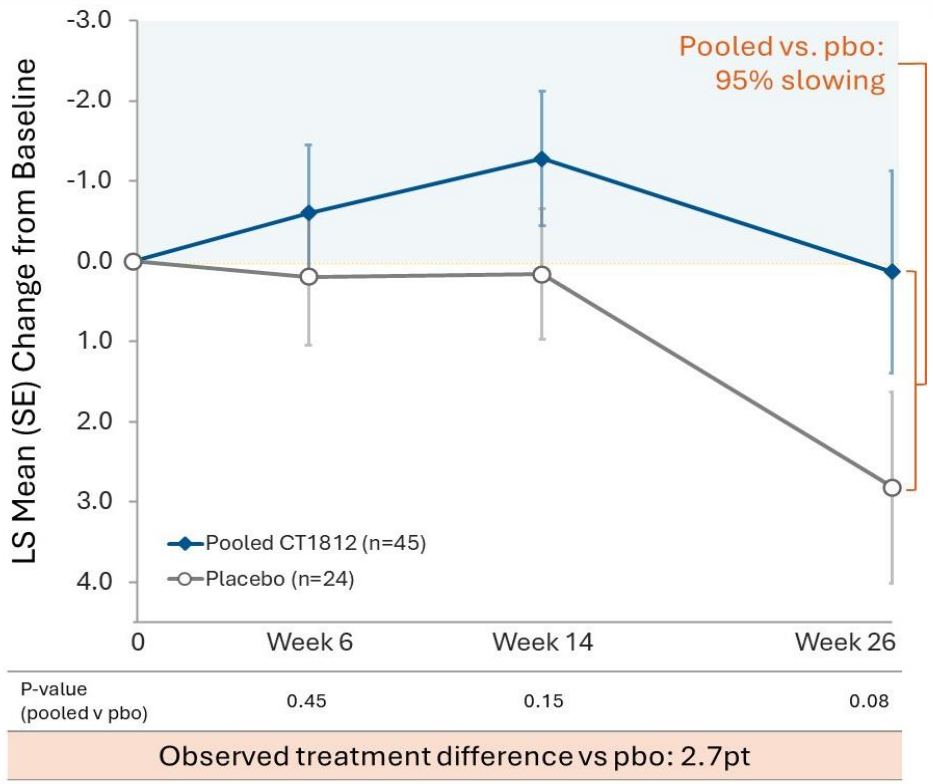
Below Median p-tau217, Treated Participants Experienced Profound Cognitive Effect

Preservation of ADAS-Cog 11 in participants below median plasma p-tau217†

mITT population (n=150)



Below median p-tau217 (n=69)



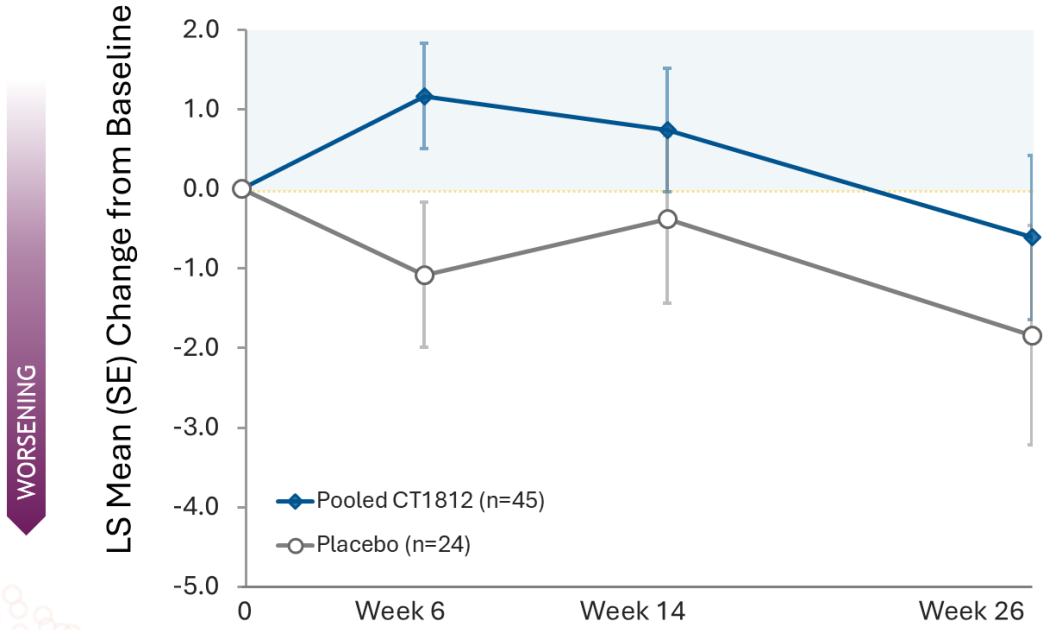
† *Median plasma p-tau217 level is 1.0pg/mL at baseline*

Below Median p-tau217, Treated Participants Experienced Greater/Earlier Preservation of Function

Function and global impression preserved in participants below median plasma p-tau217*

ADCS-ADL

Below median plasma p-tau217 (n=69)

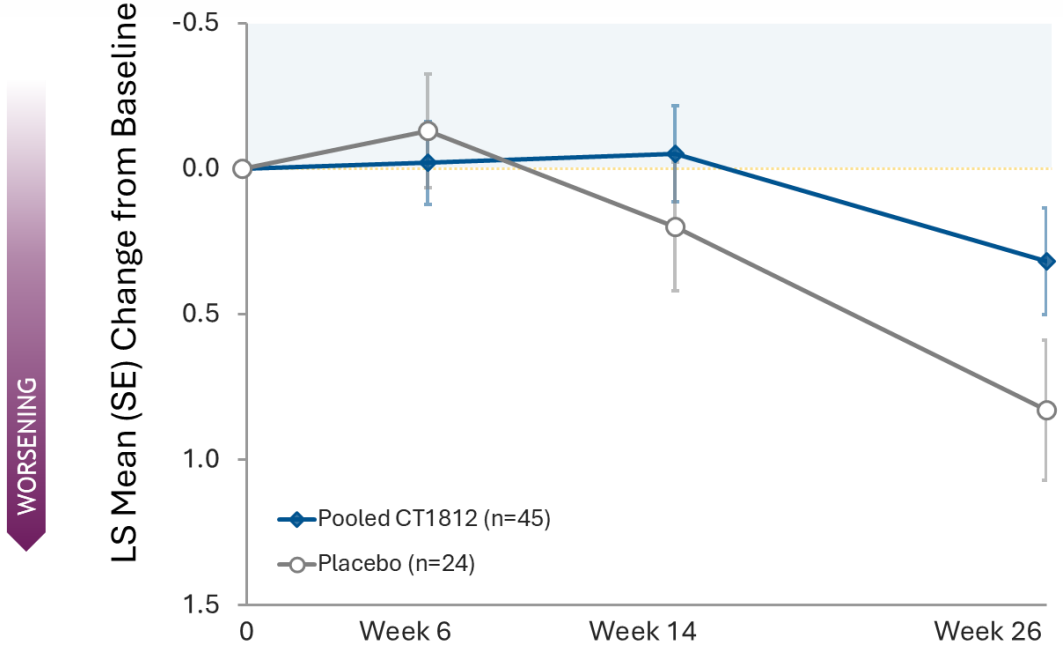


P-value (pooled v pbo)	0.05	0.40	0.47

Observed treatment difference vs pbo: 1.24 pt

ADCS-CGIC

Below median plasma p-tau217 (n=69)



P-value (pooled v pbo)	0.65	0.37	0.09

Observed treatment difference vs pbo: 0.51 pt

** Median plasma p-tau217 level is 1.0pg/mL at baseline*

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CT1812 SHINE Study: Summary and Conclusions

Plasma p-tau217 biomarker identifies strong CT1812-treatment responder group

Full CTAD Presentation

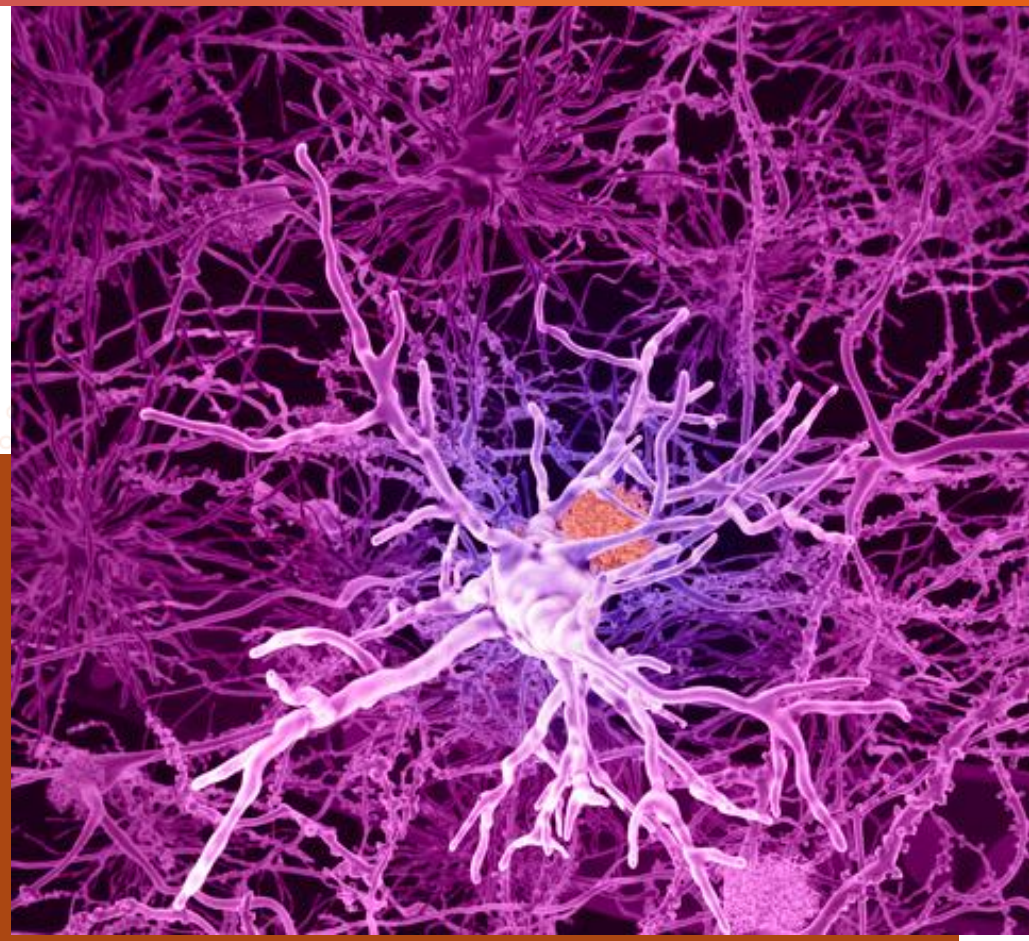
- CT1812 generally safe and well tolerated
  - Similar percentages of AEs in pooled treated and placebo groups
- All cognitive and functional measures trended in favor of CT1812

- Large cognitive impact observed in below-median plasma p-tau217 subgroup
- Will assess optimal plasma p-tau217 cut-point for future studies

SHINE trial supports advancing CT1812 to Phase 3 in mild-to-moderate Alzheimer's disease in population defined by plasma p-tau217

Alzheimer's Disease

START Study in early Alzheimer's disease



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START - A 540-Person Study in Amyloid-positive Early AD

First study to allow lecanemab as background therapy in combination with CT1812

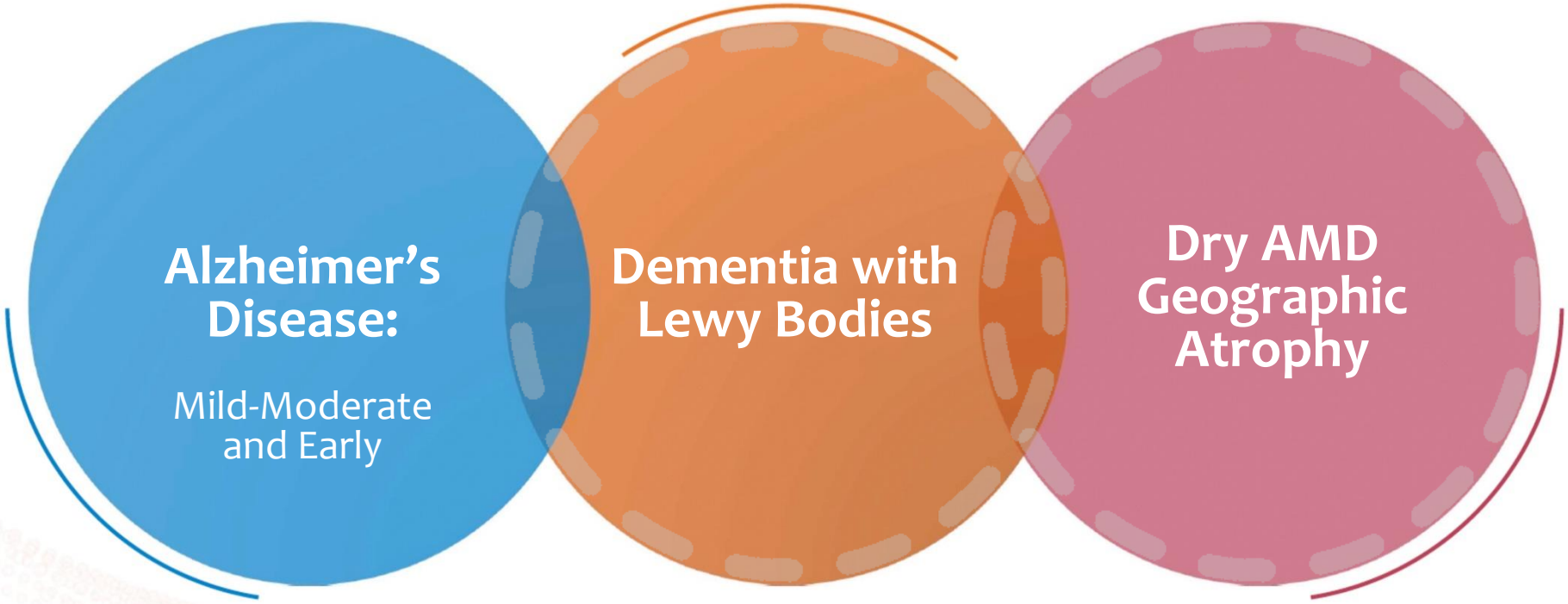
Enrollment Criteria	Treatment Period 18 months	Assessments	Program Objectives

- Ages 50-85
- Diagnosis of MCI due to AD or mild AD dementia
- Brain amyloid via PET
- MRI
- MMSE: 20-30
	Randomized 1:1:1
	CT1812 200 mg
	CT1812 100 mg
	Placebo
	Oral QD Administration
	Recruiting 540 adults with early AD at 30+ sites, including ACTC centers of excellence
		- Safety
		- Cognitive and functional testing:
		  - CDR-SB
		  - ADAS-Cog 13,
		  - ADCS-ADL-MCI
		- Biomarkers
		  - Fluid
		  - imaging
			✓ Identify efficacy signal(s)
			✓ Confirm safety and tolerability after longer exposure
			✓ Identify dose(s) for Phase 3

START COG0203 study (NCT05531656) partially funded by $81M NIA grant R01AG065248

MCI, mild cognitive impairment; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; ADL, activities of daily living; QD, daily; NIA, National Institute on Aging; ACTC, Alzheimer's Clinical Trials Consortium

CT1812 is Also Being Investigated in two Additional Indications



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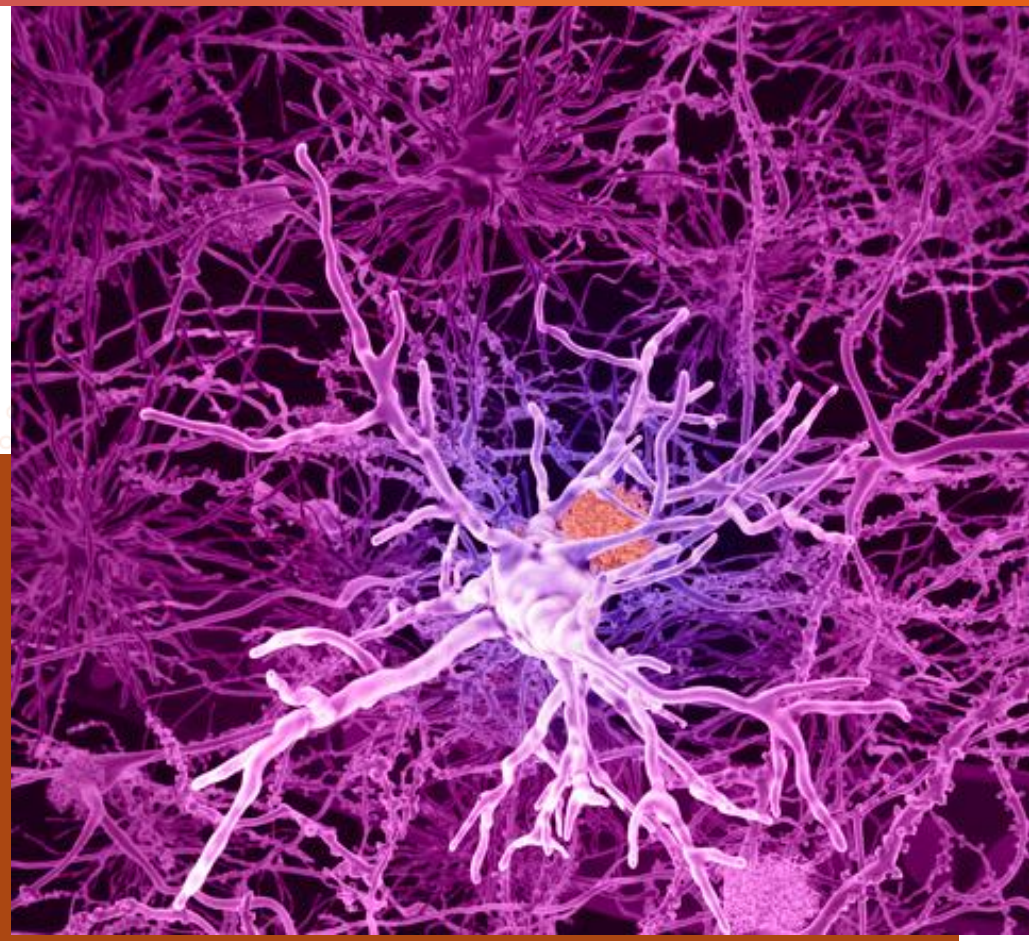
Dementia with Lewy Bodies

"The most common dementia you've never heard of"



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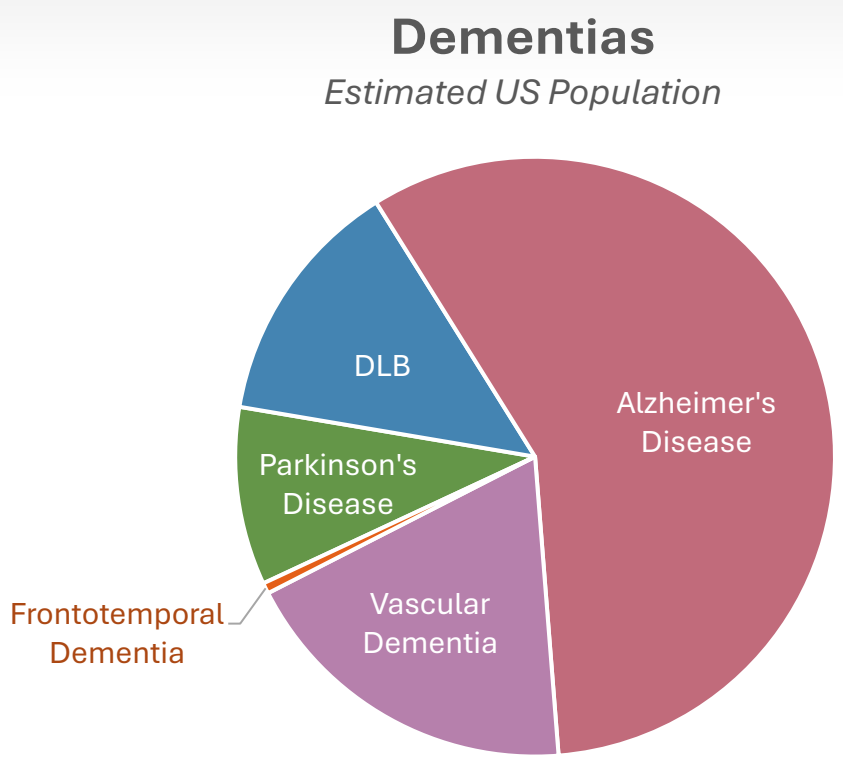
Lewy Body Dementias are Second only to AD in Prevalence

- In the U.S. an estimated 1.4 million people[1] have dementia with Lewy bodies (DLB)
- It is estimated that 50-80% of patients with DLB have Aβ as well as α-synuclein[2] pathology
- Core symptoms of DLB include:
  - Progressive cognitive decline
  - Fluctuating cognition with variations in attention
  - Impaired visuospatial perception
  - Recurrent visual hallucinations
  - REM sleep disorder



1) Lewy Body Dementia Association. About LBD. Available from: https://www.lbda.org/about-lbd
2) Int J Mol Sci. 2023 Jun; 24(12): 10215. doi: 10.3390/ijms241210215

SHIMMER Study in Dementia with Lewy Bodies

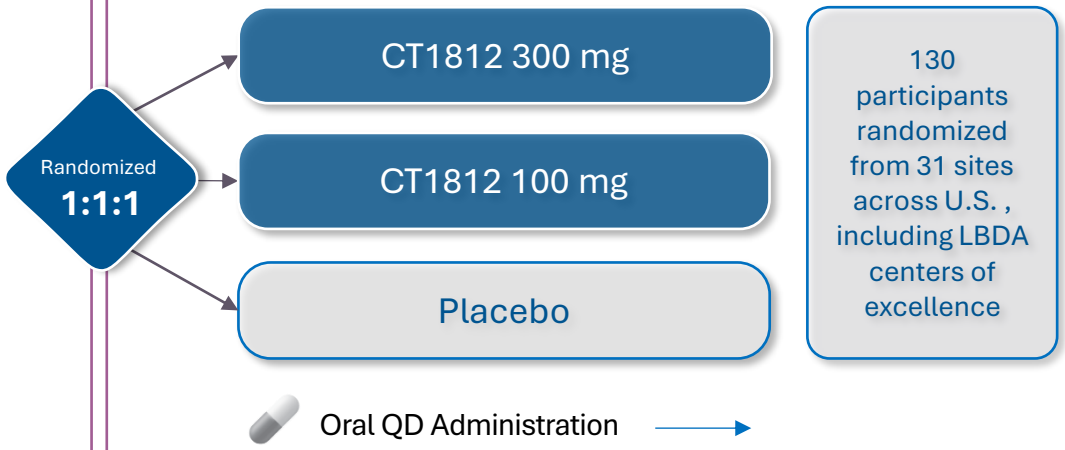
Topline YE 2024

Conducted in collaboration with experts at LBDA and University of Miami

Enrollment Criteria

- Age 50-85
- DLB diagnosis
- MRI
- MMSE: 18-27

Treatment Period
6 months



130 participants randomized from 31 sites across U.S. , including LBDA centers of excellence

Assessments

- Safety/tolerability
- Global CGIC
- Cognition
  - MoCA, MMSE, CDR
- Function
  - UPDRS III
  - ADL
- Behavior
  - Epworth Sleep
  - Fluctuations
- Biomarkers

Program Objectives

- ✓ Identify efficacy signal(s)
- ✓ Confirm safety and tolerability profile
- ✓ Identify dose(s) for Phase 3
- ✓ Explore impact on behavioral symptoms of sleep and fluctuations

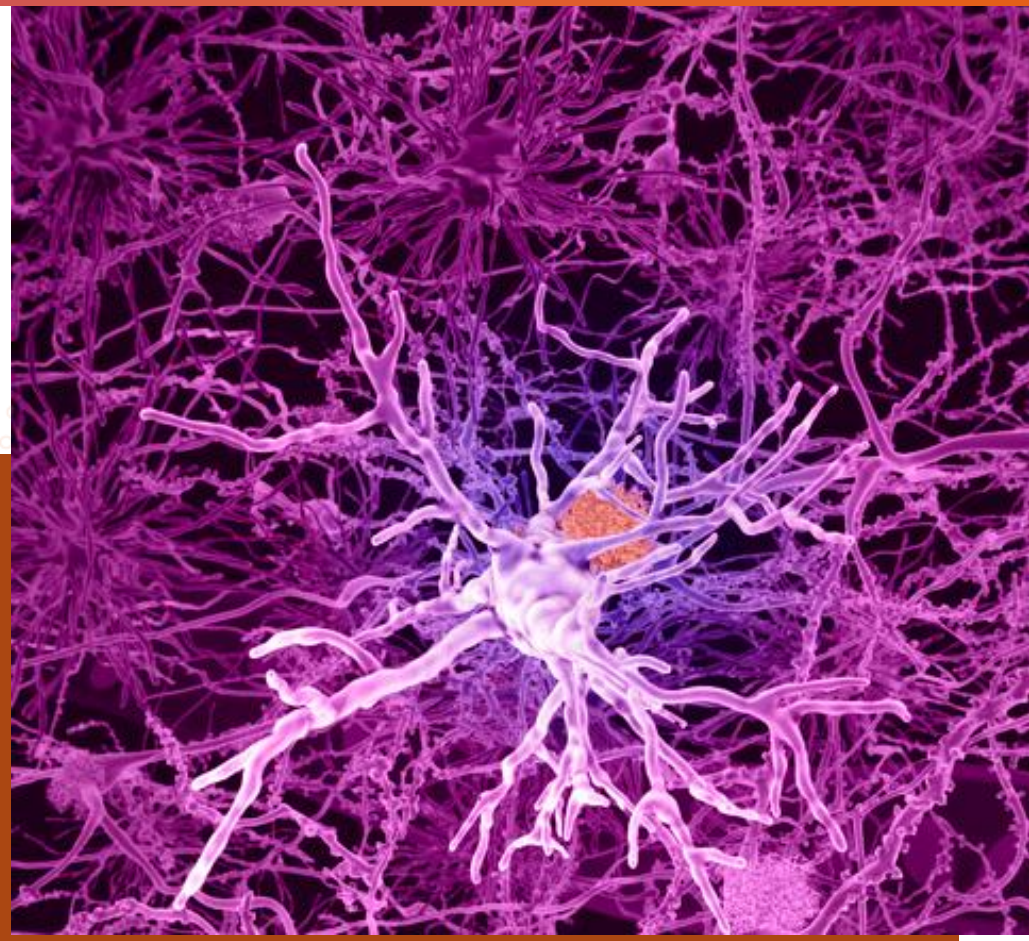
SHIMMER COG1201 study (NCT05225415) partially funded by $30M NIA grant R01AG071643

DLB, Dementia with Lewy Bodies; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; QD, daily; NIA, National Institute on Aging; LBDA, Lewy Body Dementia Association

SHIMMER COG1201 COGNITION Therapeutics

Geographic Atrophy

Damage to the macula resulting from advanced dry age-related macular degeneration (dry AMD)



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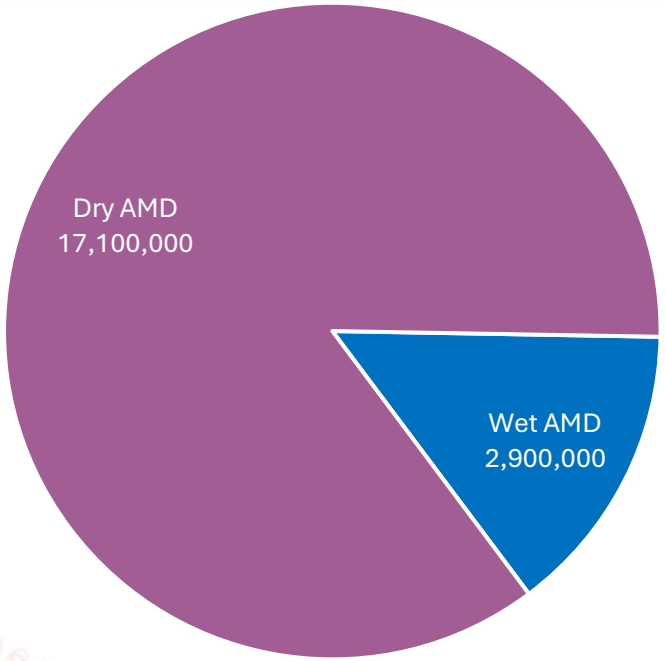
An Urgent Need Exists for New GA Treatments

Geographic Atrophy causes ~20% of cases of legal blindness in North America[1]

US AMD population: Appx 20M [1]



Trinity, LLC forecast; data inhouse

- Dry AMD: last stage of progression is GA
- Two drugs approved for GA in US: Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol)
  - Slow GA lesion growth by 14% - 20%
  - Require monthly IVT
  - Neither approved in EU
- Downregulate complement to interrupt cascade
  - Reduce inflammation
  - Prevent RPE cell damage

1) *BrightFocus Foundation. Age-Related Macular Degeneration: Facts & Figures: https://bityl.co/SMdy*
2) *BrightFocus Foundation. Geographic Atrophy: https://bityl.co/SeNd*
3) *DelveInsight's Geographic Atrophy Market Insight, Epidemiology and Market Forecast*

Rationale for CT1812 in Dry AMD/Geographic Atrophy

Opportunity: crosses blood-retinal barrier to reach retina without an injection

What is dAMD/GA	Geographic atrophy (GA), the most advanced form of dry AMD, effects ~5M people WW and is associated with significant vision loss
Unmet Need	Complement inhibitors require injections into eye(s)
Pathophysiology	Death of retinal pigment epithelium (RPE) cells drives loss of photoreceptors (neurons required for sight) *In vitro* evidence supports CT1812 rescue of RPE cells
MAGNIFY	Proof-of-concept Phase 2 study in adults with GA

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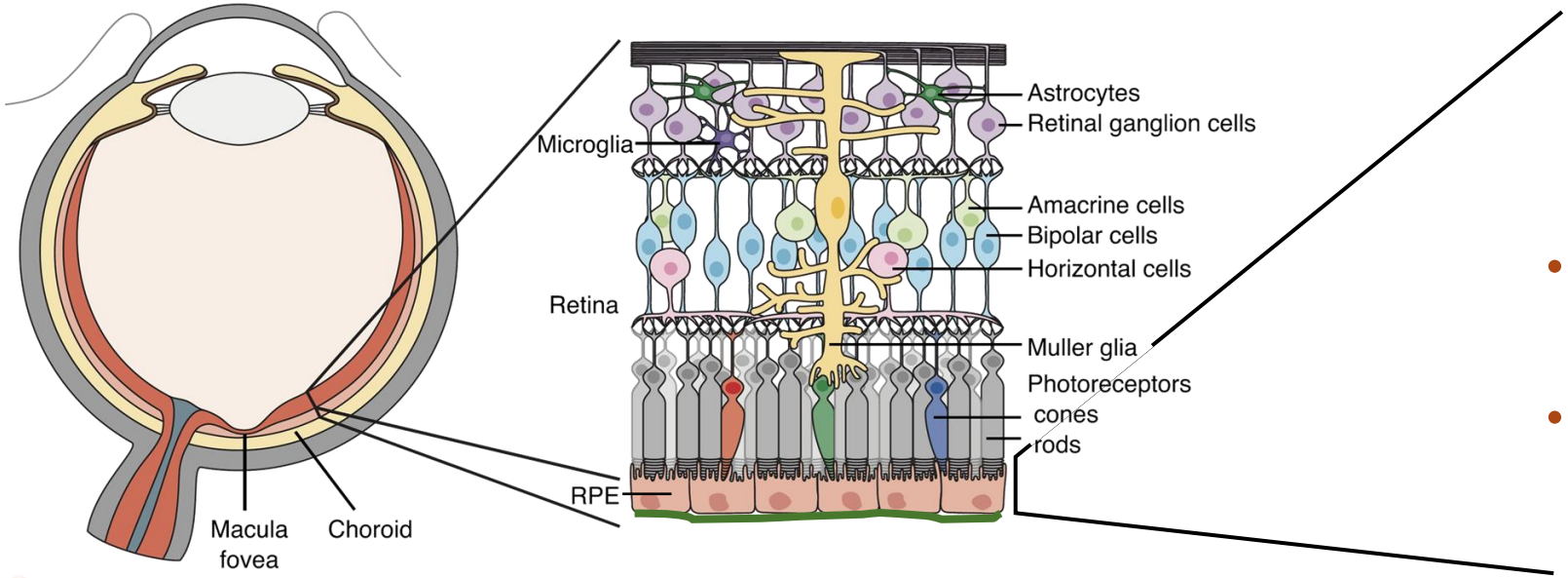
CT1812 Protects RPE Cells and the Photoreceptors they Support



- Photoreceptors – specialized neurons necessary for sight – require support from retinal pigment epithelial (RPE) cells that are damaged in dry AMD
- CT1812 has been shown to rescue RPE cells *in vitro*
- CT1812's potential to preserve vision through this mechanism is being tested in Phase 2

Figure modified from Orozco et al., Cell Reports 2020

MAGNIFY Trial in dAMD/GA

Potential first oral drug for geographic atrophy

Enrollment Criteria	Treatment Period 18 months	Assessments	Program Objectives
- Age: ≥ 50 - Diagnosis of dry AMD - BCVA ≥ 24 letters (ETDRS) - GA lesion ≥ 2.5 and ≤17.5mm2	Randomized 1:1 CT1812 200 mg Placebo Oral QD Administration Recruiting 246 adults with GA secondary to dry AMD	- Change in GA lesion area (FAF) - Ellipsoid zone area (SD-OCT) - Drusen volume (SD-OCT) - Safety	✓ Identify efficacy signal(s) ✓ Assess potential to treat two eyes simultaneously ✓ Confirm safety and tolerability profile at 200mg dose

BVCA, best corrected visual acuity; FAF, fundus autofluorescence; SD-OCT, spectral domain optical coherence tomography

Clinical Information Generated to Date Supports 3 Indications

Ongoing Trials Expand CT1812 into New Indications

COG0203 - START

Early-to-mild Alzheimer's disease
Actively recruiting

COG1201 - SHIMMER

Mild-to-moderate DLB
Topline data YE2024

COG2201 - MAGNIFY

GA secondary to dry AMD
Actively recruiting

SHINE

- 153 participants
- Consistent slowing cognitive decline (ADAS-Cog 11 and 13, MMSE, Cog Composite)
- Trends in functional benefit

SEQUEL[1]

- 16 participants
- Normalization of brain waves across EEG measures
- Significant improvement in AEC-c and relative theta in central region

SPARC[2]

- 23 participants
- Preservation of brain atrophy via volumetric MRI
- No change in SV2A treated or pbo

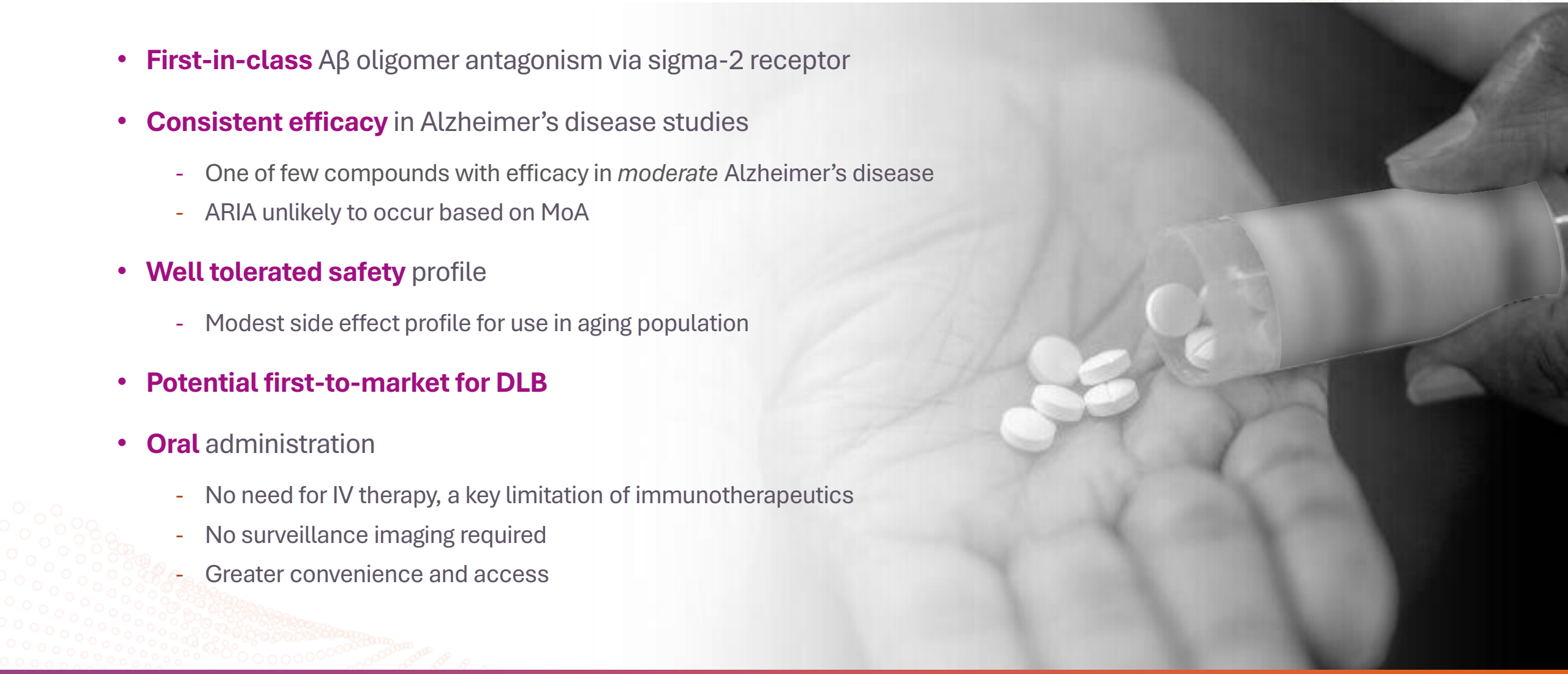
SNAP[3]

- 3 participants
- Rapid displacement of Aβ oligomers via CSF
- Replication of preclinical findings via MEI

1) Vijverberg E et al. J Prev Alzheimers Dis (2024) 2) van Dyck, CH et al. Alz Res Therapy 16, 20 (2024) 3) LaBarbera, KM et al. Transl Neurodegener 2023, 12(24)

Summary: the Promise of CT1812

- **First-in-class** Aβ oligomer antagonism via sigma-2 receptor
- **Consistent efficacy** in Alzheimer's disease studies
  - One of few compounds with efficacy in *moderate* Alzheimer's disease
  - ARIA unlikely to occur based on MoA
- **Well tolerated safety** profile
  - Modest side effect profile for use in aging population
- **Potential first-to-market for DLB**
- **Oral** administration
  - No need for IV therapy, a key limitation of immunotherapeutics
  - No surveillance imaging required
  - Greater convenience and access



Current Financial Position

As of quarter ended September 30, 2024

Cash and cash equivalents $22.0 M

Expected cash runway into 2Q 2025

Grant funding for CT1812 studies

Preclinical through Phase 2	~$171 M
Approximate funding used	($117.4 M)
Remaining grant funding	$53.6M

COGNITION™ Therapeutics

Thank You

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