COGNITION™ Therapeutics

Developing disease-modifying medicines for degenerative disorders

Mid 2023

Forward-looking Statements

FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. All statements contained in this presentation, other than statements of historical facts or statements that relate to present facts or current conditions, including but not limited to, statements regarding our cash, financial resources and product candidates, including CT1812, and any expected or implied benefits or results, including that initial clinical results observed with respect to CT1812 will be replicated in later trials, our clinical development plans, are forward-looking statements. These statements, including statements related to the timing and expected results of our clinical trials, involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance, or achievements to be materially different from any future results, performance, or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "might," "will," "should," "expect," "plan," "aim," "seek," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "forecast," "potential" or "continue" or the negative of these terms or other similar expressions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition, and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, some of which cannot be predicted or quantified and some of which are beyond our control. Factors that may cause actual results to differ materially from current expectations include, but are not limited to: competition, our ability to secure new (and retain existing) grant funding, our ability to grow and manage growth, maintain relationships with suppliers and retain our management and key employees; our ability to successfully advance our current and future product candidates through development activities, preclinical studies and clinical trials and costs related thereto; uncertainties inherent in the results of preliminary data, preclinical studies and earlier-stage clinical trials being predictive of the results of early or later-stage clinical trials; the timing, scope and likelihood of regulatory filings and approvals, including regulatory approval of our product candidates; changes in applicable laws or regulations; the possibility that the we may be adversely affected by other economic, business or competitive factors, including ongoing economic uncertainty; our estimates of expenses and profitability; the evolution of the markets in which we compete; our ability to implement our strategic initiatives and continue to innovate our existing products; our ability to defend our intellectual property; the impact of the COVID-19 pandemic on our business, supply chain and labor force; and the risks and uncertainties described more fully in the "Risk Factors" section of our annual and quarterly reports filed with the SEC that are available on www.sec.gov. You should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that we may face. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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Projections, estimates, industry data and information contained in this presentation, including the size of and growth in key end markets, are based on information from third-party sources and management estimates. Although we believe that these third party-sources are reliable, we cannot guarantee the accuracy or completeness of these sources. Our management's estimates are derived from third-party sources, publicly available information, our knowledge of our industry and assumptions based on such information and knowledge. Our management's estimates have not been verified by any independent source. All of the projections, estimates, market data and industry information used in this presentation involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such information. In addition, projections, estimates and assumptions relating to us and our industry's future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including, but not limited to, those described above, that could cause future performance to differ materially from our expressed projections, estimates and assumptions or those provided by third parties.

Multiple Rigorous Phase 2 Programs Underway

Clinical Study	Indication	US Prevalence	Grant Funding*	
SEQUEL (n=23)	Mild-moderate AD	~ 5 million	$5.4 Million	✓ Recently Completed
SHINE (n=144)	Mild-moderate AD	~ 5 million	$30 Million	
START (n=540)	Early AD	~ 3.4 million	$81 Million	✓ Site Activated
SHIMMER (n=120)	Mild-moderate DLB	~ 1.4 million	$30 Million	
MAGNIFY (n=246)	GA secondary to dry AMD	~ 1.5 million	Equity	✓ FPI Enrolled

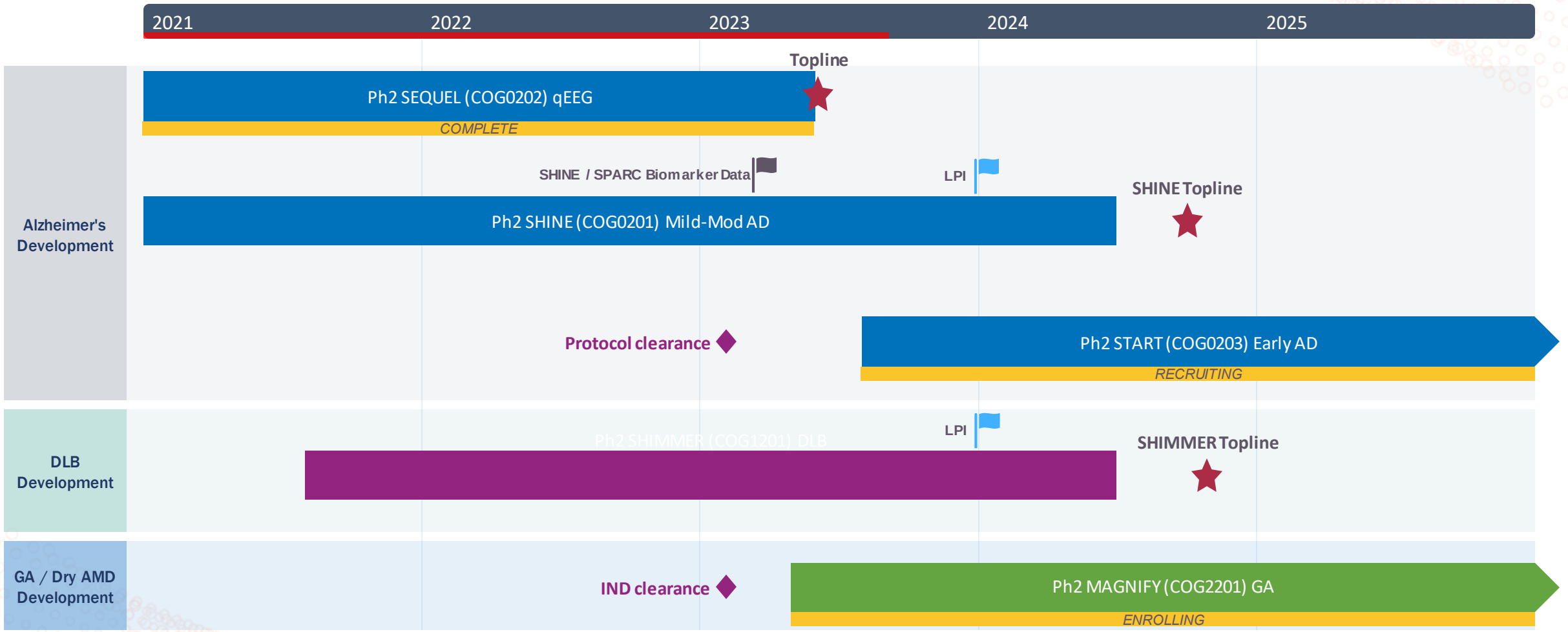
**Grant funding through completion of studies*

Note: CT1812 and other pipeline candidates are not approved for use in the US or other jurisdictions

Compelling Investment Thesis

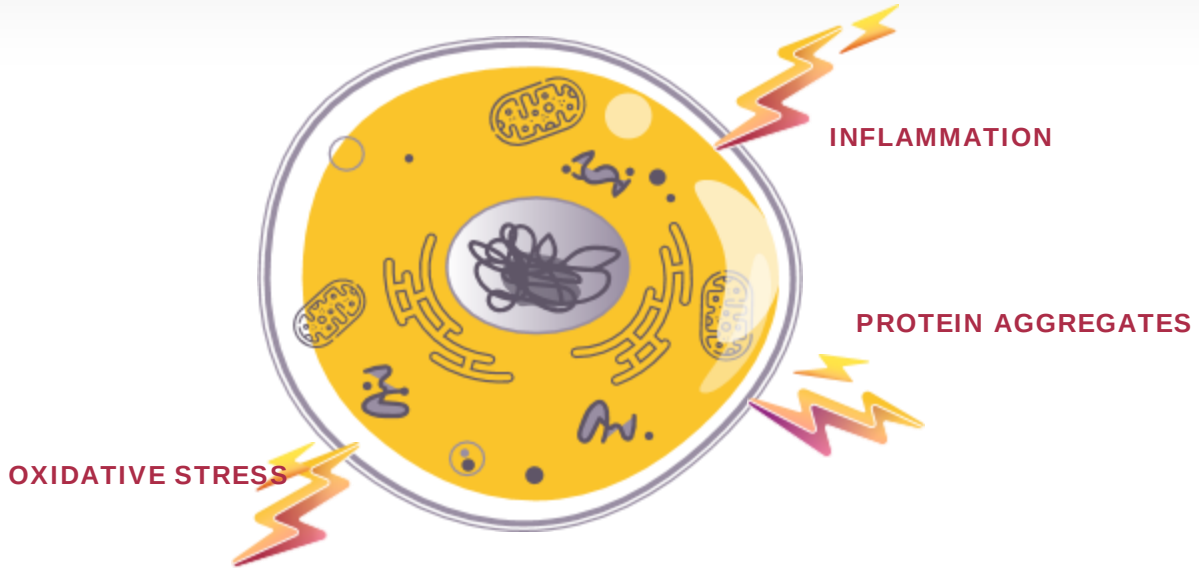
Novel Approach Validated Science	Strong Financials	CT1812 Oral Once-Daily	Development Focused on Major Commercial Ops
Protect synapses from toxic proteins and other stressors to facilitate restoration of neuronal function	$170+ Million in cumulative non-dilutive grant funding Expected cash runway into 2H2024	Oligomer receptor: well characterized target Highly brain penetrant Selective and saturable binding IP through 2035 (potential PTE > 2040)	Four ongoing Ph2 trials AD, DLB, GA/dry AMD are significant conditions with large patient populations

CGTX Near-term Catalysts



Pathogenic Proteins, Oxidative Stress, Inflammation Accumulate with Age

- Build-up of these stressors impairs key cellular functions:
  - Autophagy
  - Cholesterol synthesis
  - Protein trafficking
- Loss of these processes leads to neuronal degeneration and death
- **Neuronal loss** drives declines in cognition, vision and motor functions in diseases like Alzheimer's disease, DLB and dry AMD



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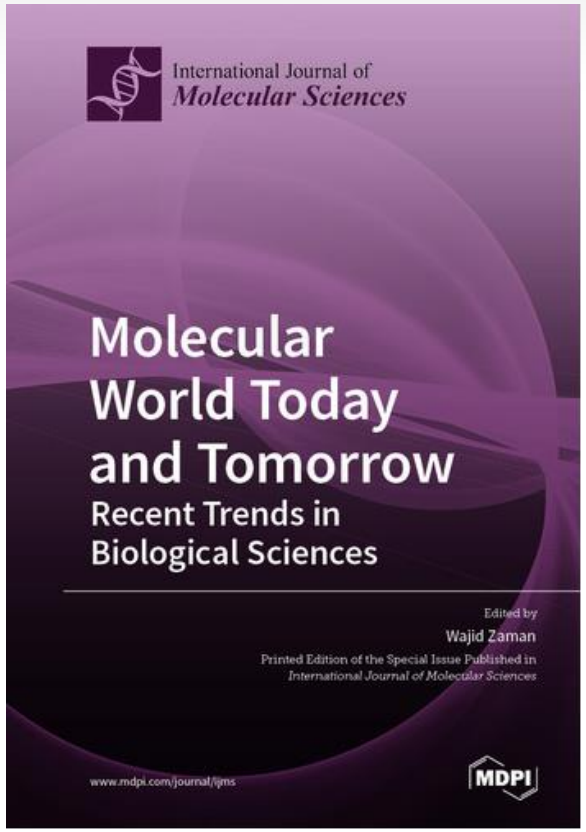
Loss of Specialized Neurons Drives Degenerative CNS Diseases

- Over time, pathogenic proteins, oxidative stress, and inflammation damage neurons:
  - Cortical & hippocampal neurons in Alzheimer's disease
  - These as well as dopaminergic neurons in Parkinson's disease and dementia with Lewy bodies (DLB)
  - Photoreceptors, retinal ganglion cells in dry age-related macular degeneration (dry AMD)
- Cognition's aim:
  - Protect neurons in the CNS from toxic stressors

Published in the *International Journal of Molecular Sciences*



Find it on the Cognition website

Review

Sigma-2 Receptors – From Basic Biology to Therapeutic Target: A Focus on Age-Related Degenerative Diseases

Britney N. Lizama [1], Jennifer Kahle [2], Susan M. Catalano [1], Anthony O. Caggiano [1], Michael Grundman [3,4], and Mary E. Hamby [1,*]

[1] Cognition Therapeutics, Inc. Pittsburgh, PA, USA
[2] IHS International, San Diego CA
[3] Global R&D Partners, LLC, San Diego, California, USA
[4] Dept. of Neurosciences, University of California, San Diego, USA

Abstract: There is a large unmet medical need to develop disease-modifying treatment options for individuals with age-related degenerative diseases of the central nervous system. The sigma-2 receptor (S2R), encoded by *TMEM97*, is expressed in brain and retinal cells, and regulates cell functions via its co-receptor progesterone receptor membrane component 1 (PGRMC1), and through other protein–protein interactions. Studies describing functions of S2R involve the manipulation of expression or pharmacological modulation using exogenous small-molecule ligands. These studies demonstrate that S2R modulates key pathways involved in age-related diseases including autophagy, trafficking, oxidative stress, and amyloid-β and α-synuclein toxicity. Furthermore, S2R modulation can ameliorate functional deficits in cell-based and animal models of disease. This review summarizes the current evidence-based understanding of S2R biology and function, and its potential as a therapeutic target for age-related degenerative diseases of the central nervous system, including Alzheimer's disease, α-synucleinopathies, and dry age-related macular degeneration.

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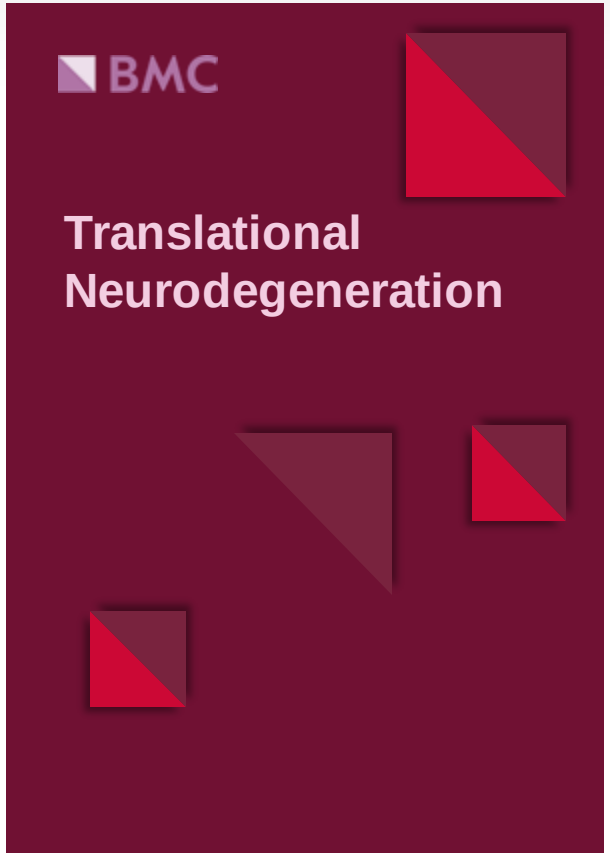
Published in the journal, *Translational Neurodegeneration*



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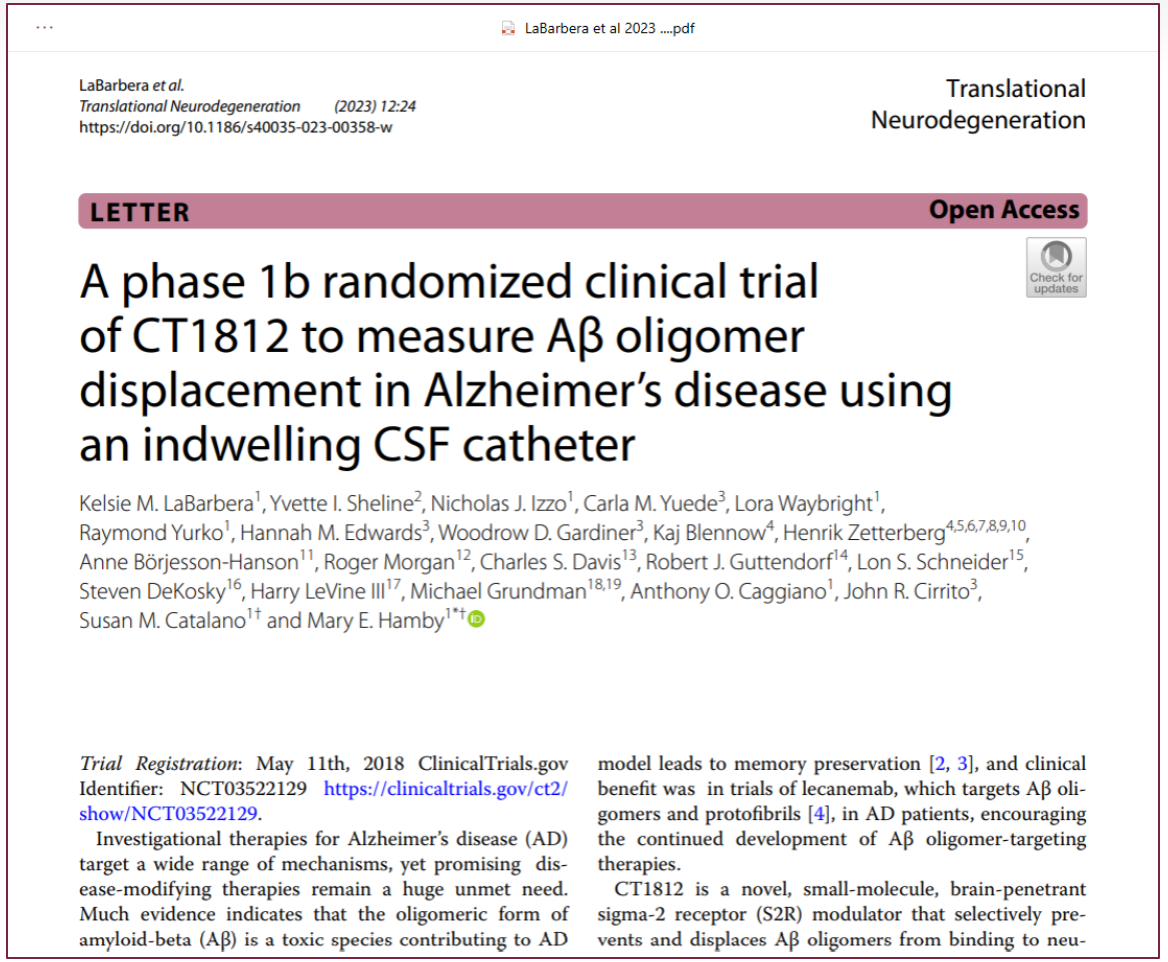

LaBarbera et al 2023 ....pdf

LaBarbera *et al.*
Translational Neurodegeneration (2023) 12:24
https://doi.org/10.1186/s40035-023-00358-w

Translational
Neurodegeneration

LETTER Open Access

A phase 1b randomized clinical trial of CT1812 to measure Aβ oligomer displacement in Alzheimer's disease using an indwelling CSF catheter

Kelsie M. LaBarbera[1], Yvette I. Sheline[2], Nicholas J. Izzo[1], Carla M. Yuede[3], Lora Waybright[1], Raymond Yurko[1], Hannah M. Edwards[3], Woodrow D. Gardiner[3], Kaj Blennow[4], Henrik Zetterberg[4,5,6,7,8,9,10], Anne Börjesson-Hanson[11], Roger Morgan[12], Charles S. Davis[13], Robert J. Guttendorf[14], Lon S. Schneider[15], Steven DeKosky[16], Harry LeVine III[17], Michael Grundman[18,19], Anthony O. Caggiano[1], John R. Cirrito[3], Susan M. Catalano[1†] and Mary E. Hamby[1*†]

Trial Registration: May 11th, 2018 ClinicalTrials.gov Identifier: NCT03522129 https://clinicaltrials.gov/ct2/show/NCT03522129.

Investigational therapies for Alzheimer's disease (AD) target a wide range of mechanisms, yet promising disease-modifying therapies remain a huge unmet need. Much evidence indicates that the oligomeric form of amyloid-beta (Aβ) is a toxic species contributing to AD model leads to memory preservation [2, 3], and clinical benefit was in trials of lecanemab, which targets Aβ oligomers and protofibrils [4], in AD patients, encouraging the continued development of Aβ oligomer-targeting therapies.

CT1812 is a novel, small-molecule, brain-penetrant sigma-2 receptor (S2R) modulator that selectively prevents and displaces Aβ oligomers from binding to neu-

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Cognition Library

LaBarbera, et al. A phase 1b randomized clinical trial of CT1812 to measure Aβ oligomer displacement in Alzheimer's disease using an indwelling CSF catheter. Transl Neurodegener 2023, 12(24)	Izzo, et al. Proceedings from the Fourth International Symposium on σ-2 Receptors: Role in Health and Disease. 7(6) *ENEURO* .0317-20.2020 1–7
Lizama, et al. Sigma-2 Receptors—From Basic Biology to Therapeutic Target: A Focus on Age-Related Degenerative Diseases. *Int. J. Mol. Sci.* 2023, 24(7), 6251	Limegrover, et al. Alzheimer's Protection Effect of A673T Mutation May Be Driven by Lower Aβ Oligomer Binding Affinity. *J Neurochem.* 2020; 00: 1–15
Colom-Cadena, et al. TMEM97 increases in synapses and is a potential synaptic Aβ binding partner in human Alzheimer's disease. *bioRxiv* 2021.02.01.428238	Colom-Cadena, et al. The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. *Alz Res Therapy* 12, 21 (2020)
LaBarbera, et al. Modeling the mature CNS: A predictive screening platform for neurodegenerative disease drug discovery. *J Neurosci Methods.* 2021 Jul 1;358:109180.	Grundman, et al. A phase 1 clinical trial of the sigma-2 receptor complex allosteric antagonist CT1812, a novel therapeutic candidate for Alzheimer's disease. *Alzheimers Dement (N Y).* 2019 Jan 23; 5:20-26
Rishton, et al. Discovery of Investigational Drug CT1812, an Antagonist of the Sigma-2 Receptor Complex for Alzheimer's Disease. *ACS Med Chem Lett.* 2021 Aug 9;12(9):1389-1395.	Izzo, et al. Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers II: Sigma-2/PGRMC1 receptors mediate Abeta 42 oligomer binding and synaptotoxicity. *PLoS One*. 2014 Nov 12; 9(11):e111899
Izzo, et al. Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification. *Alzheimer's Dement.* 2021 Aug; 17(8):1365-1382	Izzo, et al. Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers I: Abeta 42 oligomer binding to specific neuronal receptors is displaced by drug candidates that improve cognitive deficits. *PLoS One*. 2014 Nov 12; 9(11):e111898
Limegrover, et al. Sigma-2 receptor antagonists rescue neuronal dysfunction induced by Parkinson's patient brain-derived α-synuclein. *J Neurosci Res.* 2021; 00: 1– 16.	

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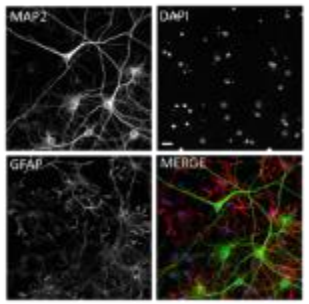
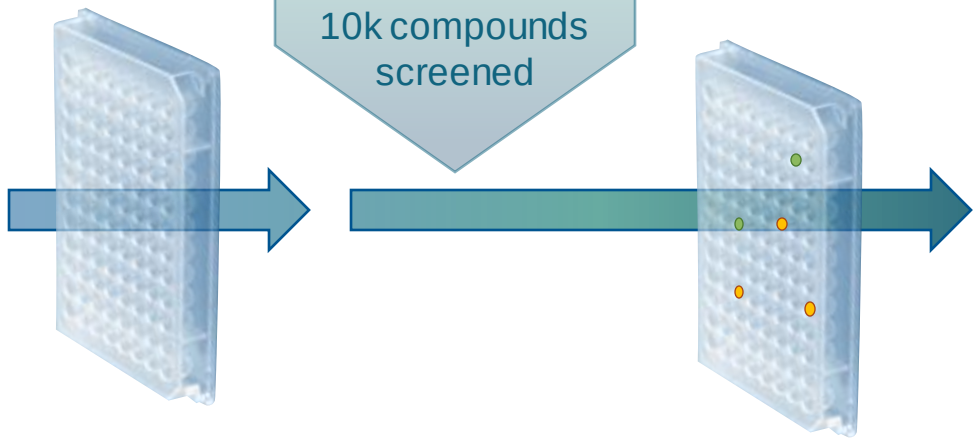
Platform Enabled Therapeutics Company Built on Novel Library & Screening Assay

Extensive IP on candidates developed from foundational platform





Novel proprietary chemical library

More than 10k compounds screened

Novel phenotypic screening assay

>21 DIV primary hippocampal/cortical neuronal cultures *in vitro* models mature nervous system *in vivo*

Disease-relevant Functional readouts

Autophagy, Lipid membrane trafficking

5 distinct chemical series, each with 100s of analogues

Candidate identification and development

CT1812, CT2168 CT2047, CT2638

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Functional, Phenotypic Screening for Novel Drug Discovery

Novel library and screening assay lead to characterization of σ-2 in neurological disease

- Co-founders developed unique screening technology employed at Cognition
- Based on unbiased phenotypic screens in the target cell population of mature primary neurons
- Initial screens for compounds that stop or mitigate age-related damage led to the identification of CT1812
- Importantly this process also identified σ-2 receptors as key regulators of major damage response pathways integral to many neurodegenerative diseases

Alzheimer's Disease

Our Approach

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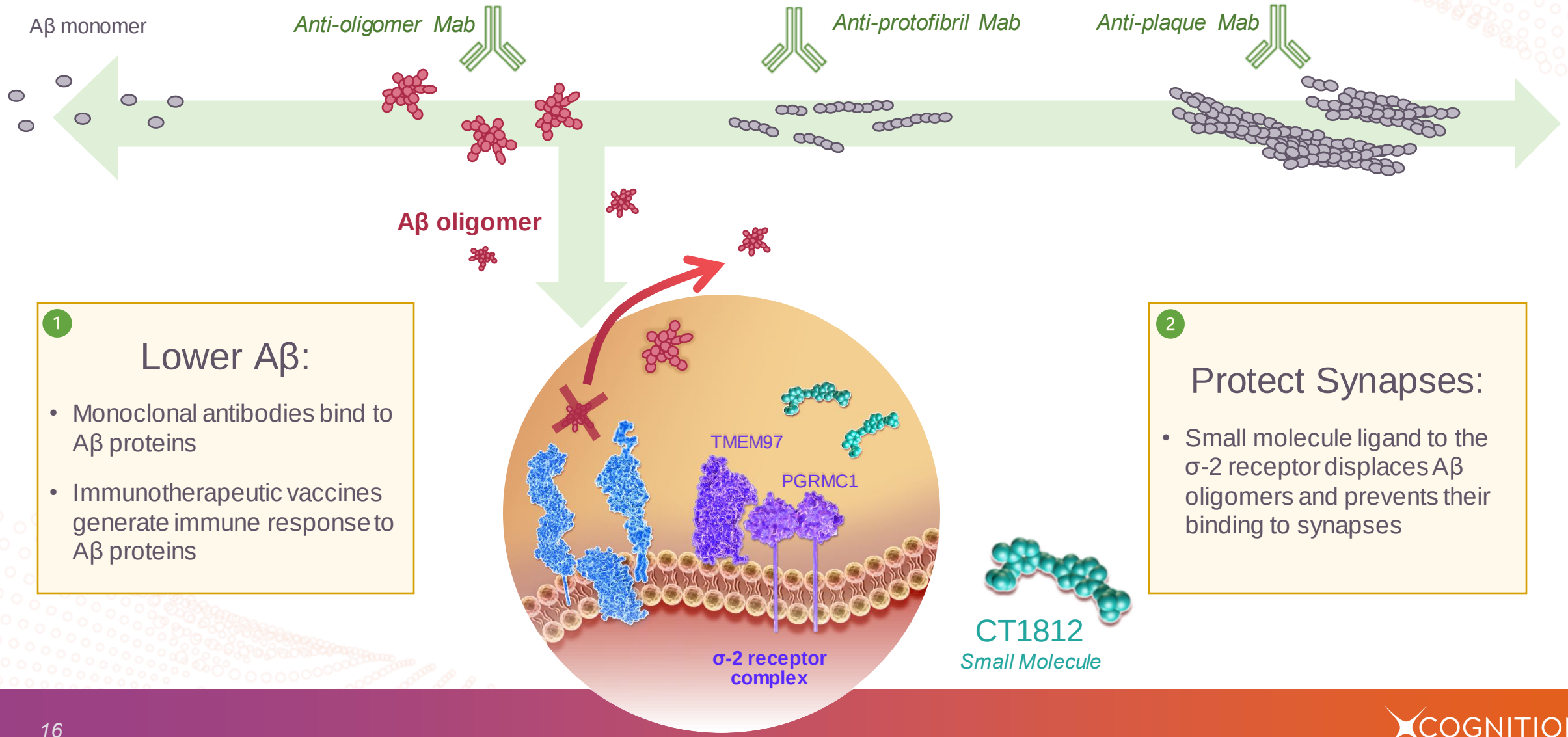
Multiple Approaches Address Toxic Interaction at the Receptor



1

Lower Aβ:

- Monoclonal antibodies bind to Aβ proteins
- Immunotherapeutic vaccines generate immune response to Aβ proteins

2

Protect Synapses:

- Small molecule ligand to the σ-2 receptor displaces Aβ oligomers and prevents their binding to synapses

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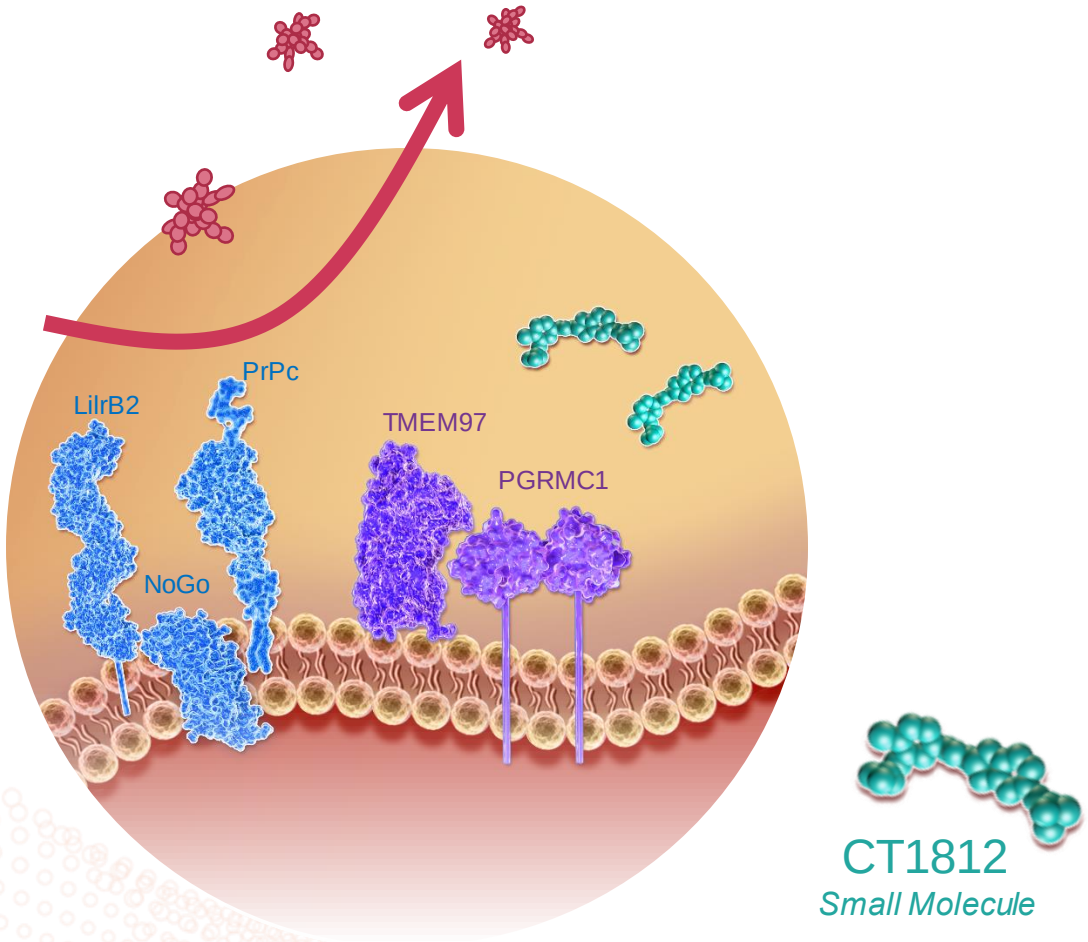
CT1812 May Inhibit Oligomer-induced Toxicity



- Oral, QD small molecule
- Penetrates the blood-brain barrier (BBB)
- Binds selectively to the σ-2 receptor
- Displaces oligomers from neurons and prevents re-binding
- Facilitates restoration of neuronal function

- Izzo N.J, et al. Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification. Alzheimer's Dement. 2021;1–18
- Izzo N.J, et al. Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers II: Sigma-2/PGRMC1 receptors mediate Abeta 42 oligomer binding and synaptotoxicity PLoS One. 2014 Nov 12; 9(11):e111899
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- Limegrover, CS, et al. Alzheimer's Protection Effect of A673T Mutation May Be Driven by Lower Aβ Oligomer Binding Affinity. J Neurochem. 2020; 00: 1– 15. doi:10.1111/jnc.15212

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Our MoA Video

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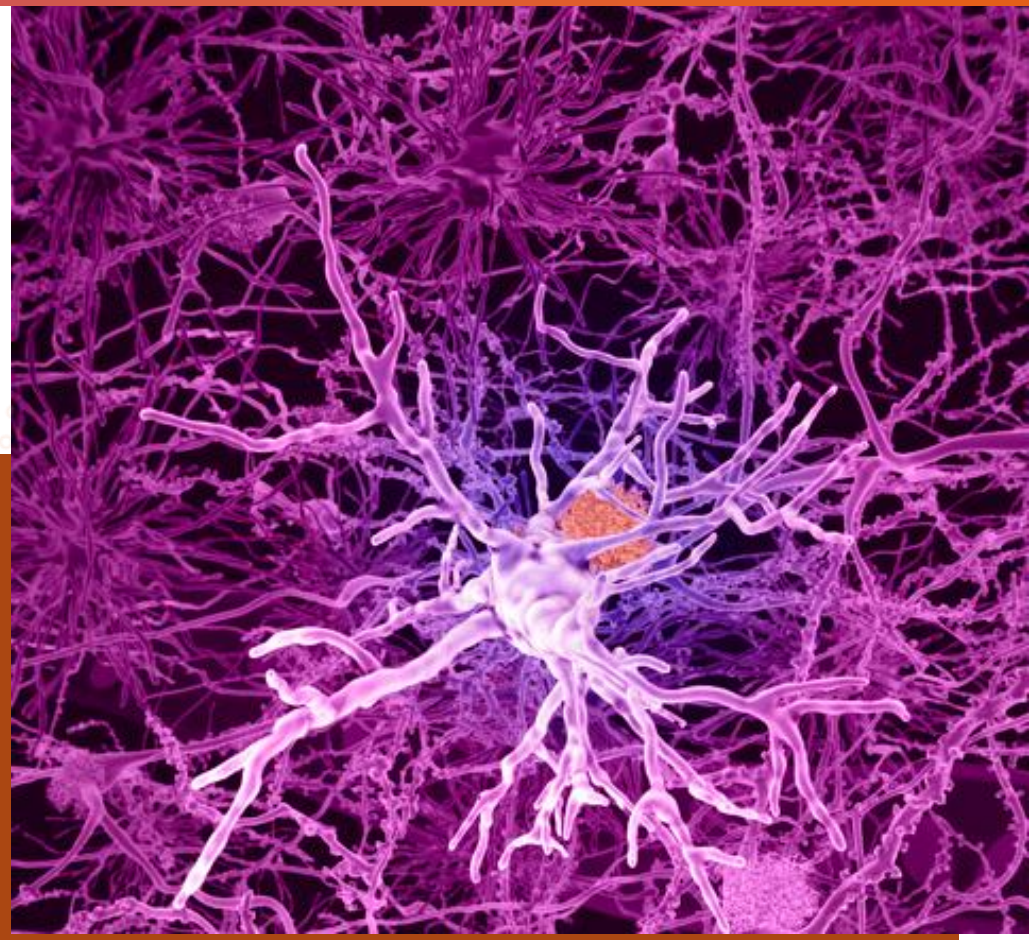
CT1812:

Results from our Alzheimer's Disease Program:

Preclinical



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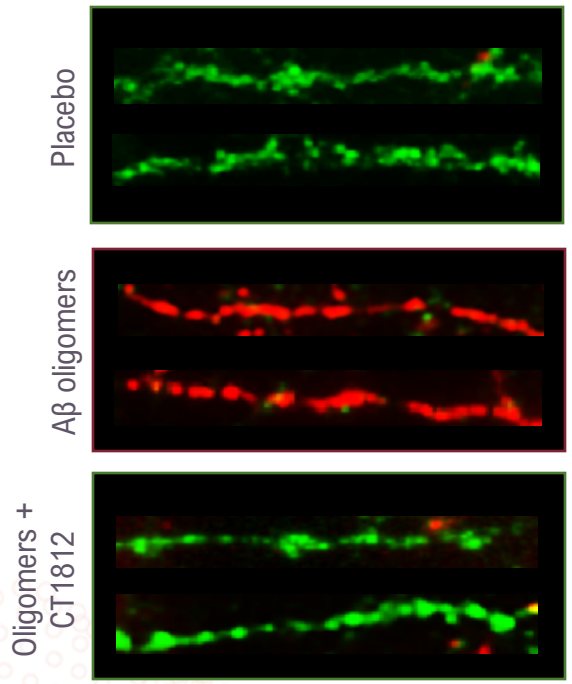
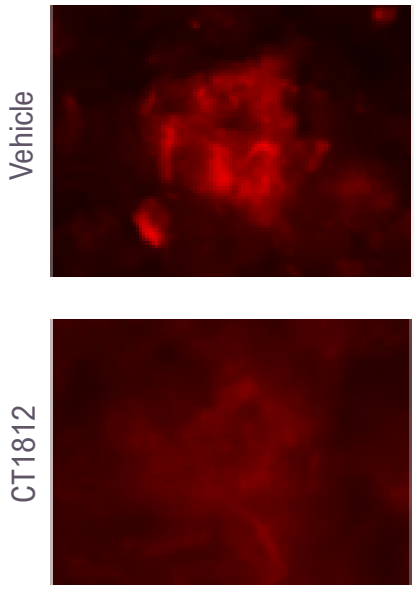
Rigorous Testing Supports Hypothesis

CT1812 Displaces Oligomers from Synapses *in vitro*



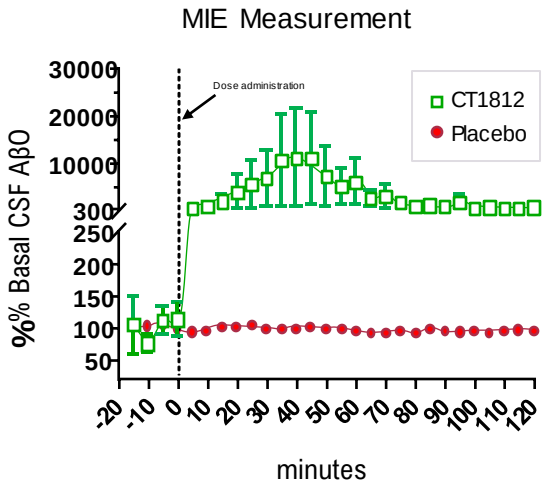
Neurons with synapses (drebrin immunodetection) exhibiting oligomer binding (6E10 immunodetection)

Displaces Oligomers from AD Patient Brain Tissue



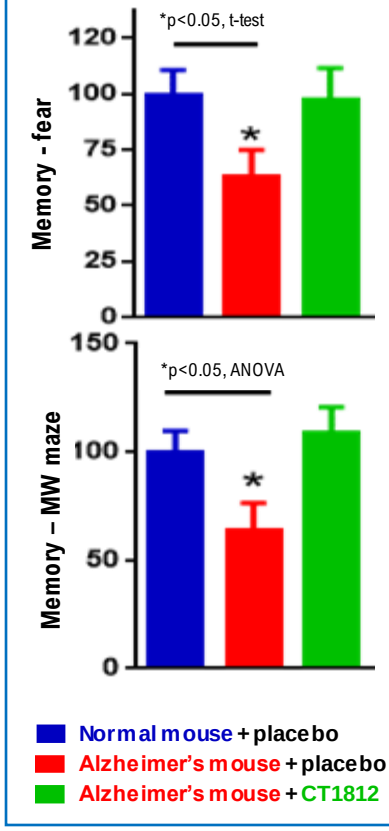
Postmortem Alzheimer's-confirmed brain tissue section (ThioS labeling)

Displaces Oligomers in Mouse Model of Alzheimer's Disease



Microimmunoelectrodes coated with oligomer-specific antibody detect soluble Aβ in transgenic hAPP/PS1 mice

Restores Cognitive Function in Mice



Izzo NJ et al. Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification. Alzheimer's Dement. 2021 Aug; 17(8):1365-1382

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Unique Protective Effect: *A673T-APP Mutation Supports CT1812 MoA*

Received: 16 June 2020 | Revised: 30 September 2020 | Accepted: 1 October 2020

DOI: 10.1111/jnc.15212

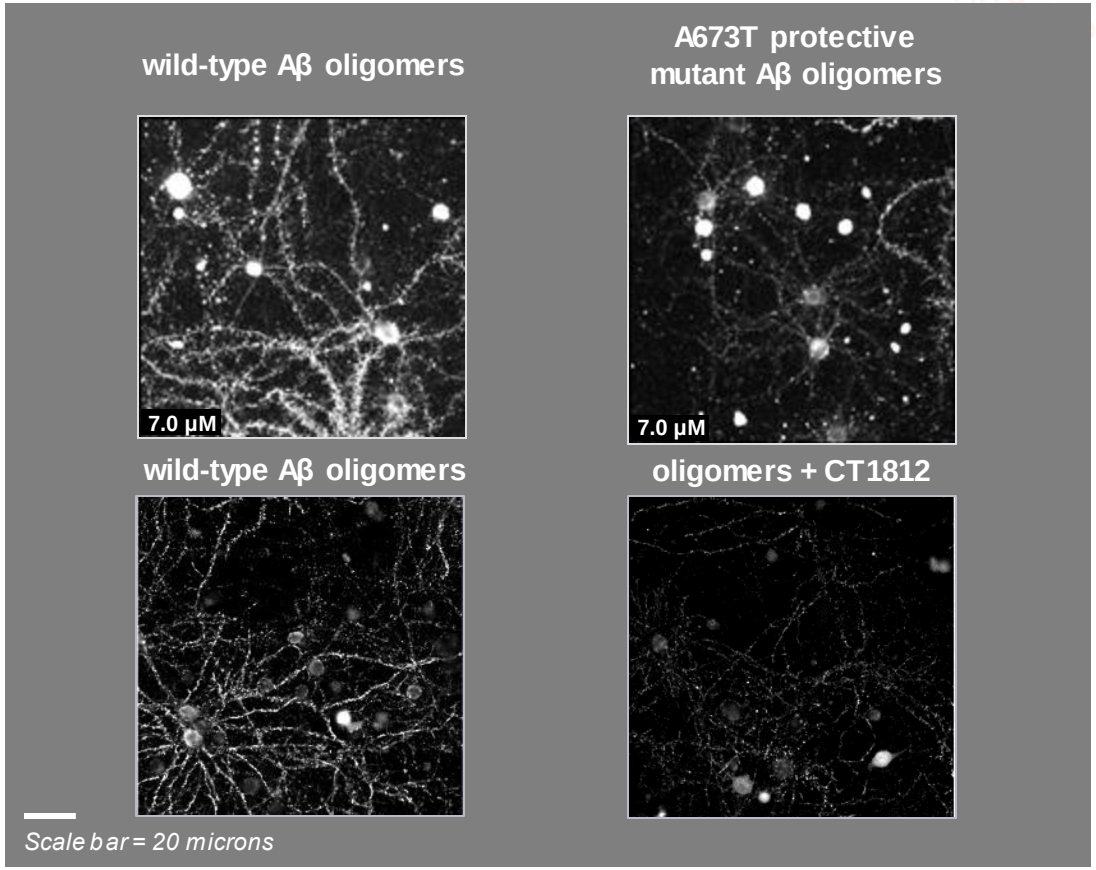
ORIGINAL ARTICLE

Journal of Neurochemistry JNC WILEY

Alzheimer's protection effect of A673T mutation may be driven by lower Aβ oligomer binding affinity

Colleen S. Limegrover[1] | Harry LeVine III[2] | Nicholas J. Izzo[1] | Raymond Yurko[1] | Kelsie Mozzoni[1] | Courtney Rehak[1] | Kelsey Sadlek[1] | Hank Safferstein[1] | Susan M. Catalano[1]

- First variant associated with protection against Alzheimer's disease[1] – 'Icelandic Mutation'
- Mutant Aβ oligomers bind with *four-fold lower affinity* to neuronal synapses than WT protein
- Carriers are *four times less likely* to get Alzheimer's disease than non-carriers[2]
- To our knowledge, CT1812 is the only drug that mimics the protective effects of this mutation



1) Jonsson, T et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 488, 96–99 (2012)
2) Andrews SJ et al. Protective Variants in Alzheimer's Disease. Curr Genet Med Rep. 2019 March ; 7(1): 1–12

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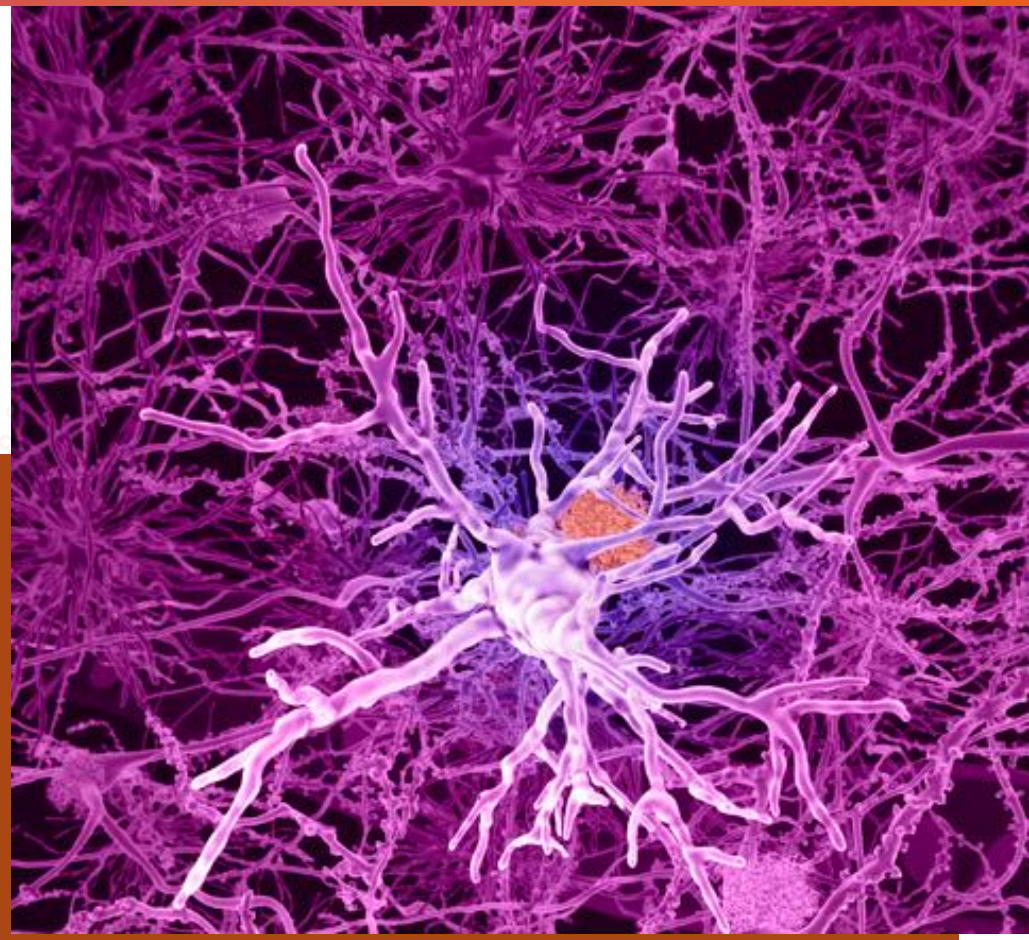
CT1812:

Results from our Alzheimer's Disease Program:
Clinical Findings



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Evidence Mounts of CT1812 Impact on Dementias

Studies of CT1812 to date present evidence of:

- Target engagement — SNAP[1]
- Anatomical effect — SPARC[3]
- Preliminary cognitive improvement — SHINE-A[2]
- Neurophysiology — SEQUEL[4]

Biomarker evidence of effect on pathways[2]

- Synapse Health
- Neuro-inflammation
- Amyloid Biology

NIA funded proof-of-concept studies ongoing:

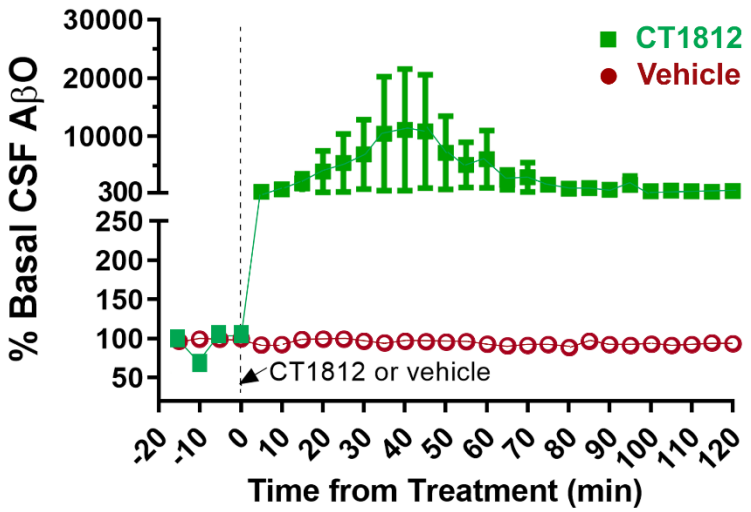
1. SHINE COG0201 — Mild-Moderate Alzheimer's disease → 2024 Readout
2. SHIMMER COG1201 — Dementia with Lewy Bodies → 2024 Readout
3. START COG0203 — Early Alzheimer's disease → Long-term treatment

1. *AD/PD™ 2022*
2. *LaBarbera, et al. Transl Neurodegener 2023*
3. *SPARC results submitted for publication*
4. *Abstract of SEQUEL imaging results submitted for upcoming presentation*

SNAP (COG0105): *Demonstration of Target Engagement*

Published in Translational Neurodegeneration in 2023

MIE Measurement: *in vivo*



NOTE: Microimmunoelectrodes coated with oligomer-specific antibody detect soluble Aβ in transgenic hAPP/PS1 mice

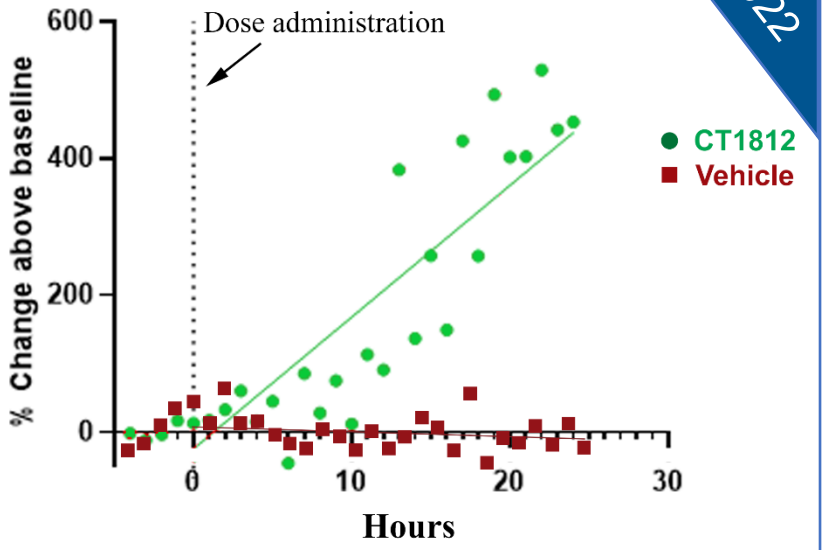
Izzo et al. Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification. Alzheimer's Dement. 2021 Aug; 17(8):1365-1382

Oligomer Displacement in Mice

Replicates in Alzheimer's Patients

AD/PD 2022

MIE Measurement: SNAP



LaBarbera et al. A phase 1b randomized clinical trial of CT1812 to measure Aβ oligomer displacement in Alzheimer's disease using an indwelling CSF catheter. Transl Neurodegener 2023, 12(24)

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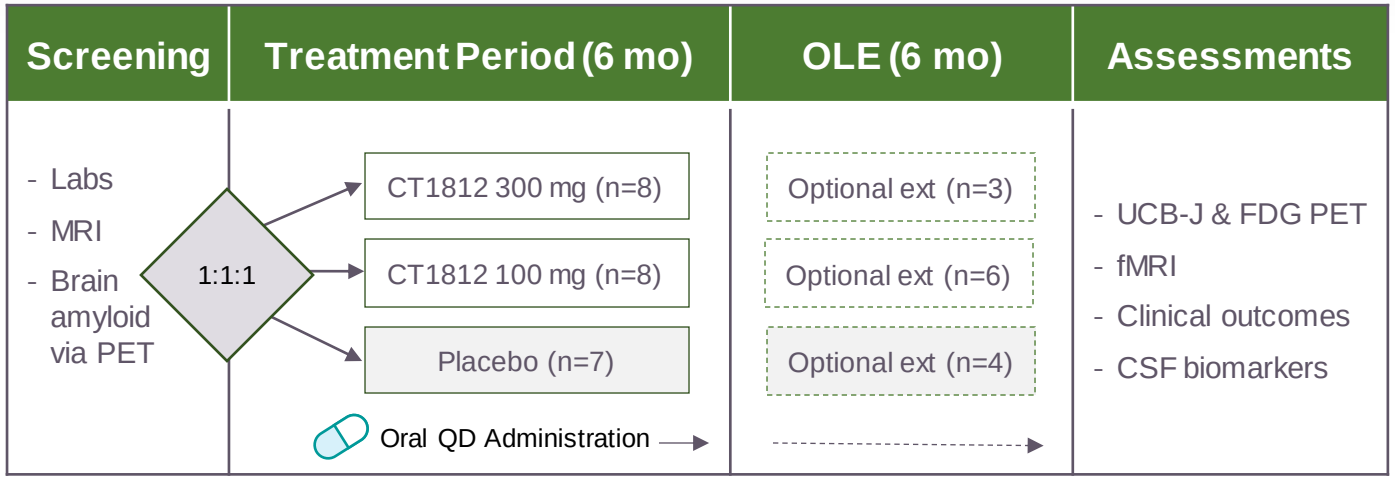
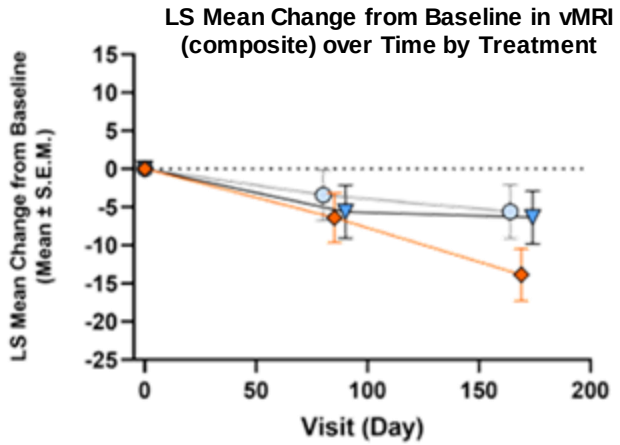
SPARC (COG0105): *Evidence that Target Engagement has Anatomic Impact*



PIs Christopher H. van Dyck, M.D. at the Yale Alzheimer's Disease Research Unit and Richard E. Carson, Ph.D. at the Yale PET Center

SPARC COG0105 study partially funded by NIA grant R01AG057553

Change in Brain Volume: SPARC



MRI Brain Volume (cm^3) 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

AAIC 2022

- Identified biomarkers altered by CT1812 treatment; two of top five relate to synapse health/function

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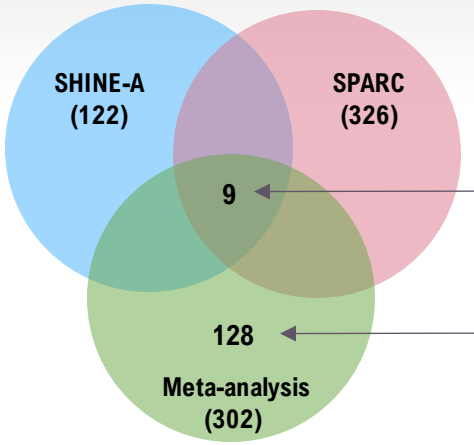
Presented at AD/PD 2023

Culmination of biomarker work previously presented at 2022 AAIC & AD/PD

- Results of a meta-analysis of CSF samples from Phase 2 SHINE & Phase 1b SPARC studies presented at AD/PD
- Identified biomarkers of CT1812 activity that replicated across two independent studies and patient cohorts
- Findings will inform our understanding of CT1812's impact on the pathways involved in Alzheimer's disease progression

[*Find it on the Cognition website*]



- Replication of biomarker changes by CT1812 vs placebo across two independent cohorts
  - 9 biomarkers with cross-trial replication and similar directionality and degree of change
  - 128 biomarkers that may require increased power to detect significance

GO term	Biological Process (Replicated Biomarkers; CT1812 vs placebo)	strength	FDR p-value
GO:1902003	Regulation of amyloid-beta formation	2.14	6.00E-06
GO:1902430	Negative regulation of amyloid-beta formation	2.41	1.55E-05
GO:1902993	Positive regulation of amyloid precursor protein catabolic process	2.17	6.17E-05
GO:1905908	Positive regulation of amyloid fibril formation	2.82	9.19E-05
GO:0050808	Synapse organization	1.28	0.00089
GO:1900272	Negative regulation of long-term synaptic potentiation	2.35	0.00089
GO:1902947	Regulation of tau-protein kinase activity	2.31	0.00089
GO:1902950	Regulation of dendritic spine maintenance	2.35	0.00089
GO:0048638	Regulation of developmental growth	1.2	0.0015
GO:1900221	Regulation of amyloid-beta clearance	2.2	0.0015

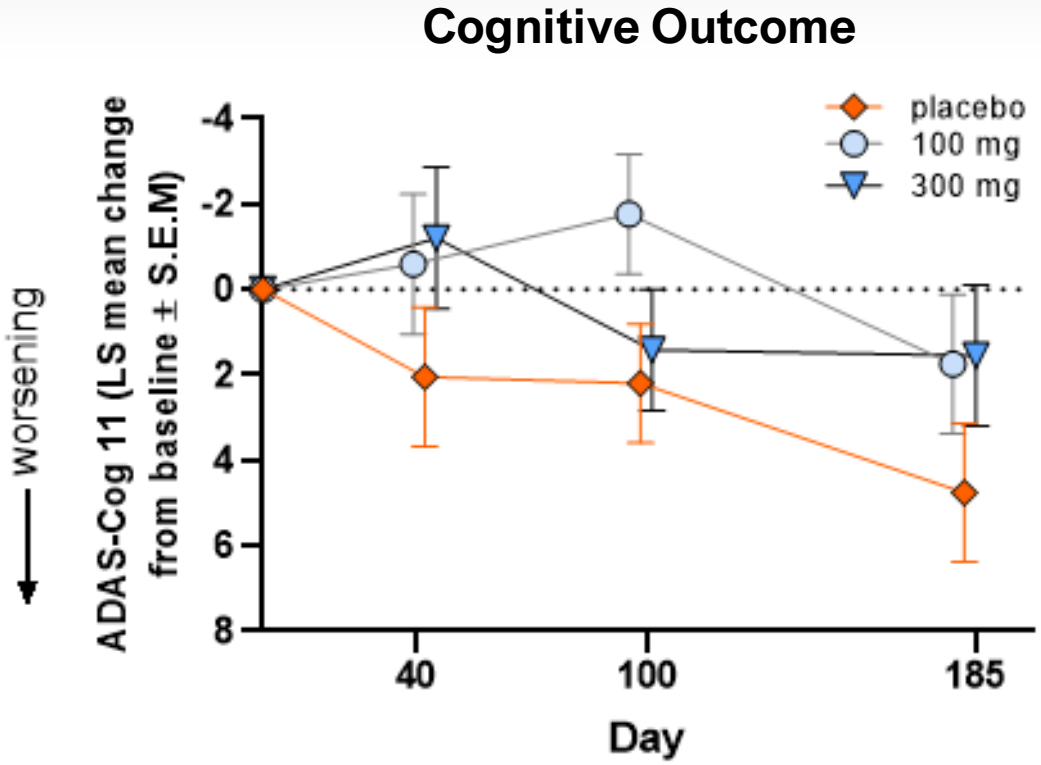
COGNITION™ Therapeutics

Phase 2 Safety and Efficacy Study in Adults with Mild-to-moderate Alzheimer's Disease

Enrollment Criteria	Treatment Period (6 mo)	Assessments
- Diagnosis of Alzheimer's disease - MMSE 18-26 - Labs - MRI - Brain amyloid via PET	1:1:1 → CT1812 300 mg (n=48) 1:1:1 → CT1812 100 mg (n=48) 1:1:1 → Placebo (n=48) Cohort A: 24 participants Total anticipated: 144 participants Oral QD Administration →	- Cognitive testing - Biomarkers (CSF/Plasma)

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

Clinical Evidence of Cognitive Benefit



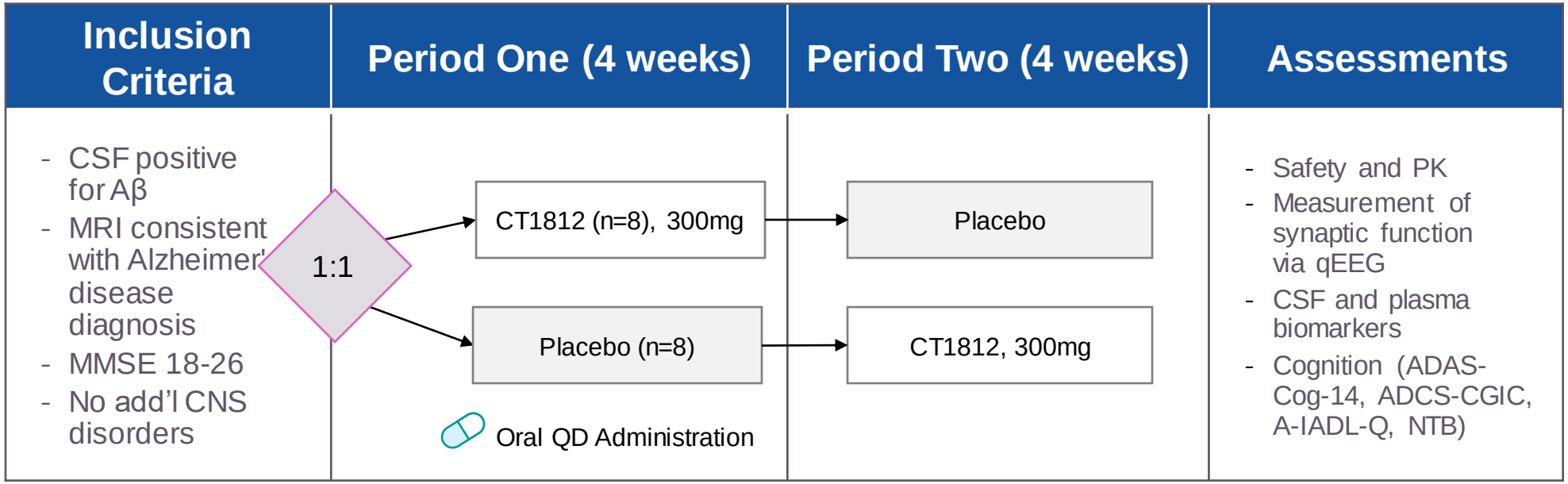
- SHINE interim analysis (n=24) yields promising evidence:
  - 3-point difference (ADAS-COG 11) between treated and untreated participants at Day 185
  - Clinically meaningful magnitude of change
  - Trend towards slower cognitive decline in CT1812-treated vs placebo-treated participants

SHINE COG0201 Study (NCT03507790) funded by NIA grant R01AG058660

COGNITION Therapeutics

SEQUEL (COG0202): *Single-site qEEG Study in 16 Adults with Mild-to-moderate Alzheimer's Disease*

Two-group cross-over design

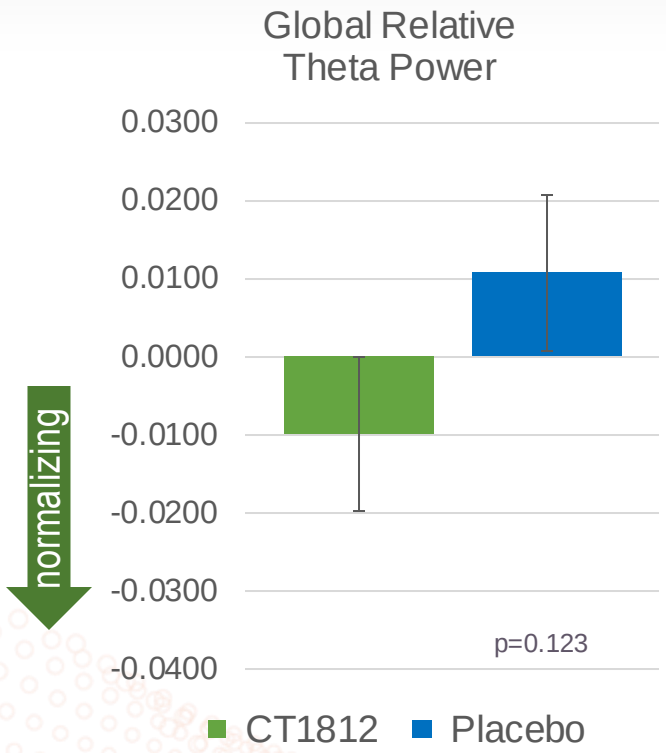


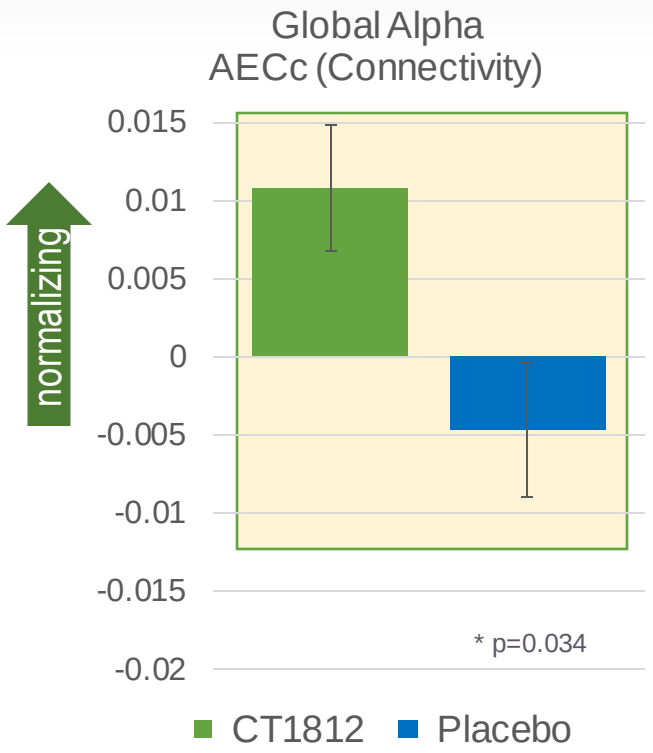
https://clinicaltrials.gov/ct2/show/NCT04735536

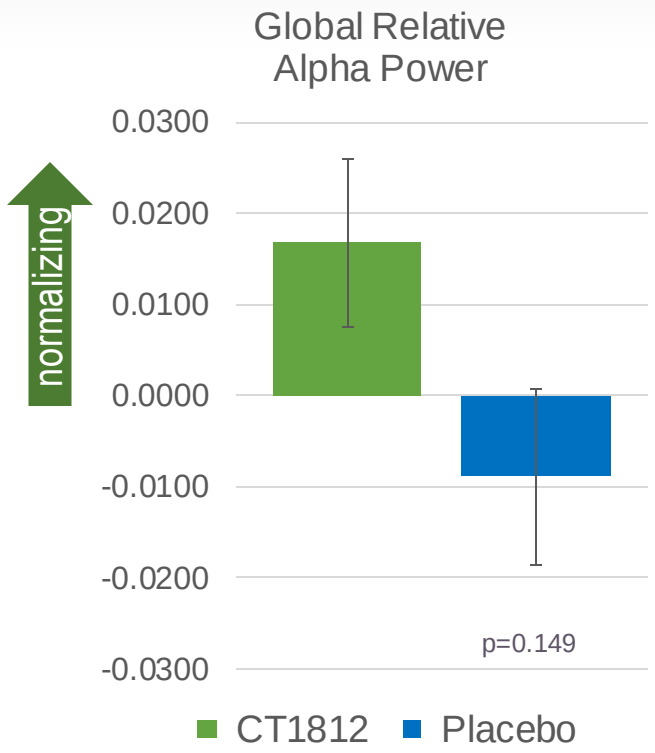
Quantitative EEG refers to the analysis of digital EEG signals using sophisticated mathematical algorithms that can identify and differentiate between nuances of brain wave patterns.

SEQUEL Topline Results

Safety and tolerability profile consistent with previous studies







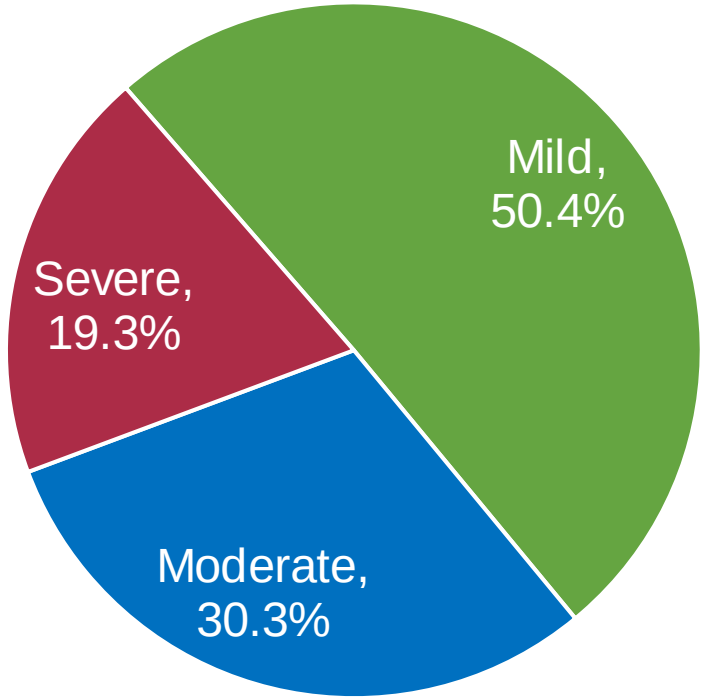
** Nominally significant*

COGNITION™ Therapeutics

Expanding into *Early* Alzheimer's Disease

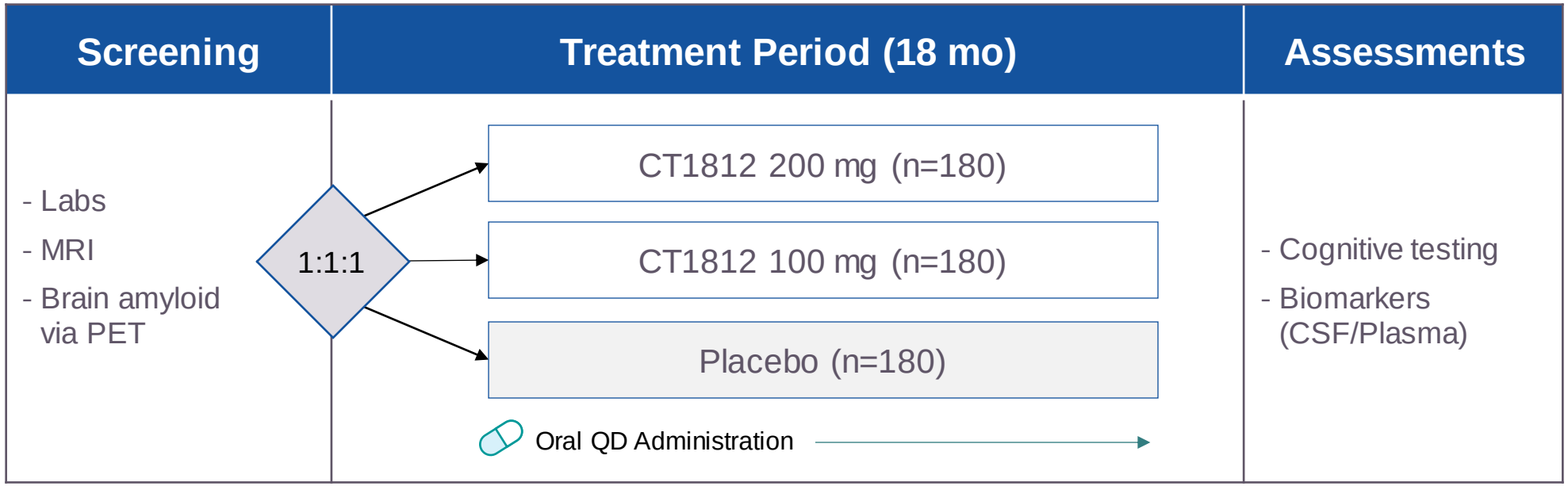
- Enrolling 540 adults with early-to-mild Alzheimer’s disease
  - ~6.7 million in the U.S. have Alzheimer's, 50% with mild disease
- 50-60 U.S. sites including ACTC centers of excellence
- $81M NIA grant award
- Opening sites 1H23

Stages of Disease Afflicting Current Population of Alzheimer’s Patients



Phase 2 Efficacy Study in 540 Adults with *Early* Alzheimer's Disease

Conducted in collaboration with Alzheimer's Clinical Trials Consortium



START COG0203 study (NCT05531656) partially funded by $81M NIA grant R01AG065248
ACTC funded by NIA grant U24AG057437

BREAKING News First site activated in Phase 2 START Study …

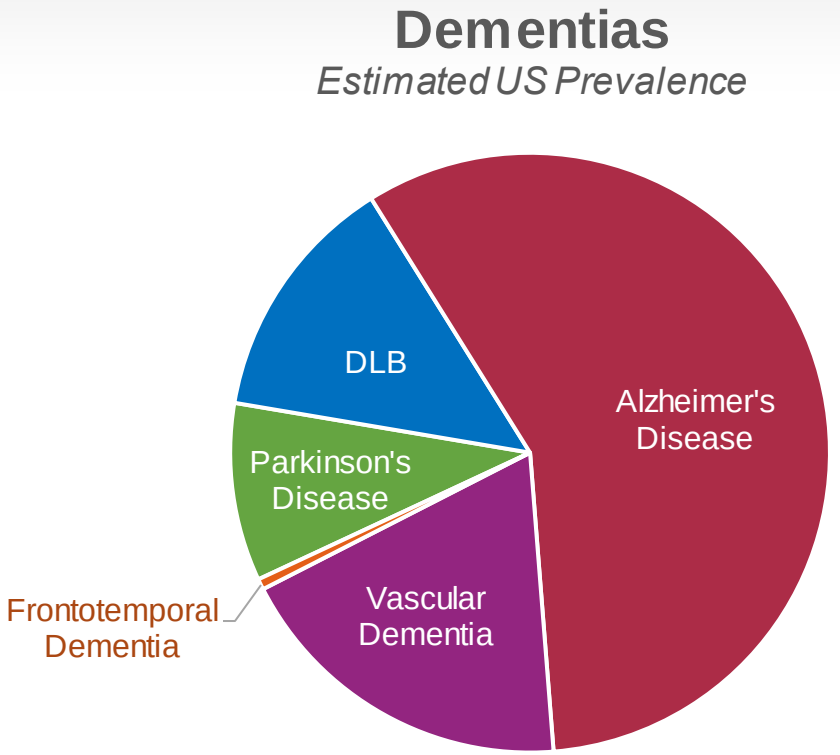
Dementia with Lewy Bodies (DLB)

Second Most Common Dementia

COGNITION™ Therapeutics

Synucleinopathies are 2nd only to AD in Prevalence

- In the U.S., approximately 13 million people have a form of dementia[1]
  - Dementia with Lewy bodies (DLB): 1.4 million
  - Parkinson's disease: 1 million
- Direct healthcare costs:
  - DLB: $31.5 billion[2]
  - PD: $25 billion[3]



α-synuclein oligomers, which disrupt key cellular processes, are a hallmark of both disorders

1) Milken Institute report: (2019) Reducing the Cost and Risk of Dementia: Recommendations to Improve Brain Health and Decrease Disparities.
2) LBDA (extrapolated): LBD is the Most Expensive Dementia in America and Yingjia Chen et al Alzheimers Dement. 2019
3) MJFF and The Lewin Group: Economic Burden and Future Impact of Parkinson's Disease (2019)

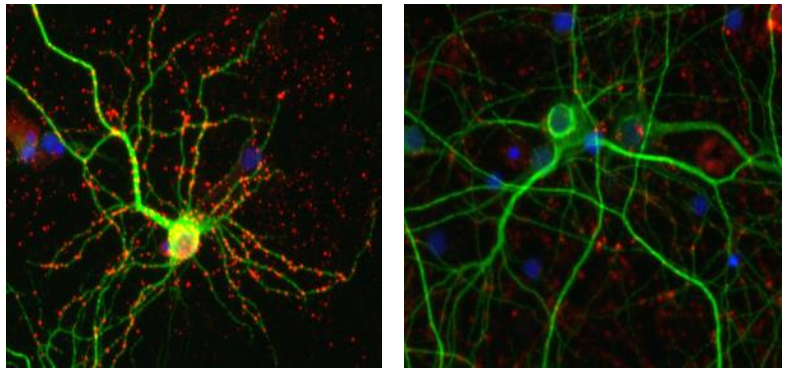
σ-2 Modulators May be Disease Modifying in Synucleinopathies

Cellular evidence that σ-2 modulators have a beneficial impact

σ-2 antagonist blocks the binding / internalization of α-synuclein oligomers at synapses

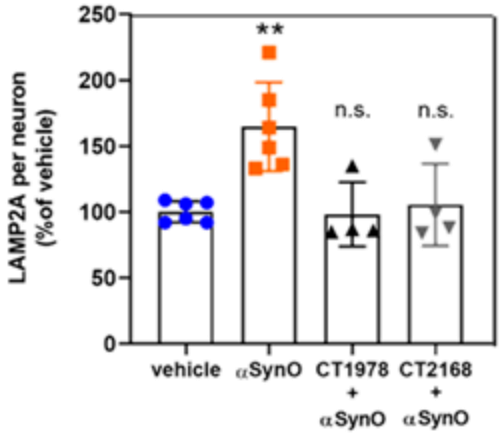
α-synuclein oligomers

α-synuclein oligomers + CT1812

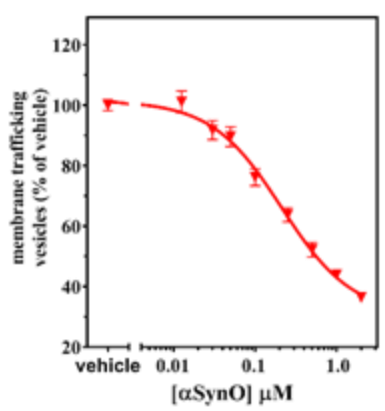


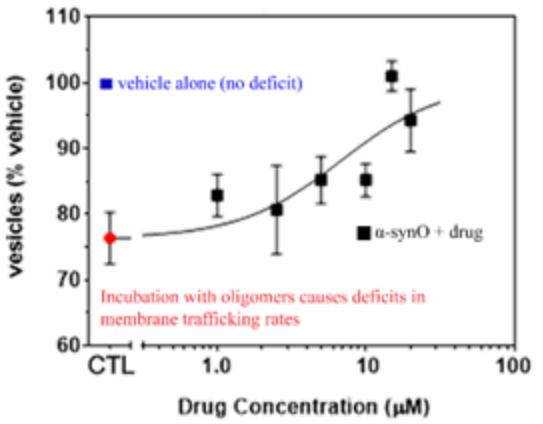
α-Synuclein oligomers in red

σ-2 antagonist (blk & gry) reverses effect of α-syn oligomers on LAMP2a (org)



α-synuclein oligomer-induced trafficking deficits (red) are reversed by σ-2 antagonist (blk)



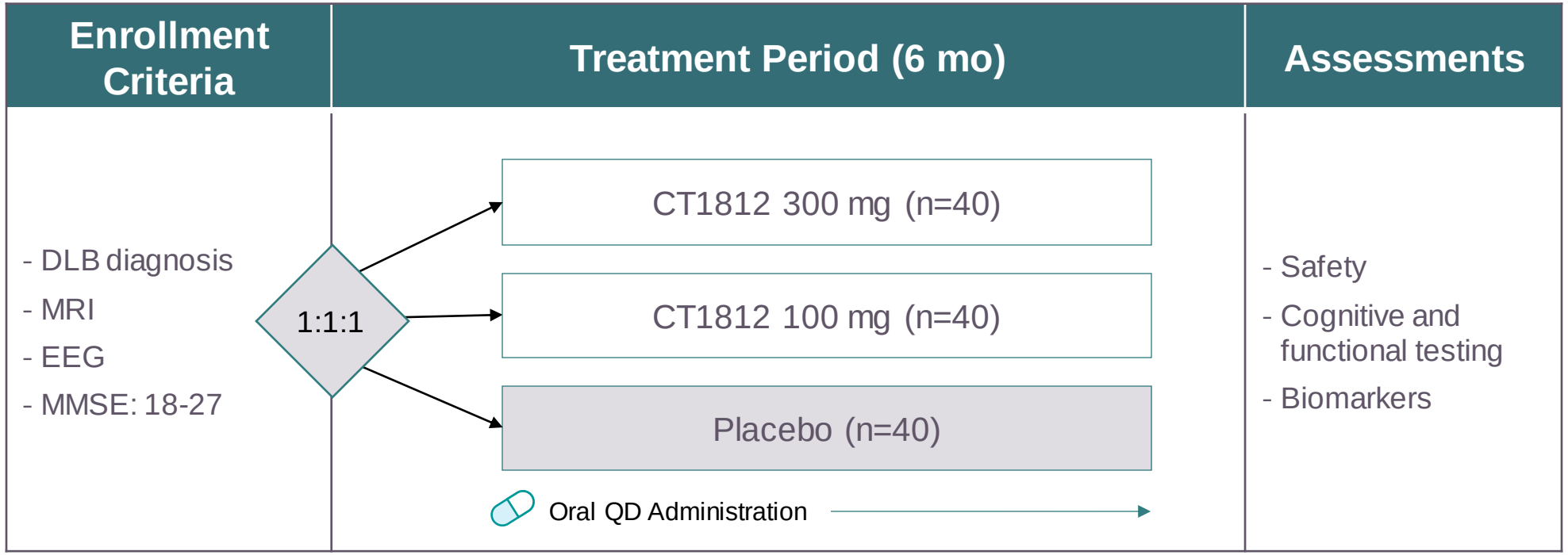


Limegrover CS, et al. J Neurosci Res. 2021. doi: 10.1002/jnr.24782

COGNITION™ Therapeutics

Phase 2 Safety and Efficacy Study in Adults with Mild-to-moderate DLB

Conducted in collaboration with Lewy Body Dementia Association & U Miami



Principal investigator: James E. Galvin, MD, MPH, professor of neurology and director of the Comprehensive Center for Brain Health

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

Evidence Mounts of CT1812 Impact on Dementias

Studies of CT1812 to date present evidence of:

- Target engagement — SNAP[1]
- Anatomical effect — SPARC[3]
- Preliminary cognitive improvement — SHINE-A[2]
- Neurophysiology — SEQUEL[4]

Biomarker evidence of effect on pathways[2]

- Synapse Health
- Neuro-inflammation
- Amyloid Biology

NIA funded proof-of-concept studies ongoing:

1. SHINE COG0201 — Mild-Moderate Alzheimer's disease
2. SHIMMER COG1201 — Dementia with Lewy Bodies
3. START COG0203 — Early Alzheimer's disease

→ 2024 Readout

→ 2024 Readout

→ Long-term treatment

1. *AD/PD™ 2022*
2. *LaBarbera, et al. Transl Neurodegener 2023*
3. *SPARC results submitted for publication*
4. *Abstract of SEQUEL imaging results submitted for upcoming presentation*

Dry Age-related Macular Degeneration (dry AMD)

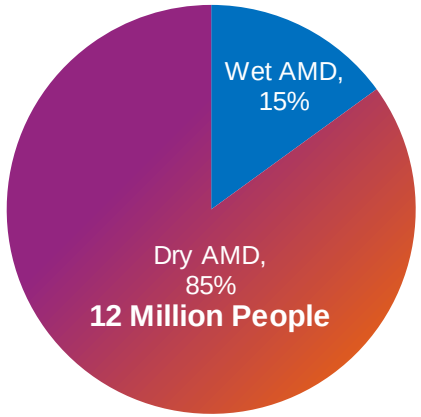
COGNITION™ Therapeutics

Dry AMD and Geographic Atrophy

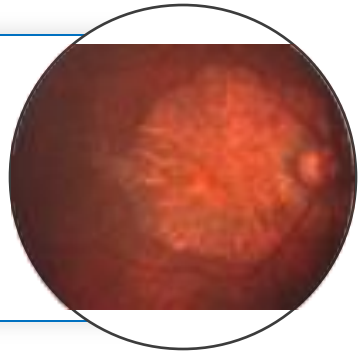
*Leading cause of severe vision loss in people over 50 (AAO)**

- AMD is the leading cause of blindness in people over 60yr
- Dry AMD is a progressive condition and accounts for up to 90% of all AMD cases
  - Advanced dry AMD, or GA, affects approximately two million people in the U.S.
- Unlike wet AMD, there is only one approved drug for dry AMD
  - Until 2023, dietary supplements were SoC
  - For reference, wet AMD market is $7 billion worldwide

15 million people in North America have AMD



Geographic atrophy is a progressive degeneration of the macula associated with late-stage AMD. Regions of atrophy result in a blind spot in the visual field.



* *American Academy of Ophthalmology*

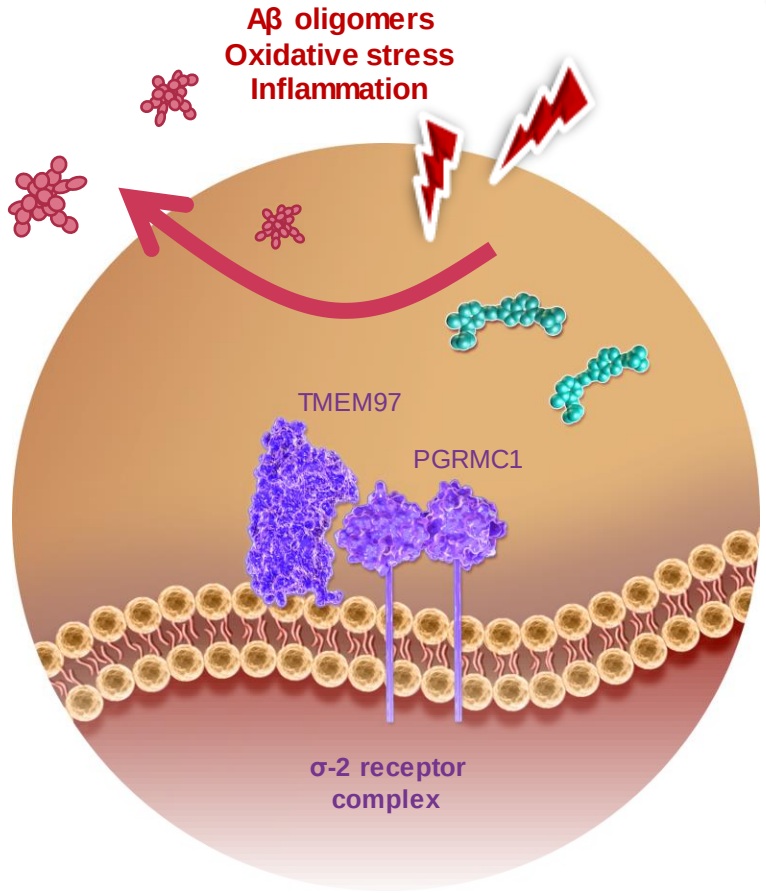
COGNITION™ Therapeutics

Rationale for σ-2 Modulators in Geographic Atrophy

Goal: Protect RPE cells from disease-relevant stressors

σ-2 receptors:

- Expression: in RPE cells, retinal ganglion cells, photoreceptors in retina
- Biology: regulates autophagy, protein trafficking, lipid metabolism dysregulated in AMD
- Target validation: TMEM97 knockdown is protective
- Human genetics: linked to dry AMD
- Biomarker evidence from AD trials



Our Findings are Supported in Literature

ELSEVIER

Cellular Signalling
Volume 86, October 2021, 110078

TMEM97 ablation aggravates oxidant-induced retinal degeneration

Hongtao Shen [a 1], Jing Li [a 1], Tyler Heisler-Taylor [b], Ryan Makin [c d], Huan Yang [e], Timur A. Mavlyutov [e], Bradley Gelfand [c d f], Colleen M. Cebulla [b], Lian-Wang Guo [a d]

"We observed increased RPE damage and photoreceptor loss in TMEM97 KO (vs WT) mice treated with NaIO3. Similarly, knockout of TMEM97 in RPE cells *in vitro* exacerbated oxidative stress..."

International Journal of *Molecular Sciences*

MDPI

Article

Development of a CRISPRi Human Retinal Pigmented Epithelium Model for Functional Study of Age-Related Macular Degeneration Genes

Jiang-Hui Wang [1,2,†], Daniel Urrutia-Cabrera [1,2,†], Jarmon G. Lees [3,4], Santiago Mesa Mora [1,2], Tu Nguyen [1,2], Sandy S. C. Hung [1,2], Alex W. Hewitt [1,2,5], Shiang Y. Lim [3,4], Thomas L. Edwards [1,2] and Raymond C. B. Wong [1,2,*]

"our results provide the first evidence that TMEM97 plays an important role in regulating oxidative stress and cell survival of human RPE..."

GCAT TACG GCAT *genes*

MDPI

Brief Report

Retinal Photoreceptor Protection in an AMD-Related Mouse Model by Selective Sigma-1 or Sigma-2 Receptor Modulation

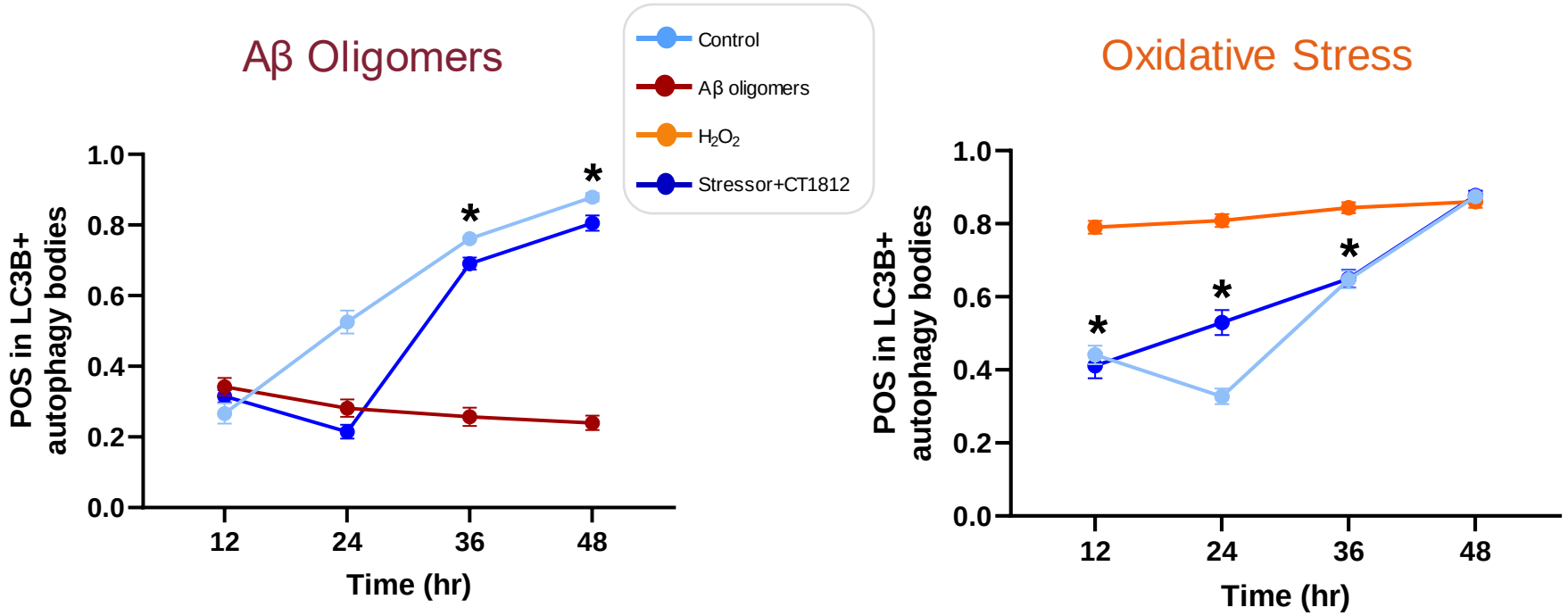
Timur A. Mavlyutov [1,†], Jing Li [2,†], Xinying Liu [3], Hongtao Shen [2], Huan Yang [1], Christopher R. McCurdy [4], Bikash Pattnaik [3,5,6,*] and Lian-Wang Guo [1,2,6,7,*]

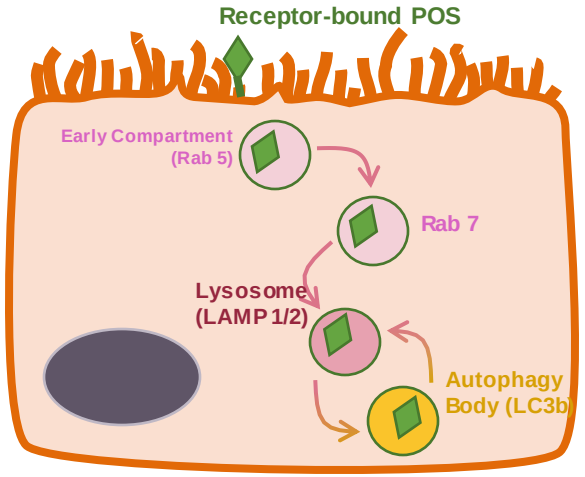
"S2R-selective ligand ...appeared to largely rescue light-induced photoreceptor loss ... TMEM97/S2R ablation exacerbated retinal degeneration..."

σ-2 Receptor Modulators Rescue Lysosomal Trafficking Deficits in RPE

ARVO 2022

CT1812 rescues crucial function of RPE to traffic & degrade photoreceptor outer segments cargos following toxic insults





Malagise E et al. Sigma-2 receptor modulators rescue POS trafficking deficits in RPE cell-based models of dry AMD. Poster presented at: 2022 ARVO

COGNITION™ Therapeutics

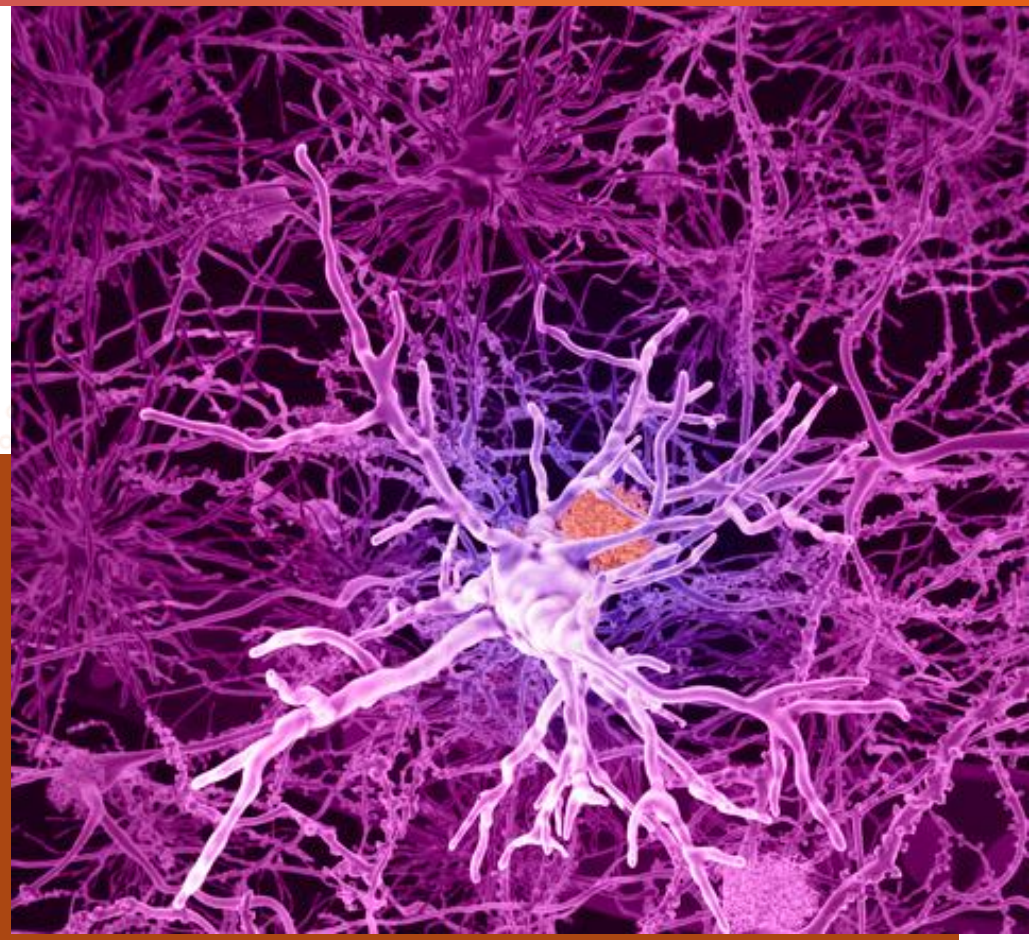
Phase 2 will Assess CT1812 in GA Secondary to Dry AMD

Enrollment Criteria	Treatment Period (24 mo)	Safety (4 wk)	Assessments
- Age: ≥ 50 - Diagnosis of dry AMD - BCVA ≥ 24 letters (ETDRS) - GA lesion ≥ 2.5 and ≤17.5mm^2	Randomized 1:1 CT1812 200mg (n=123) Placebo (n=123) Oral QD Administration		- Change in GA lesion area (FAF) - Ellipsoid zone area (SD-OCT) - Drusen volume (SD-OCT) - Safety

BREAKING News

First participant dosed in Phase 2 MAGNIFY Study …

Closing Comments



COGNITION™ Therapeutics

"Conversations"

A Cognition Therapeutics Podcast Series

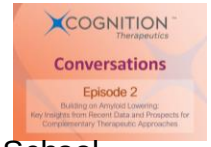
https://cogrx.com/conversations/

Episode 1: Dementia with Lewy Bodies

Featuring:
- James Galvin, University of Miami Miller School of Medicine

Episode 2: Amyloid Lowering

Key Insights from Recent Data



Featuring:
- Christopher van Dyck, Yale University School of Medicine
- Anton Porsteinsson, Univ of Rochester School of Medicine and Dentistry

Episode 3: What if it's not Alzheimer's?

The Caregiver's Perspective on Lewy Body Dementia

Featuring:
- Norma Loeb, LBD Resource Center
- Mary Lou Falcone, caregiver

Episode 4: Insights for the HCP

Recognizing Dementia with Lewy Bodies

Featuring:
- Brendan Kelley, Univ of Texas SW
- Sarah Berman, UPMC
- James Leverenz, Cleveland Clinic Lou Ruvo Ctr
- David Shprecher, Banner Sun Health

Episode 5: Proteomics & Pathways of Neurodegeneration

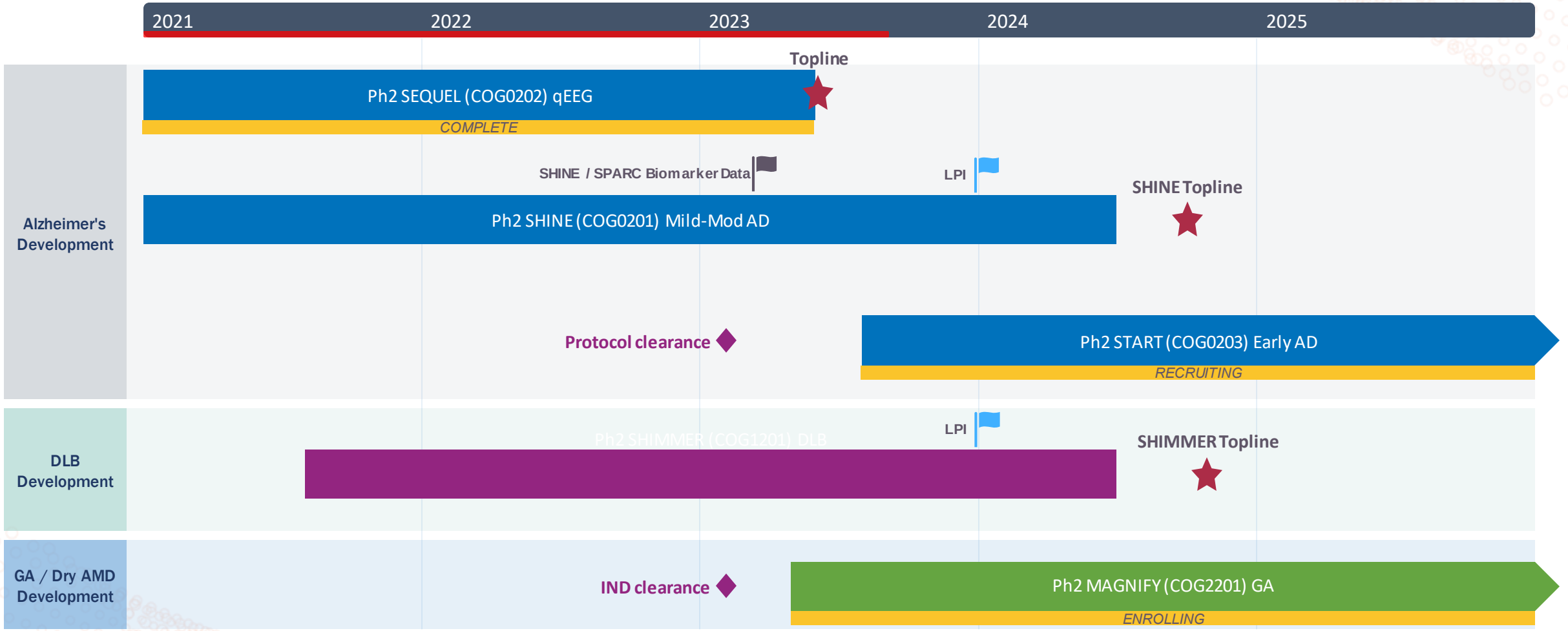
Featuring:
- Charlotte Teunissen, Amsterdam University Medical Center
- Nicholas Seyfried, Emory School of Medicine
- Henrik Zetterberg, Gothenburg University

Episode 6: Geographic Atrophy

New Strategies to Protect the Retina (2-part)

Featuring:
- C. Gustavo De Moraes, Columbia Univ. and Ora
- Jeffrey Heier, Ophthalmic Consultants of Boston
- Peter Kaiser, Cleveland Clinic College of Medicine

Multiple Near-term Catalysts



COGNITION™ Therapeutics

Financial Position

Financials as of June 30, 2023

- Cash and Cash Equivalents: $37.2 million
- Expected cash runway through third quarter of 2024

Grant funding for CT1812 studies as of June 30, 2023

- Preclinical through Phase 2: appx $171.0 million
  - Approximate funding used: ($89.2 million)
  - *Remaining grant funding:* **$81.8 million**

COGNITION™ Therapeutics

Cognition Therapeutics - in Summary

Targeting unmet needs in age-related degenerative disorders of the CNS and retina such as Alzheimer's disease, DLB, GA secondary to dry AMD, and Parkinson's disease

Functionally distinct therapeutic approach focused on the σ-2 receptor complex, backed by decades of expertise in the biology of synaptic function and plasticity

Received over $170 million in non-dilutive grant funding through key collaborations with the NIA and other thought-leading institutions

Multiple Phase 2 programs expected to conclude with data read-outs over the next 12 to 24 months

Seasoned management team with broad scientific, drug development and commercial expertise; experienced board and advisors

Thank You

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COGNITION™ Therapeutics