COGNITION™ Therapeutics

Developing disease-modifying medicines for degenerative disorders

Analyst Breakfast

April 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 and financial resources and our clinical development plans, are forward-looking statements. These statements 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; 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; 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 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.

AGENDA

8:30 – 9:00	Arrivals / Breakfast	
9:00 – 9:15	Welcome and Introductions	Lisa Ricciardi, CEO
9:15 – 9:35	The SCIENCE: Our Understanding of sigma-2 Receptor Biology	Dr. Anthony Caggiano, CMO & Head of R&D
9:35 – 9:50	Q&A / BREAK	
9:50 – 10:10	Our RATIONALE CT1812 Biomarker Program	Dr. Britney Lizama Research Scientist
10:10 – 10:35	The CLINIC: A Review of our Ongoing and Planned Clinical Trials	Dr. Paul Tiseo, VP Clinical Development
10:35 – 10:50	Q&A / BREAK	
10:50 – 11:00	2023 – 2025 Outlook	Lisa Ricciardi, CEO
11:00 – 11:15	Q&A	All

Presenters for Today's Discussion

Lisa Ricciardi
President & CEO

Andrew Einhorn
Interim CFO

Anthony Caggiano, MD, Ph.D.
CMO & Head of R&D

Mary Hamby, Ph.D.
VP, Research

Paul Tiseo, Ph.D.
VP, Clinical Development

Britney Lizama, Ph.D.
Research Scientist

COGNITION™ Therapeutics

Cognition Therapeutics Highlights

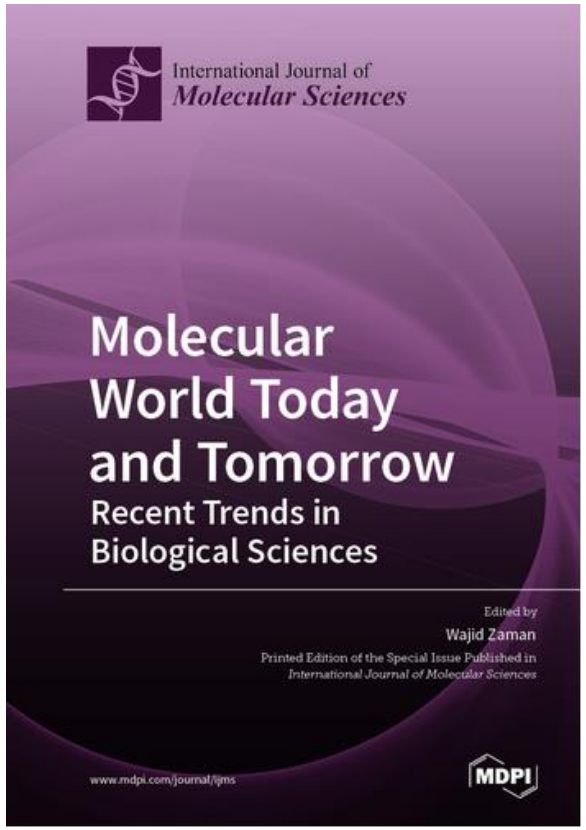
Novel Approach Validated Science	CT1812 Oral Once-Daily	Development Focused on Major Commercial Ops	Strong Financials
Protect synapses from toxic proteins and other stressors to facilitate restoration of neuronal function	Oligomer receptor: well characterized target Highly brain penetrant Selective and saturable binding	Four Phase 2 trials AD, DLB, GA/dry AMD are significant conditions with large patient populations	$170+ Million in cumulative non-dilutive grant funding Expected cash runway into first half of 2024

Rigorous Phase 2 Programs Underway and Planned

Clinical Study	Indication	US Prevalence	Grant Funding
SEQUEL (n=23)	Mild-moderate AD	~ 5 million	$5.4 Million
SHINE (n=144)	Mild-moderate AD	~ 5 million	$30 Million
START (n=540)	MCI & Early AD	~ 11 million	$81 Million
SHIMMER (n=120)	Mild-moderate DLB	~1.4 million	$30 Million
MAGNIFY (n=240)	GA secondary to dry AMD	~1.5 million	Equity

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

Published in the *International Journal of Molecular Sciences*



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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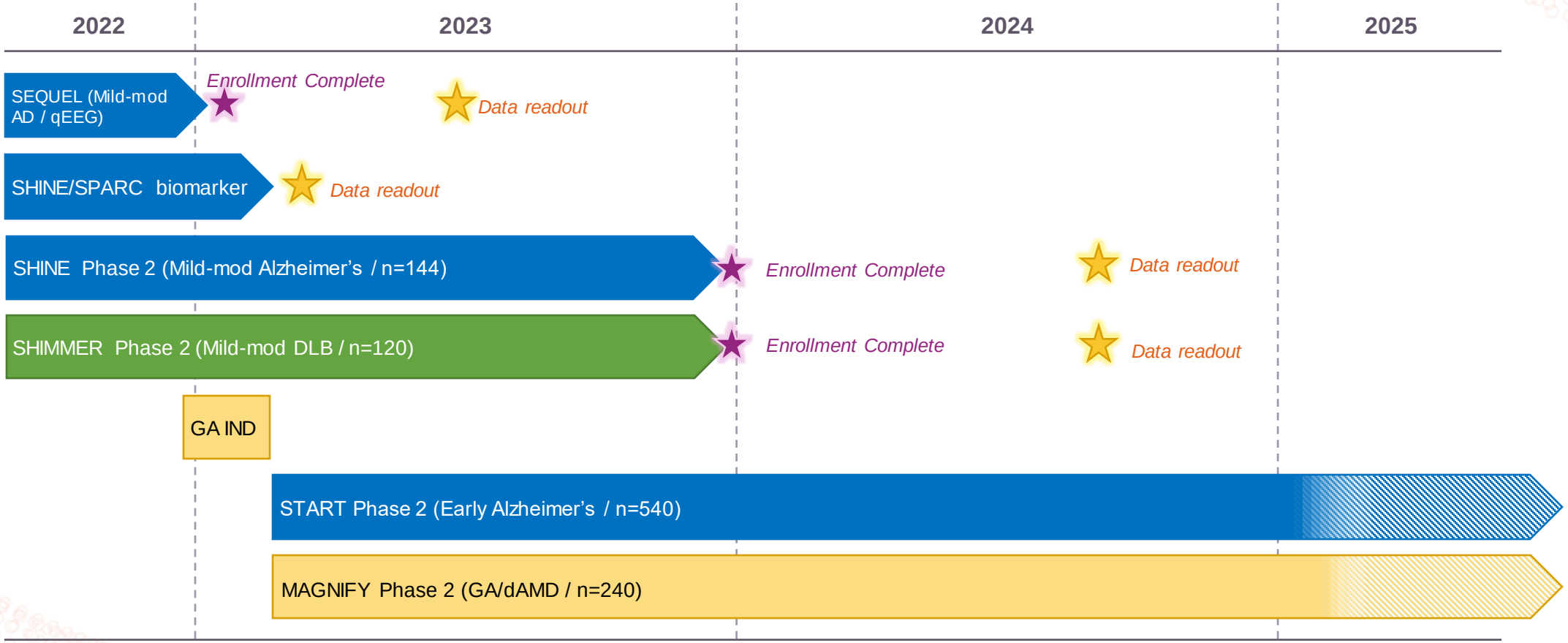
Multiple Near-term Catalysts



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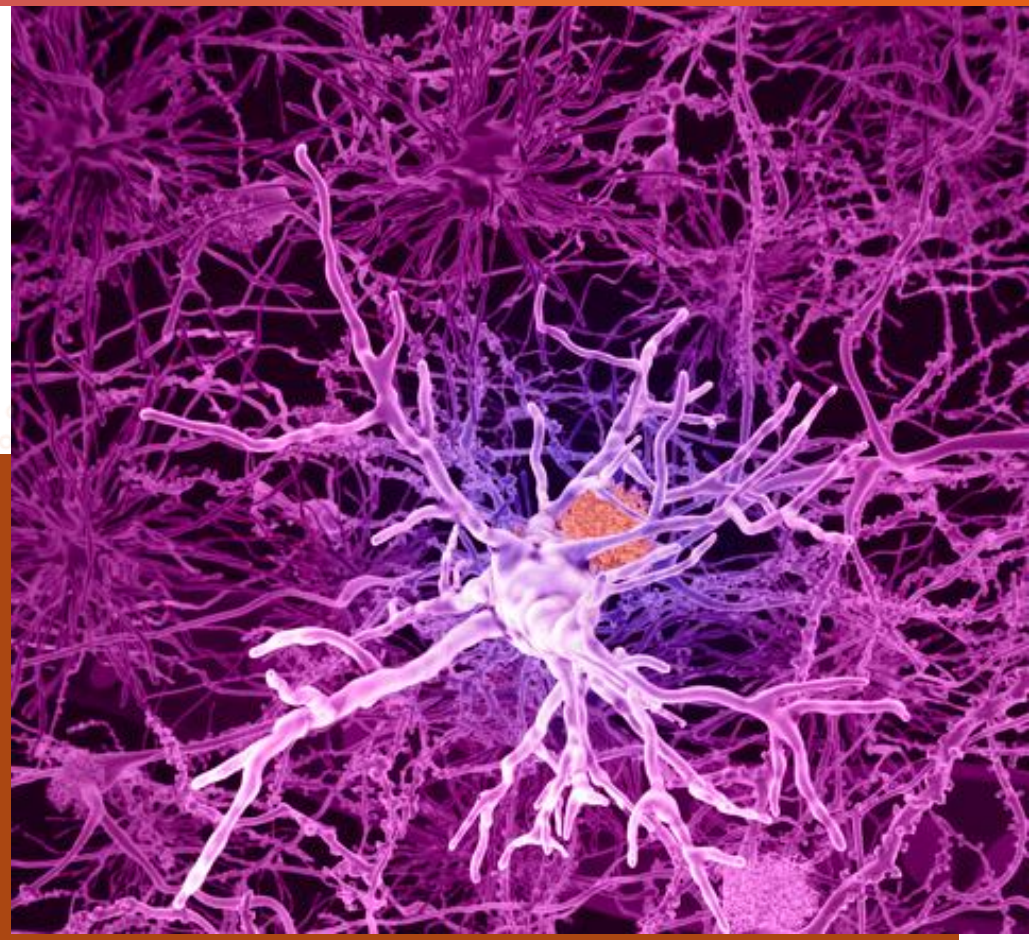
The Science:
Our Understanding of σ-2 Receptor Biology

Anthony Caggiano, MD, PhD
CMO and Head of R&D



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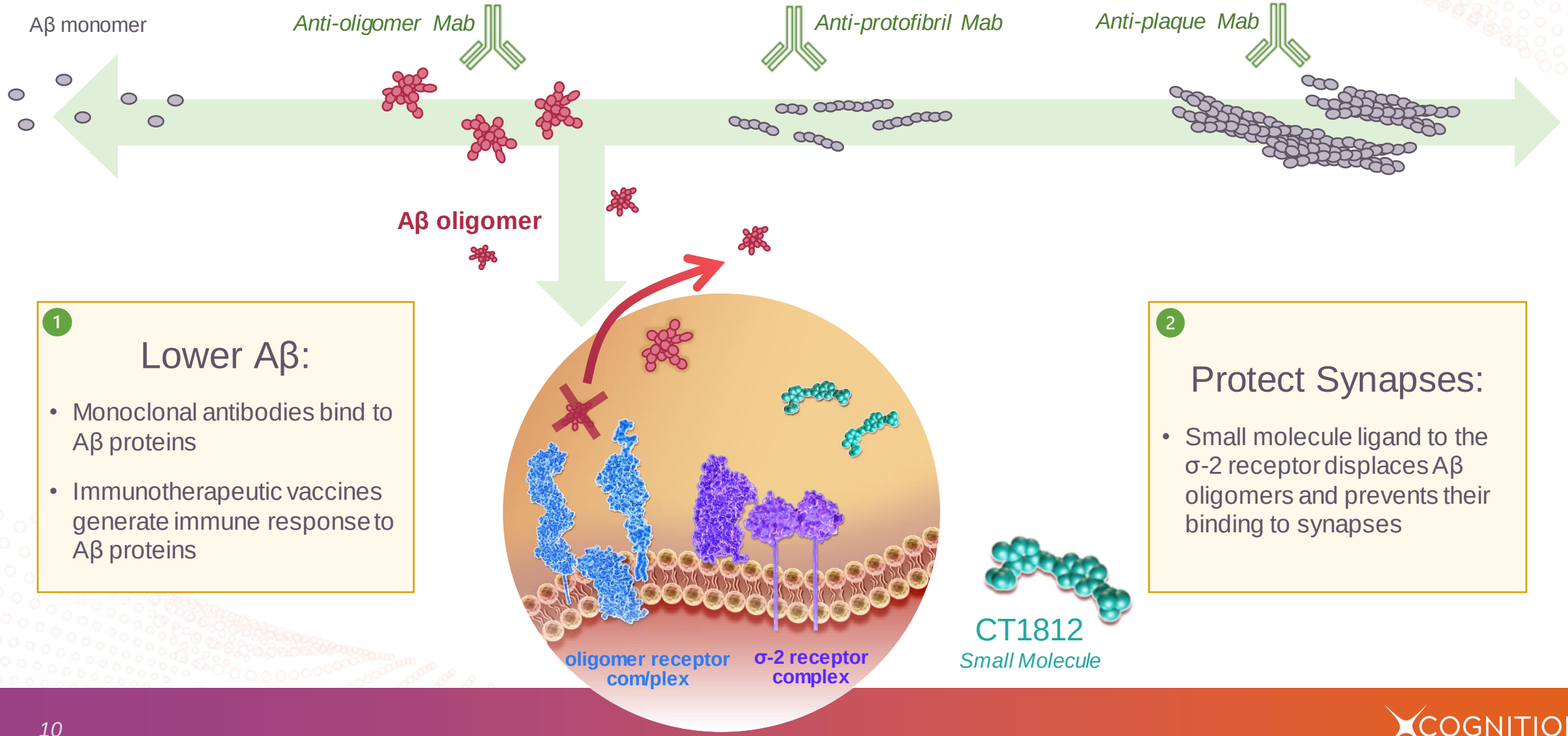
Sigma-2 Modulation to Address Amyloid Toxicity



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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MoA and Rationale Based in Foundational Science

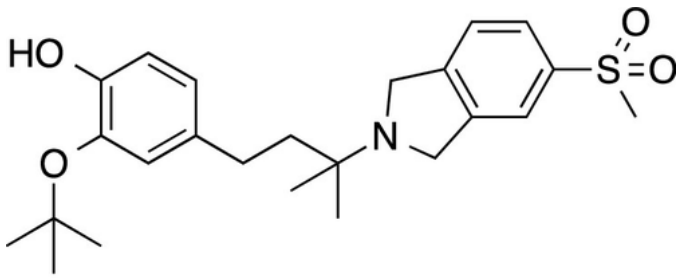
CT1812: The Molecule

ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett Letter

Discovery of Investigational Drug CT1812, an Antagonist of the Sigma-2 Receptor Complex for Alzheimer's Disease

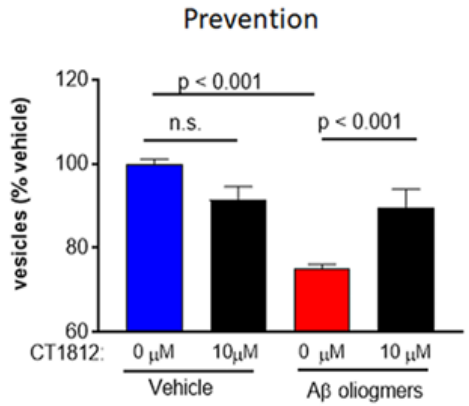
Gilbert M. Rishton, Gary C. Look, Zhi-Jie Ni, Jason Zhang, Yingcai Wang, Yaodong Huang, Xiaodong Wu, Nicholas J. Izzo, Kelsie M LaBarbera, Colleen S. Limegrover, Courtney Rehak, Raymond Yurko, and Susan M. Catalano*

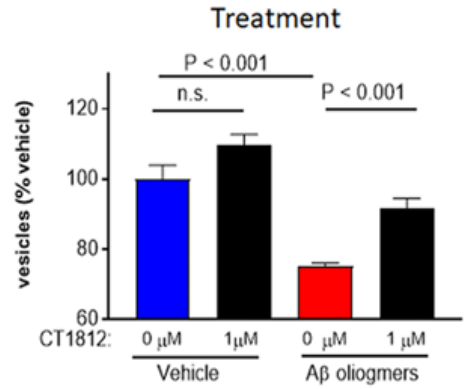


Compound 7 (CT1812)

Table 2. Physiochemical Properties and Brain-to-Plasma Ratios (AUC_{brain}/AUC_{plasma}) of Anti-AβO Compounds

cmpd	MW	cLogP	tPSA	Brain/plasma AUC	Brain/plasma 24 h postdose
(R)-2	376.2	6.48	12.3	NT	8.2
3	341.8	5.89	12.0	NT	2.0
6	357.5	4.65	32.7	5.64	5.4
7	431.6	3.26	66.8	2.51	5.7





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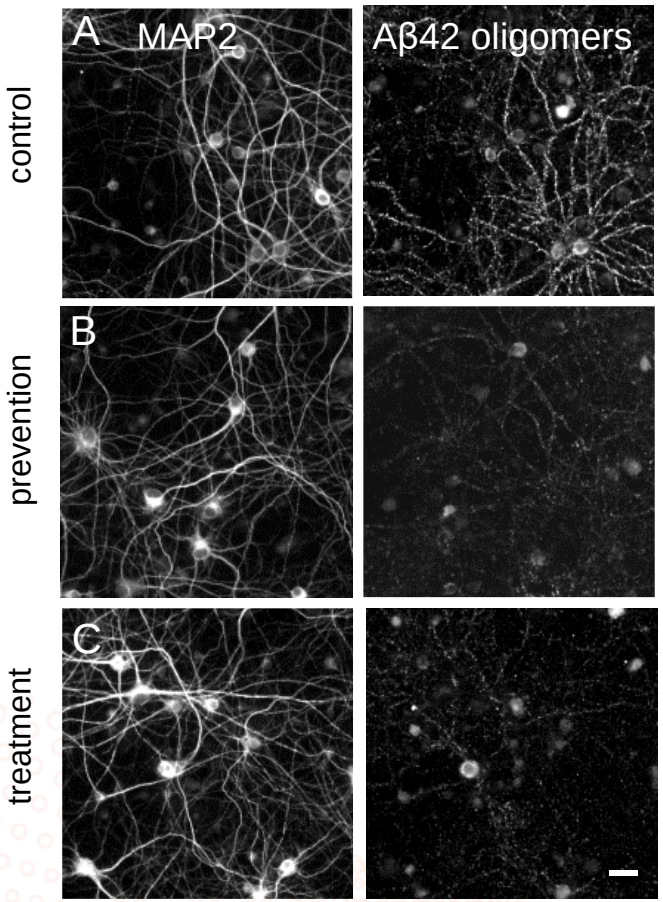
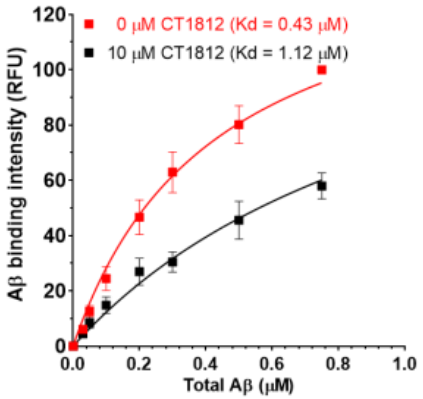
CT1812 Displaces Oligomers

in vitro displacement





LaBarbera et al.
Translational Neurodegeneration *In Press*
https://doi.org/10.1186/s40035-023-00348-y

Translational Neurodegeneration

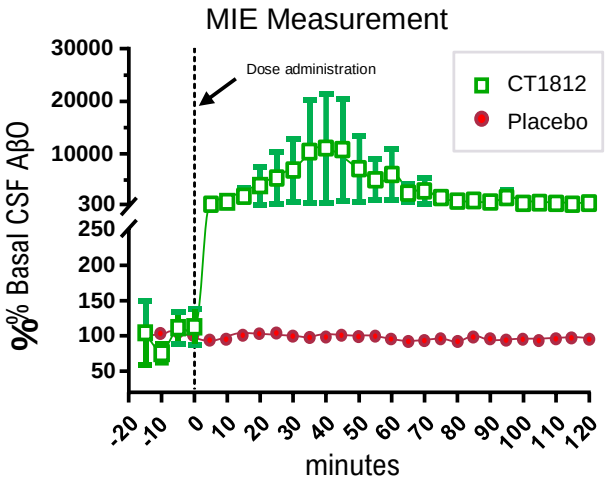
RESEARCH **Open Access**

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

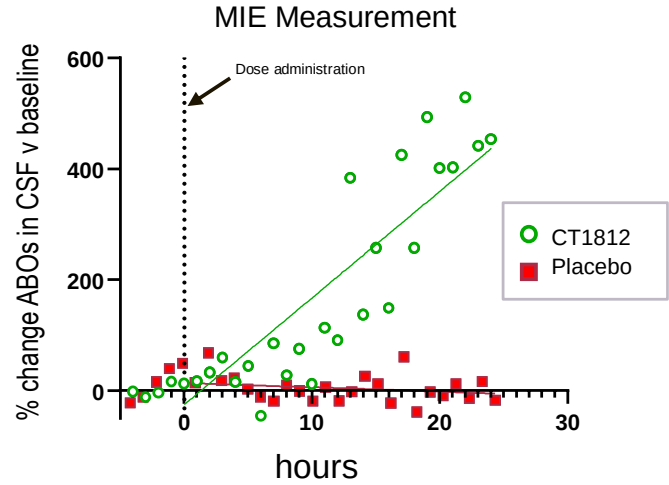
LaBarbera[1], Sheline[2], Izzo[1], Yuede[3], Waybright[1], Yurko[1], Edwards[3], Gardiner[3], Blennow[4], Zetterberg[4-10], Börjesson-Hanson[11], Morgan[12], Davis[13], Guttendorf[14], Schneider[15], DeKosky[16], LeVine, III[17], Grundman[18,19], Caggiano[1], Cirrito[3], Catalano[1], Hamby[1]

in vivo displacement

transgenic mice



humans



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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

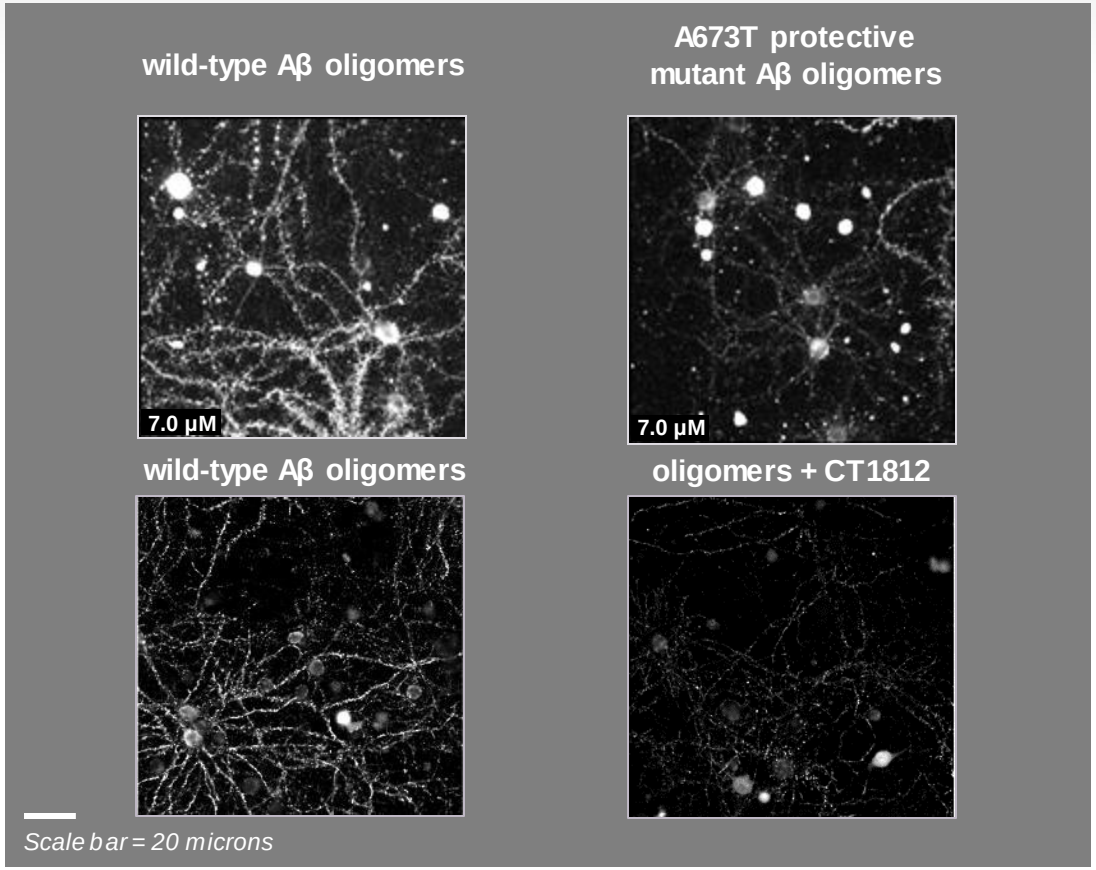
ORIGINAL ARTICLE

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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Restores Synapses and Function

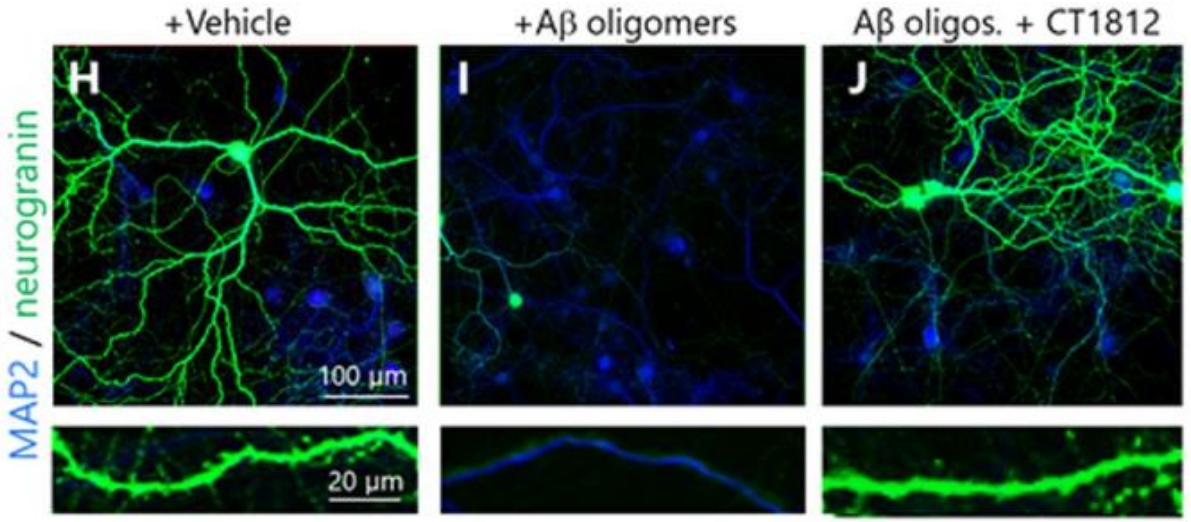
Received: 20 October 2020 | Revised: 16 December 2020 | Accepted: 2 January 2021

DOI: 10.1002/alz.12302

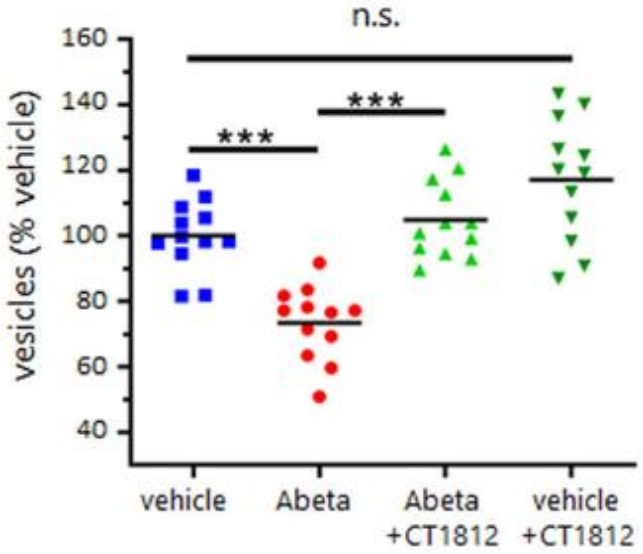
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

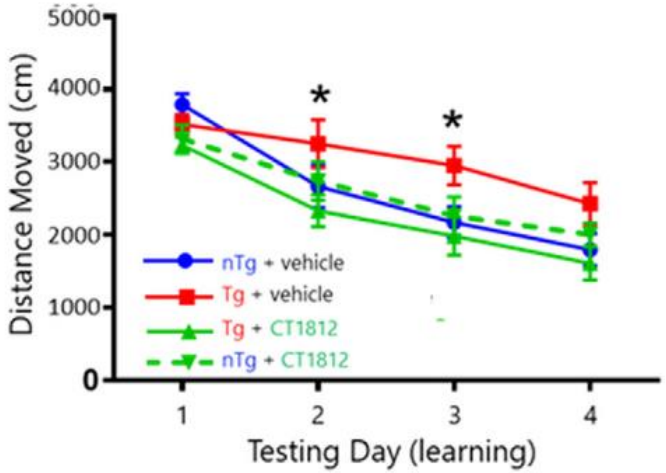
Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification



Trafficking in cultured neurons



Morris water maze – Swim length



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MOA Video

Watch online: https://vimeo.com/800999561

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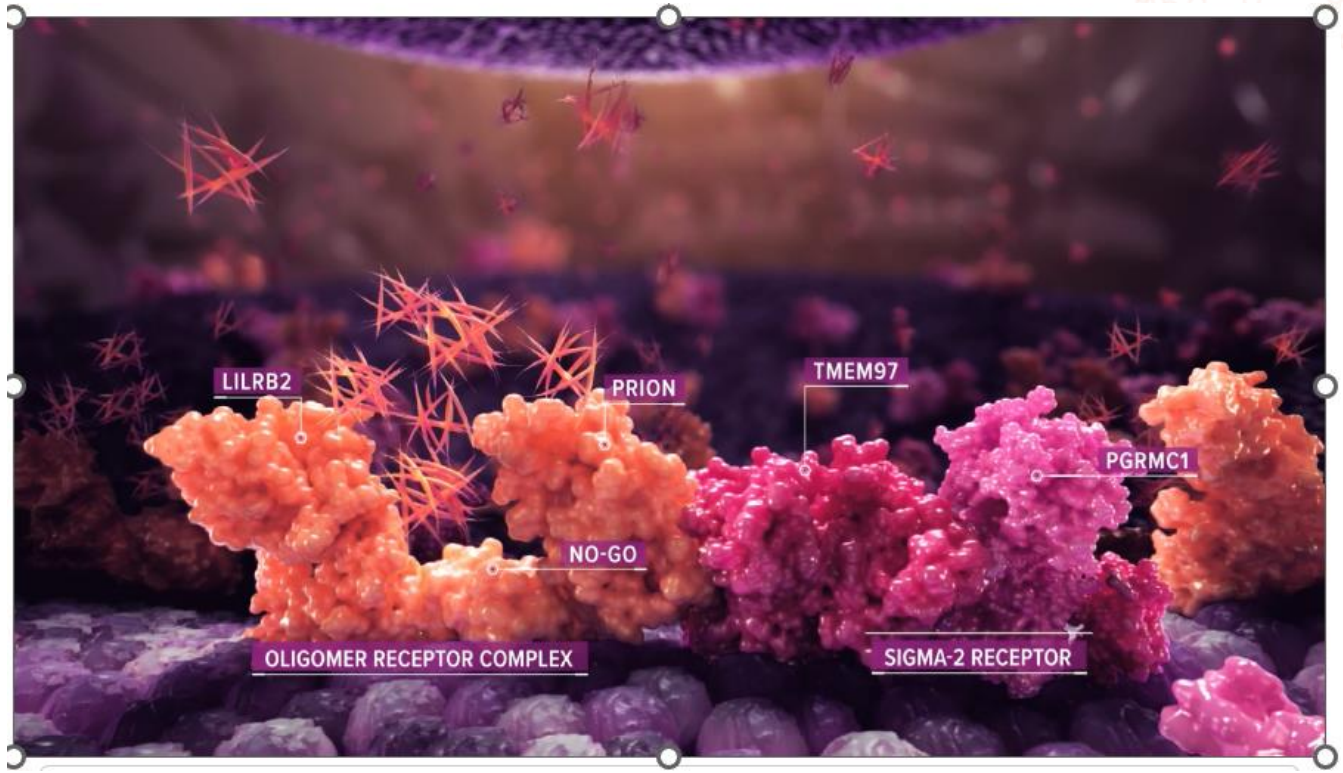
CT1812 and σ-2 Biology

- Decade long publication history supporting the biology of σ-2 in neurodegenerative conditions
- Robust basic science program defining the biological effects of σ-2 modulation and generating new molecules to address serious human disease
- The lead molecule, CT1812, is in multiple proof of concept clinical trials
- Evidence of real disease modification is being generated through our biomarker program to be presented next



CT1812 Biomarker Program

Britney Lizama, PhD
Research Scientist

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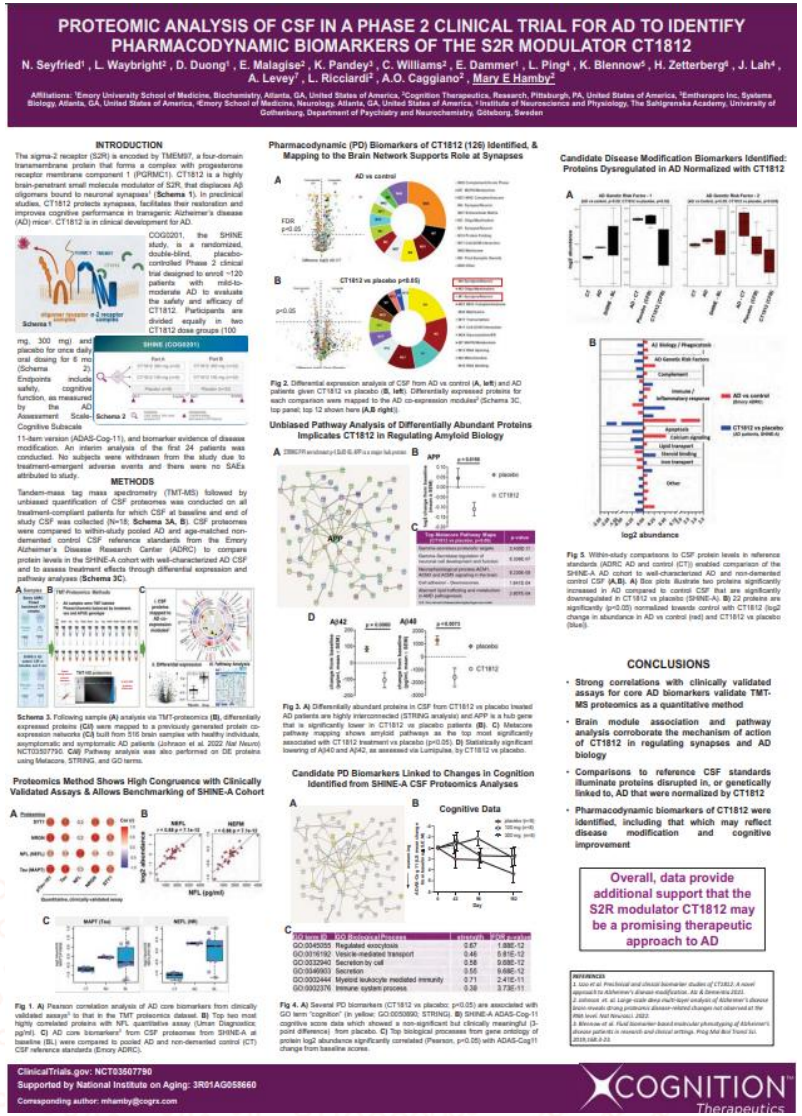
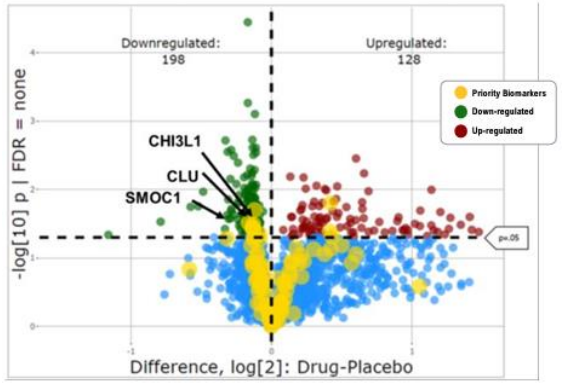
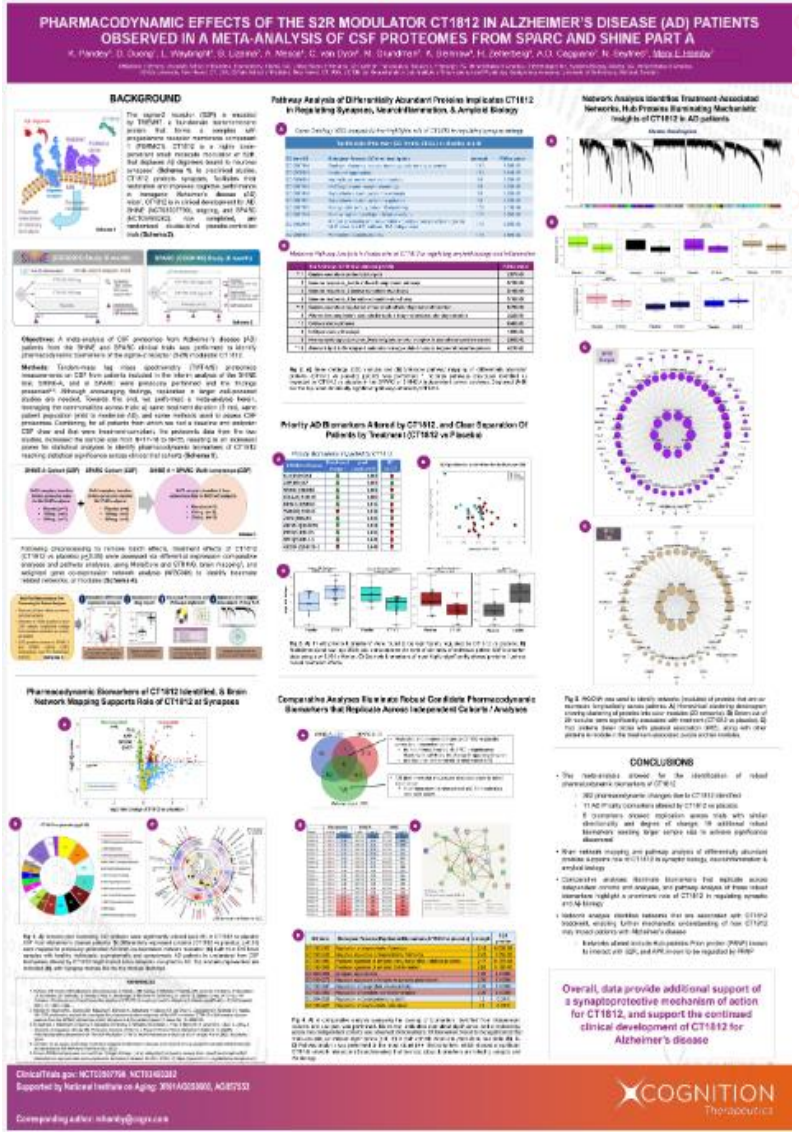
CT1812 Clinical Biomarker Posters



- **AD/PD™ 2022 International Conference on Alzheimer's and Parkinson's Diseases**; Barcelona, Spain.
- **2022 Alzheimer's Association's International Conference (AAIC)**; San Diego, CA.





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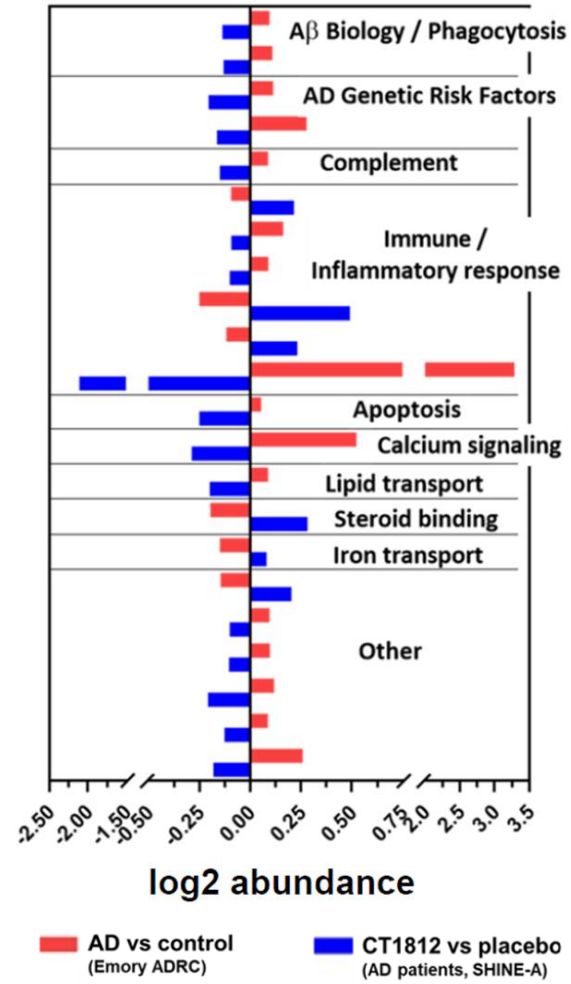
Key Takeaways from 2022 Presentations

- Strong correlations of canonical AD biomarkers from clinically validated assays confirms proteomics method as a quantitative way of assessing the impact of CT1812
  - SHINE-A and SPARC CSF AD biomarkers at baseline were similar to that of the AD group from an independent, well-characterized AD and control cohort
- Network and pathway analyses corroborate the mechanism of action of CT1812 in regulating synapses and amyloid biology
- CT1812 normalizes several key proteins dysregulated in or genetically linked to AD



Cognition Poster, AD/PD™ 2022

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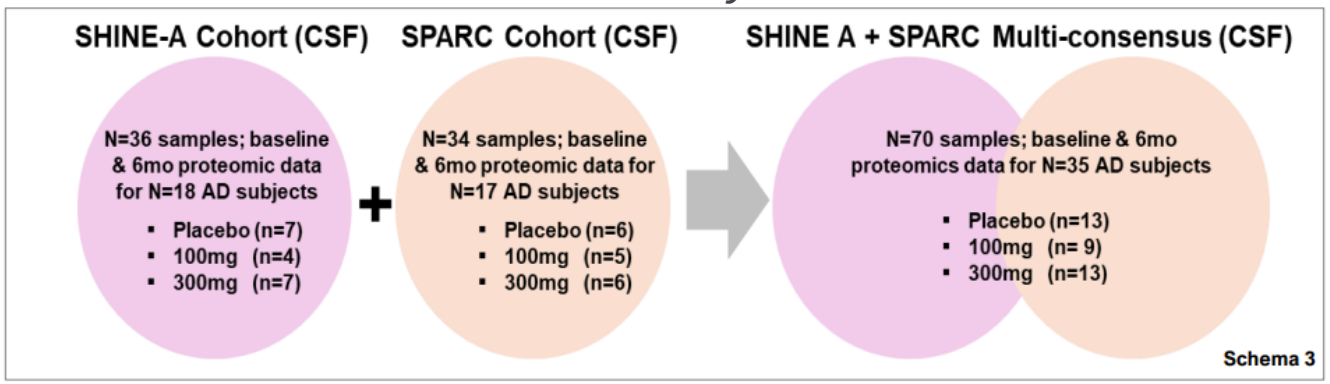
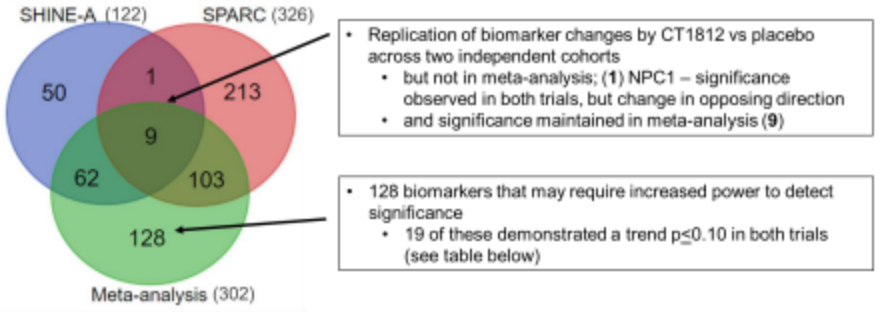
AD/PD™ 2023 International Conference on AD and PD

Meta-analysis



Comparative Analyses Illuminate Robust Candidate Pharmacodynamic Biomarkers that Replicate Across Independent Cohorts / Analyses



Amyloid biology, synapse regulation

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

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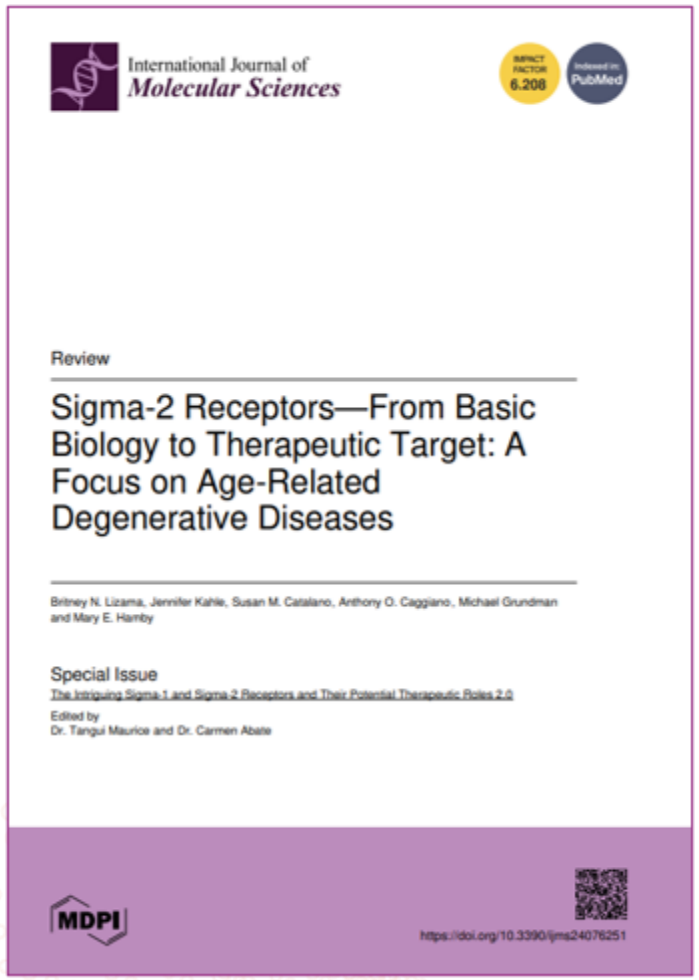
σ-2 Receptor Special Issue



- Goal: summarize the evidence-based understanding of σ-2 receptor biology and function, and its potential as a therapeutic target for age-related CNS diseases
- Diseases in focus
  - Alzheimer's disease
  - dementia with Lewy bodies
  - Dry age-related macular degeneration
  - Parkinson's disease
- Key functional roles of σ-2 receptor and molecular players
  - Protein-protein interactions
  - Putative endogenous and synthetic ligands

https://www.mdpi.com/1422-0067/24/7/6251

Overview of the Clinical Program for CT1812

Paul J Tiseo, PhD
VP & Head of Clinical Development

COGNITION™ Therapeutics

Overview of Clinical Study Program

Current PoC Studies

- **COG0201 – SHINE** (6-month study in mild-to-moderate AD)
- **COG0202 – SEQUEL** (quantitative EEG study in mild-to-moderate AD)
- **COG0203 – START** (18-month study in early AD)
- **COG1201 – SHIMMER** (6-month study in patients with dementia with Lewy bodies)

Planned PoC Study

- **COG2201 - MAGNIFY** (2-year study in dry AMD)

SEQUEL (COG0202)

Showing Impact CT1812 on Cortical Brain Wave Activity via Quantitative EEG

- Design: two-group cross-over design in patients with mild-to-moderate AD
- Single site: VUmc Alzheimer's Center (PI: E. Vijverberg, MD, PhD)

  Amsterdam UMC
  Universitair Medische Centra
- ***Objective: To evaluate changes in synaptic function through quantitative EEG, as reflected by cortical theta wave power***
- Last patient visit end of April 2023
- Topline data expected mid-year 2023

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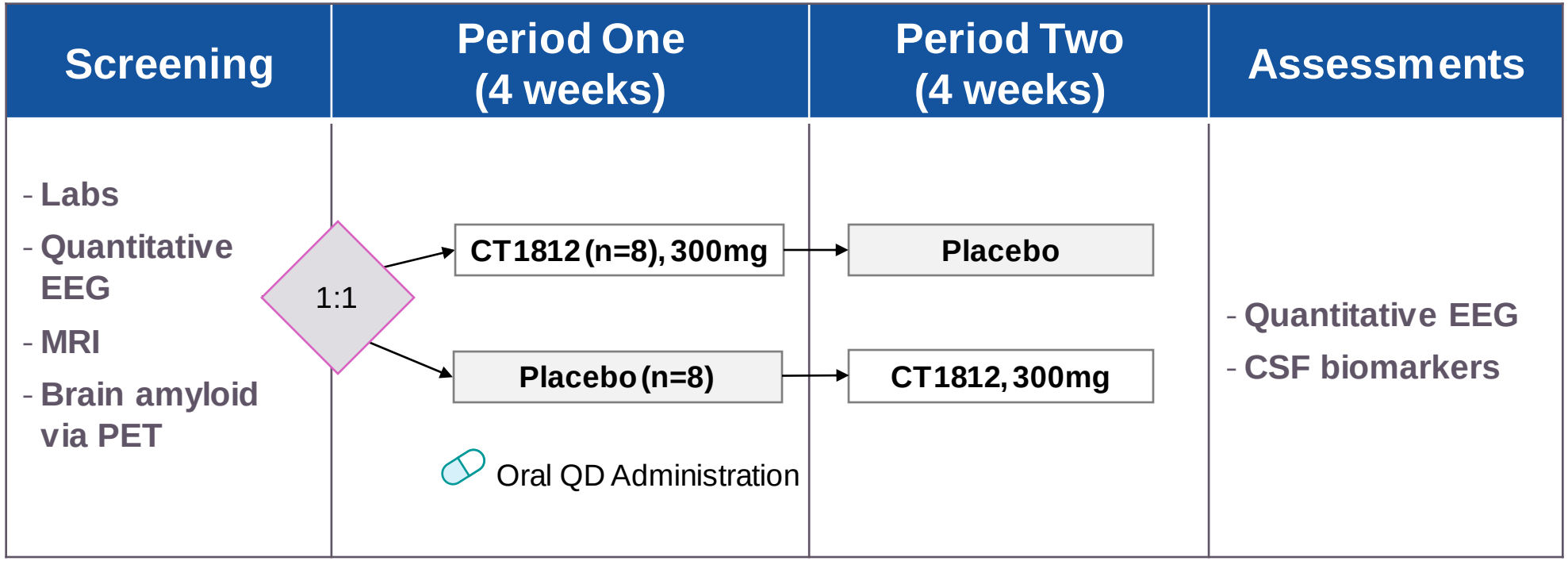
SEQUEL (COG0202): *Single-site Study Evaluating efficacy of CT1812 via quantitative EEG, as reflected by relative theta power*

LPLV: April 2023 with Topline Data: mid 2023

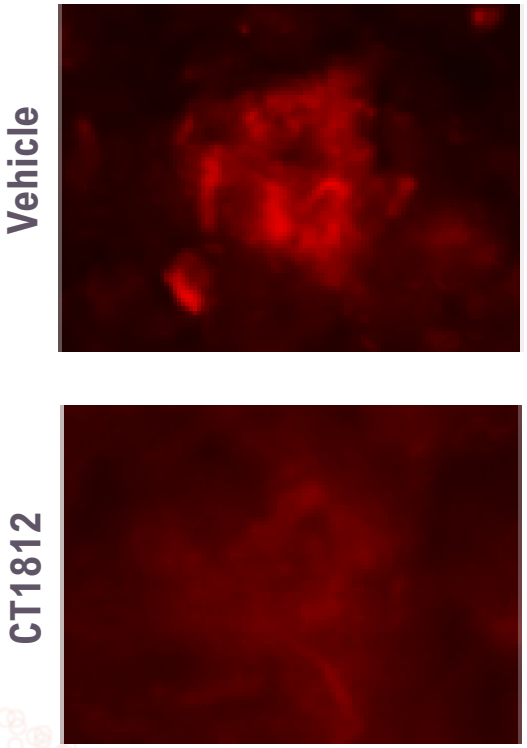


Principal investigator: Everard (Jort) Vijverberg, MD, PhD at the Amsterdam University Medical Centers

SEQUEL COG0202 study (NCT04735536) partially funded by $5.4M NIA grant (including $2.1M supplement) R01AG058710

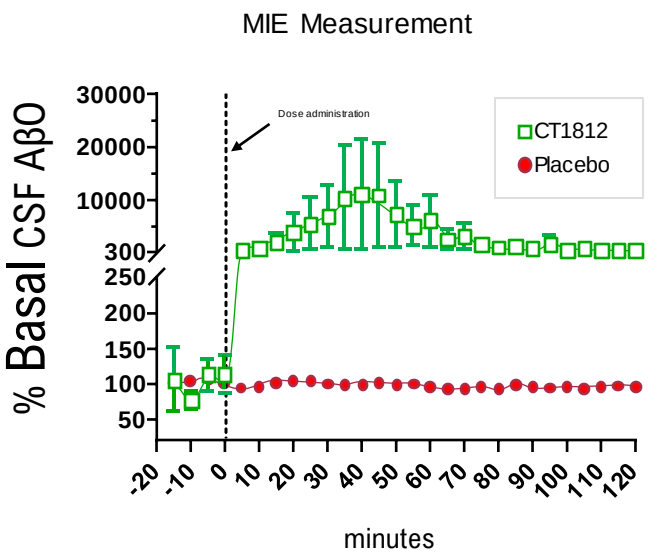
Nonclinical Testing Supports AβO Hypothesis for CT1812

Displaces Oligomers from AD Patient Brain Tissue



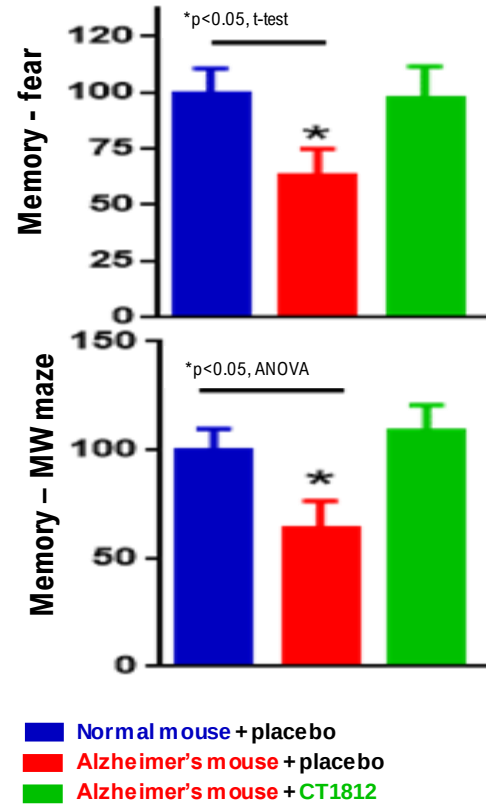
Postmortem Alzheimer's-confirmed brain tissue section (ThioS labeling)

CT1812 Displaces Oligomers in Mouse Model of AD



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

CT1812 Restores Cognitive Function in Mice

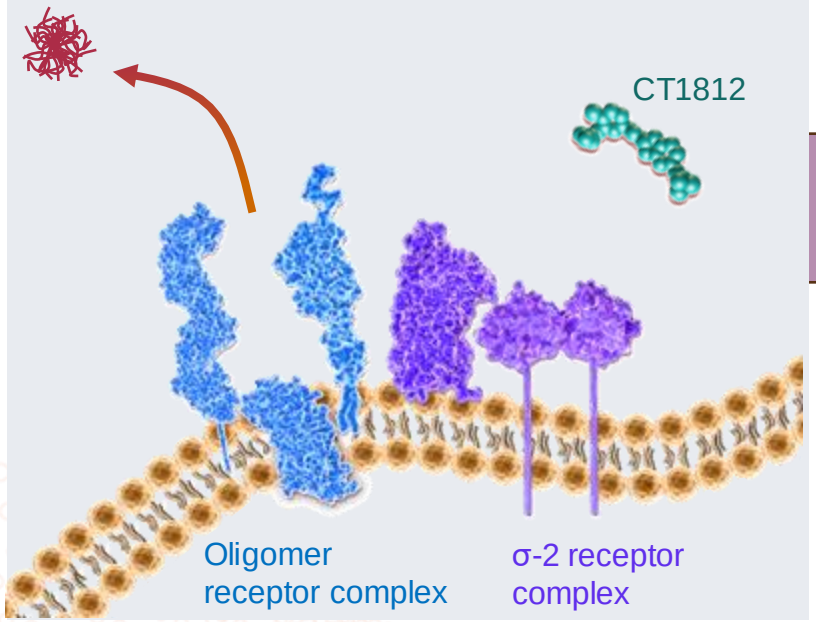


COGNITION™ Therapeutics

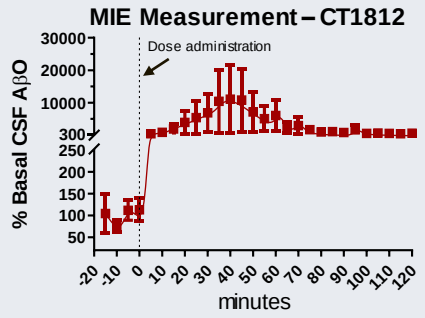
Evidence of Target Engagement: SNAP Study

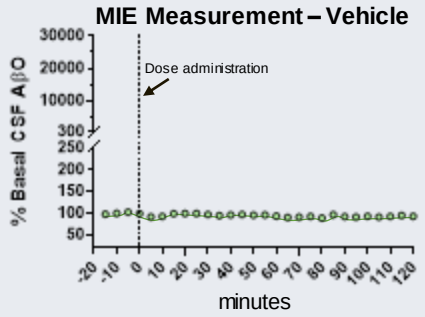
First evidence of target engagement in humans, mirrors preclinical findings, corroborating our mechanism of action

CT1812 mechanism of action: By binding to the σ-2 receptor, CT1812 displaces Aβ oligomers from synapses, thus preventing synaptic toxicity

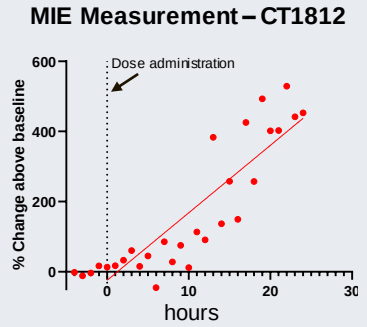


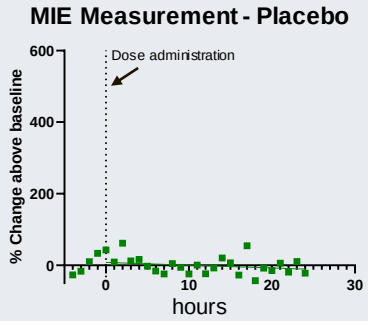
This displacement can be measured in the CSF in Alzheimer's mice treated with CT1812





…and now in people with Alzheimer's disease





COGNITION™ Therapeutics

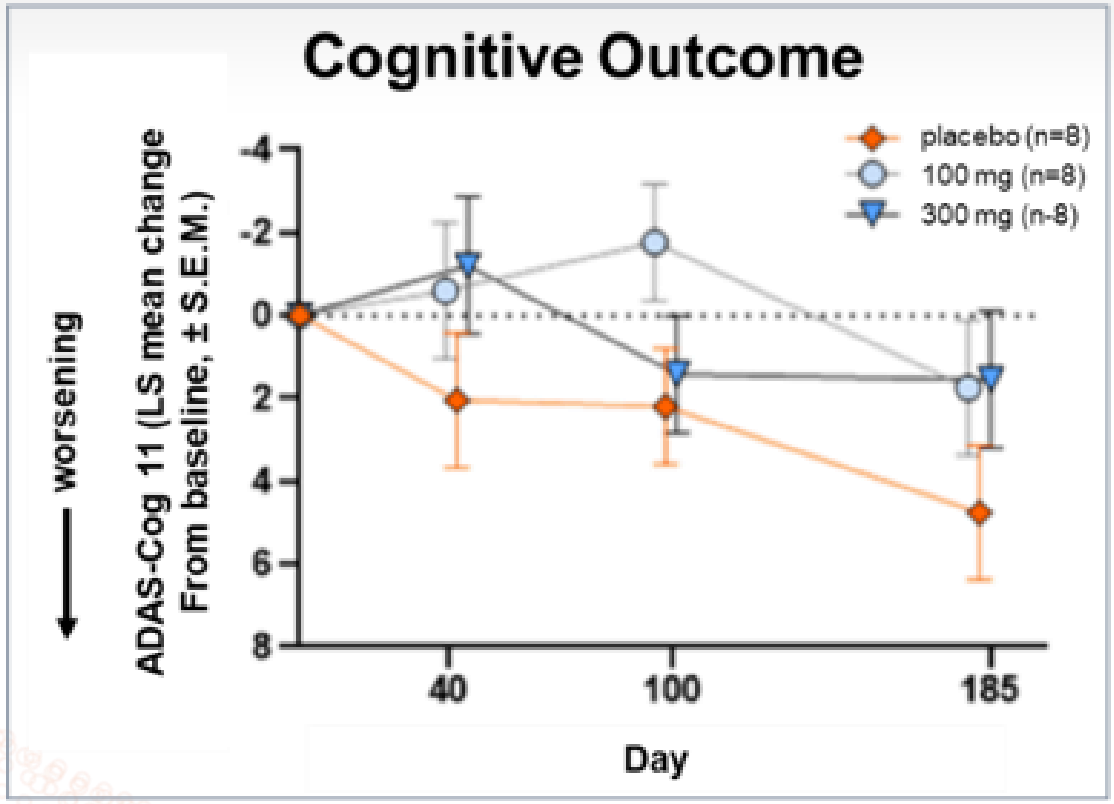
Phase 2 Safety and Efficacy Study in Adults with Mild-to-moderate Alzheimer's Disease

Screening	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) Oral QD Administration Cohort A: 24 participants Total anticipated: 144 participants	- Cognitive testing - Biomarkers (CSF/Plasma)

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

Cognitive & Biological Outcomes:

Interim analysis yields promising results (n=24)



- 3-point difference (ADAS-COG) observed between treated and untreated patients at day 185
- Clinically meaningful magnitude of change in 6 months
- Trend for improved cognitive outcomes
- Enrolling at sites in US and Europe

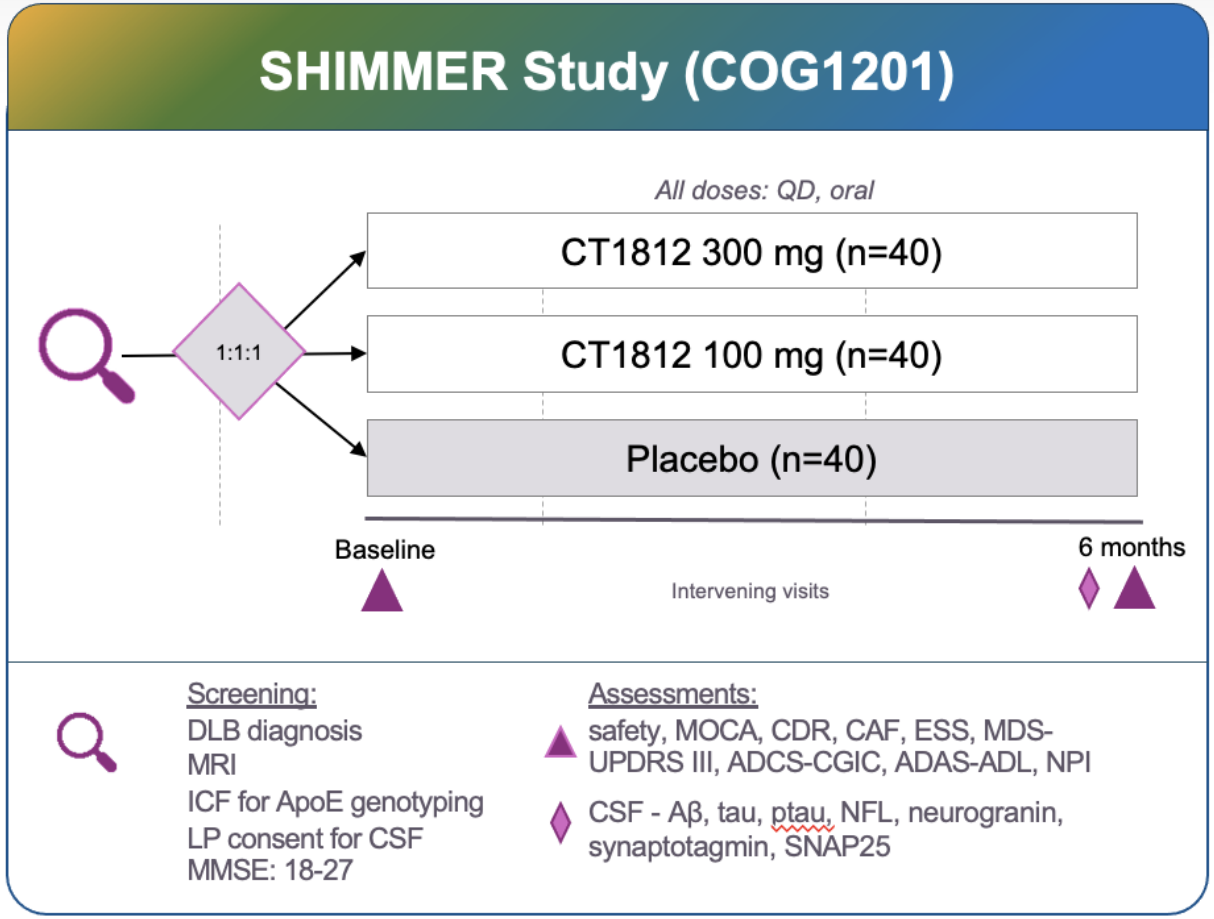
Phase 2 Study in Dementia with Lewy Bodies

SHIMMER

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

MIAMI MILLER SCHOOL of MEDICINE

- Funded by ~$30M NIA Grant
- A total of 30 sites in the US
- Study ongoing. N = 120 patients

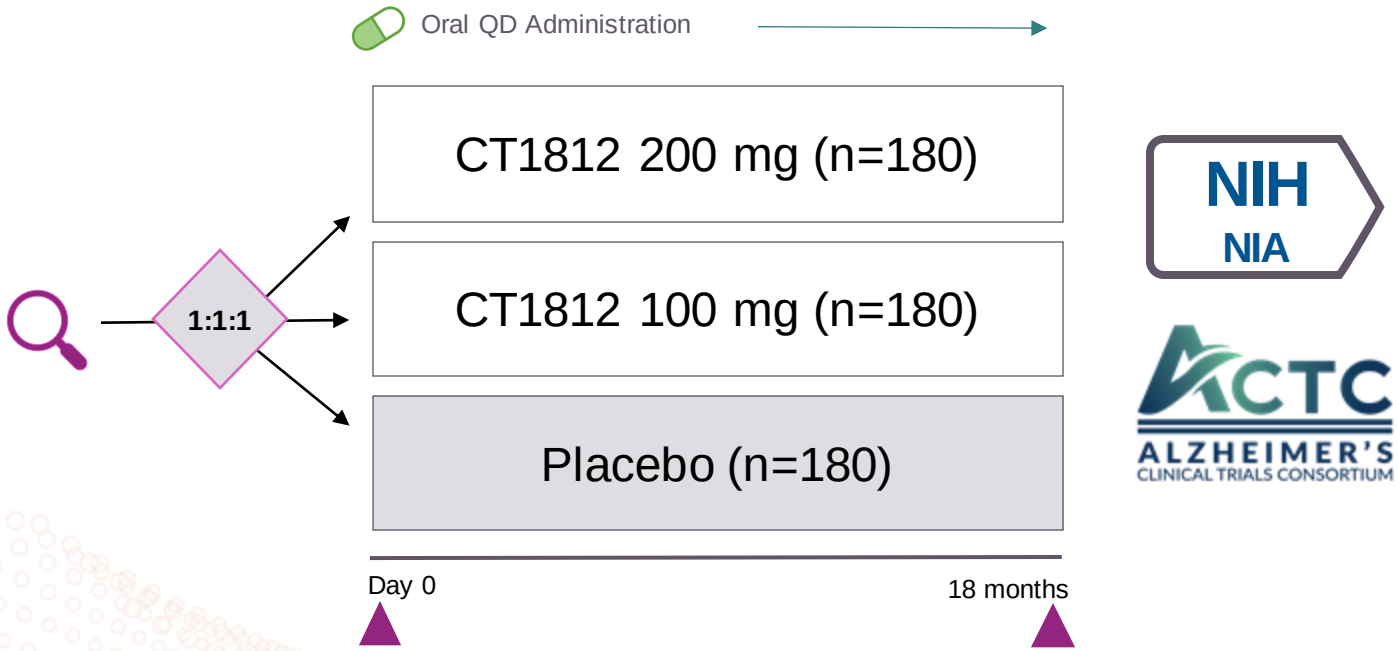


COG1201 study funded by NIA grant R01AG071643

COGNITION™ Therapeutics

Targeting Early Alzheimer's Disease

Study Design (n=540)



NIH NIA

ACTC ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

- A randomized, double-blind, placebo-controlled Phase 2 study in individuals with early-to-mild AD
- Multi-site: 50-60 U.S. sites including ACTC centers of excellence
- ***Objective: powered to show change in cognition; slowing or halting cognitive decline***
- Funding: $81M NIA grant award in collaboration with ACTC: premier Alzheimer's clinical trial group
- Status: Site activation in progress

START COG0203 Study (NCT05531656) funded by NIA grant R01AG065248

COGNITION™ Therapeutics

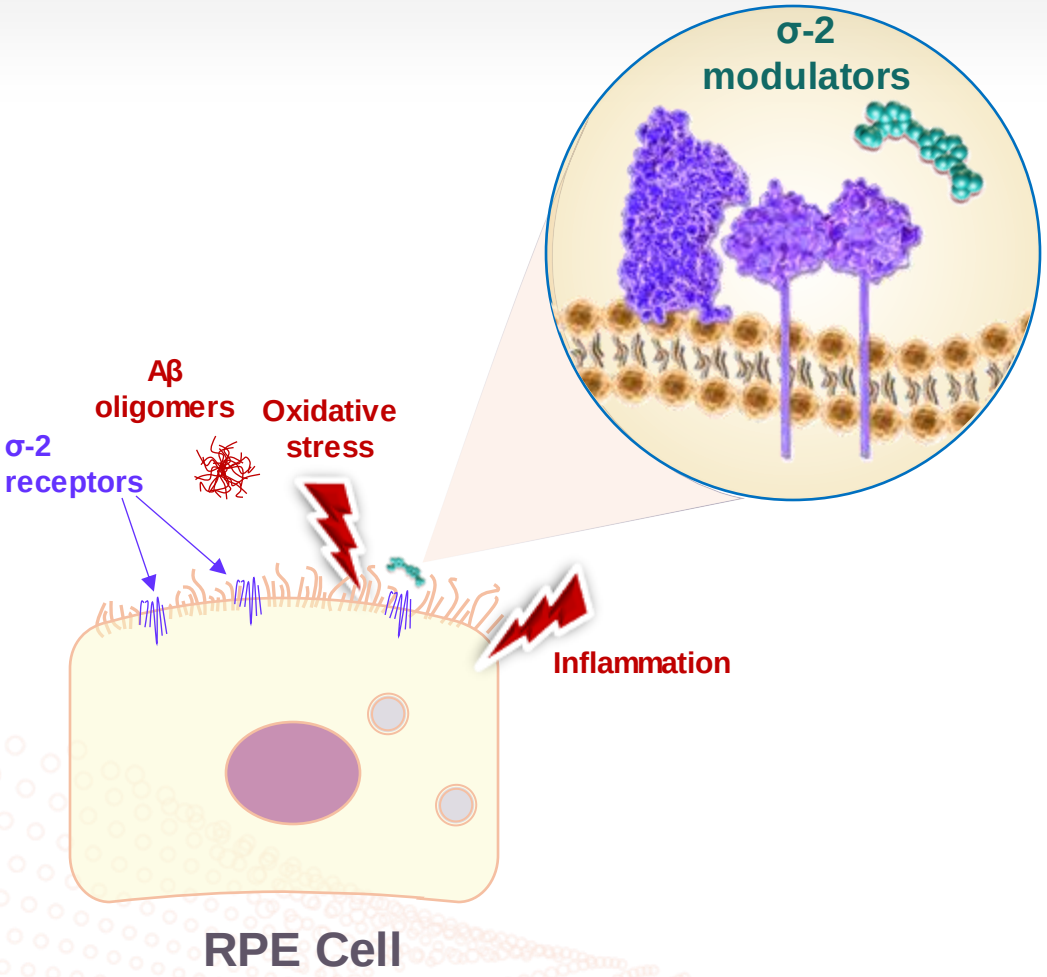
New Indication:
Geographic Atrophy Secondary to Dry Age-related Macular Degeneration

Anthony Caggiano, MD, PhD
CMO and Head of R&D

COGNITION™ Therapeutics

Rationale for σ-2 Modulators in Dry AMD

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

σ-2 receptor modulators

- **Non-invasive oral small molecule approach to reach retina**
- **Clinical biomarker support**: Proteomics analyses showed differential movement of proteins involved in dry AMD
- **Preclinical data:** regulates cell survival and inflammatory pathways, ameliorate trafficking deficits

Unbiased Pathway Analysis of Patient Clinical Trial Proteomics Data Supports Targeting σ-2 for dAMD

Proteomics datasets from two Phase 2 clinical trials

1. COG0102

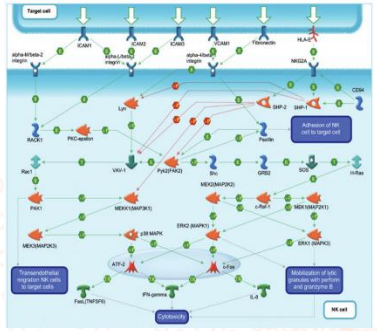
Phase 2 trial of σ-2 receptor modulator, CT1812, or placebo in mild-to-moderate AD patients

Proteomics analysis of CSF at 28 d (N=15)

2. SHINE-A

Phase 2 trial of σ-2 receptor modulator, CT1812, or placebo in mild-to-moderate AD patients

Proteomics analysis of CSF at 6mo (N=18)



MetaCore+MetaDrug™ version 20.3 build 70200

1. List of proteins differentially expressed in CSF from CT1812- vs. placebo-treated patients generated for each trial, timepoint
2. Metacore pathway analysis of CSF (CT1812 vs placebo) across trials conducted to ascertain which predesignated functional disease ontologies may be significantly affected

Top Disease Ontologies

1. Geographic atrophy
2. Central nervous system diseases
3. Cognition disorders
4. Mental disorders
5. Psychiatry and psychology
6. Macular degeneration
7. Neurocognitive disorders
8. Rett syndrome
9. Dementia
10. Movement disorders
11. Neurodegenerative diseases
12. Brain diseases
13. Basal ganglia diseases
14. Anemia
15. Infections

2022 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO)

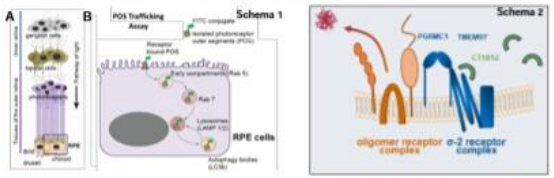
Sigma-2 receptor modulators rescue POS trafficking deficits in RPE cell-based models of dry AMD

Evi Malagise[A], Eloise Keeling[B], Nicole Knezovich[A], Lora Waybright[A], Emily Watto[A], Anthony O. Caggiano[A], Arjuna Ratnayaka[B], Mary E. Hamby[A]

(A) Cognition Therapeutics Inc., Pittsburgh, PA, USA; (B) Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, Hampshire, UK

INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of blindness. While treatments exist for wet AMD, there are no approved therapeutics for dry AMD (dAMD), which comprises 90% of all AMD cases[1]. There are several hallmarks of dAMD including inflammation, oxidative stress, and the presence of amyloid-beta oligomers (AβO), which can disrupt key homeostatic functions of retinal pigmented epithelium (RPE) cells, including the ability of RPE cells to phagocytose or recycle photoreceptor outer segments (POS; **Schema 1**)[2-5]. The sigma-2 receptor (S2R), encoded by TMEM97, is a damage sensor, regulating processes disrupted in age-related diseases[6]. Genome-wide association studies (GWAS) indicate a single nucleotide polymorphism (SNP) exists in the TMEM97 locus that confers a decreased risk of dAMD[7,8], and down-regulation of TMEM97 expression protects RPE cells from oxidative stress[9]. The S2R modulator CT1812 is currently in Phase 2 clinical trials for Alzheimer's disease and dementia with Lewy bodies, although CT1812 is not yet approved for any indication. Proteomic analyses from aged patients given CT1812 or placebo suggest S2R modulators regulate key proteins and pathways disrupted in dAMD[10-11]. S2R modulators prevent AβO from binding to neurons (**Schema 2**) and rescue deficits in neuronal functioning[6], but whether S2R modulators can limit injury from other stressors has not been investigated. Based on the role of the S2R as a key damage sensor and the link of S2R to dAMD, the hypothesis that S2R modulators could rescue AβO and oxidative stress-induced deficits was tested by assessing the ability of RPE cells to phagocytose / recycle POS (**Schema 1**).



Schema 1. A) Pathway of light from ganglion cells to RPE with drusen. **B)** POS pulsed feeding assay. FITC conjugated POS are trafficked through RPE cells via lysosomes (labeled with LAMP2) and autophagy bodies (labeled with LC3B)[2]. Co-localization of POS to lysosomes or autophagy bodies can be measured to assess normal trafficking of POS and disruptions caused by disease-relevant stressors.

Schema 2. The S2R (blue) comprises TMEM97 and PGRMC1. A representation of the S2R modulator CT1812 (green) displacing AβO (red) from binding neuronal synapses is shown[6].

AβO bind to RPE cells in a concentration and time-dependent manner

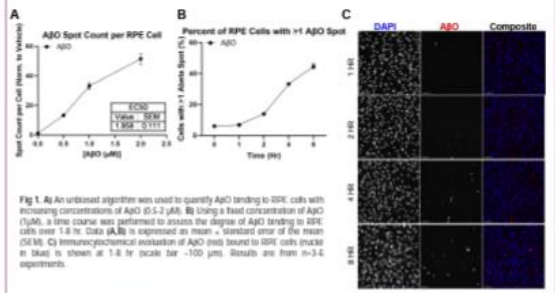


Fig 1. A) An unbiased algorithm was used to quantify AβO binding to RPE cells with increasing concentrations of AβO (0.5-2 μM). **B)** Using a fixed concentration of AβO (1μM), a time course was performed to assess the degree of AβO binding to RPE cells over 1-8 hr. Data (**A,B**) is expressed as mean ± standard error of the mean (SEM). **C)** Immunocytochemical evaluation of AβO (red) bound to RPE cells (nuclei in blue) is shown at 1-8 hr (scale bar ~100 μm). Results are from n=3-6 experiments.

A third chemically distinct S2R modulator rescues AβO and H_2O_2-induced deficits in POS trafficking

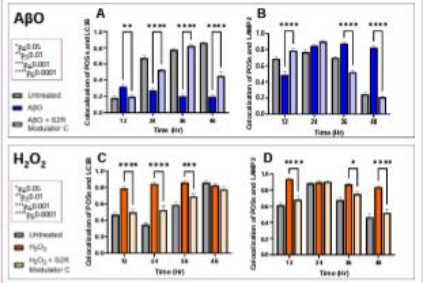
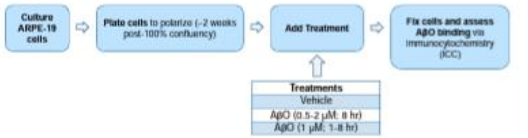


Fig 4. An unbiased algorithm was used to quantify **(A)** LC3B or **(B)** LAMP2 and POS colocalization after 1 μM AβO exposure (12-48 hr) in the presence and absence of the S2R modulator C. A significant rescue in the AβO-induced deficit was observed for LC3B with S2R modulator C at 12, 24, 36, and 48 hr ($p<0.01$), and for LAMP2 at 12, 36, and 48 hr ($p<0.0001$). Similarly, the colocalization of **(C)** LC3B or **(D)** LAMP2 with POS was assessed after exposure to 100 μM H_2O_2 (12-48 hr) in presence and absence of the S2R modulator. A significant rescue in the H_2O_2-induced deficit with S2R modulator C was observed for LC3B at 12, 24, and 36 hr ($p<0.001$), and for LAMP2 at 12, 36, and 48 hr ($p<0.05$). Statistical significance was assessed via 2-way ANOVA and Tukey's post-hoc test (n=3 from 1 experiment). Data is expressed as mean ± standard error of the mean (SEM).

METHODS

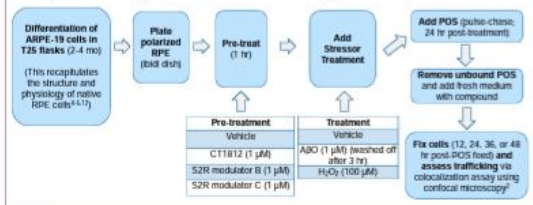
Goal 1) To characterize AβO binding in RPE cells

Experimental Design: Concentration-response and time course of AβO binding in RPE cells



Goal 2) To determine whether S2R modulators rescue AβO and H_2O_2-induced deficits in the ability of RPE cells to phagocytose POS

Experimental Design: Examination of POS trafficking over time in polarized RPE cells



S2R modulators, including CT1812, rescue AβO-induced deficits in the homeostatic recycling of POS

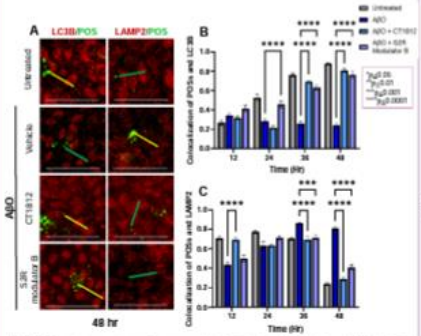


Fig 2. A) Confocal microscopy was used to measure colocalization (yellow) of LC3B (red) and LAMP2 (red) with POS (green) at 48 hr (scale bars ~50 μm). Arrows point to colocalization (yellow) or lack thereof (green). An unbiased algorithm was used to quantify **(B)** LC3B or **(C)** LAMP2 and POS colocalization after 1 μM AβO exposure (12-48 hr) in the presence and absence of a S2R modulator. **B)** A significant increase in LC3B-POS colocalization towards control levels was observed with CT1812 at 36 and 48 hr ($p<0.0001$), and with S2R modulator B at 24, 36, and 48 hr ($p<0.0001$). **C)** A significant reduction in LAMP2-POS colocalization towards control levels was observed with CT1812 at 12, 36, and 48 hr ($p<0.0001$), and with S2R modulator B at 36 and 48 hr ($p<0.001$). Statistical significance was assessed via 2 way ANOVA and Tukey's post hoc test (n=3 wells from 2 experiments). Data and expressed as mean ± standard error of the mean (SEM).

S2R modulators, including CT1812, rescue H_2O_2-induced deficits in the homeostatic recycling of POS

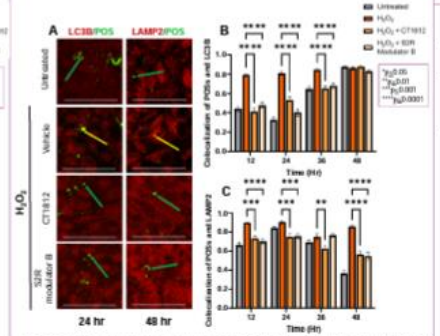
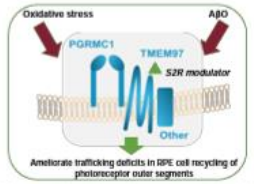


Fig 3. A) Confocal microscopy was used to measure colocalization (yellow) of LC3B (red) and LAMP2 (red) with POS (green) at 24 hr and 48 hr, respectively (scale bars ~50 μm). Arrows point to colocalization (yellow) or lack thereof (green). An unbiased algorithm was used to quantify **(B)** LC3B or **(C)** LAMP2 and POS colocalization after 100 μM H_2O_2 exposure (12-48 hr) in the presence and absence of a S2R modulator. **B)** A significant reduction in LC3B-POS colocalization towards control levels was observed with CT1812 at 12, 24, and 36 hr ($p<0.0001$), and with S2R modulator B at 12, 24, and 36 hr ($p<0.0001$). **C)** A significant reduction in LAMP2-POS colocalization towards control levels was observed with CT1812 at 12, 24, 36, and 48 hr ($p<0.01$), and with S2R modulator B at 12, 24, and 48 ($p<0.001$). Statistical significance was assessed via 2-way ANOVA and Tukey's post-hoc test (n=3 wells from 2 experiments). Data are depressed as mean ± standard error of the mean (SEM).

CONCLUSIONS

- Oxidative stress and toxic AβO disrupt trafficking of photoreceptor outer segments (POS) in RPE cells
- S2R modulators, from three chemically distinct series, rescue oxidative stress and AβO-induced deficits in POS trafficking, normalizing a key homeostatic process disrupted in dAMD
- Results expand beyond the previously elaborated mechanism of action of CT1812 and suggest CT1812 may be protective against oxidative stress, as well as AβO toxicity, in age-related degenerative diseases



Genetic evidence, clinical biomarker, and preclinical data suggest that modulation of S2R may be a promising approach to treat dAMD and supports advancing CT1812 to a Ph2 clinical trial in dAMD

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Corresponding author: mhamby@cognx.com

See Cognition Therapeutics' Booth #3126 for Clinical Trial details

COGNITION Therapeutics

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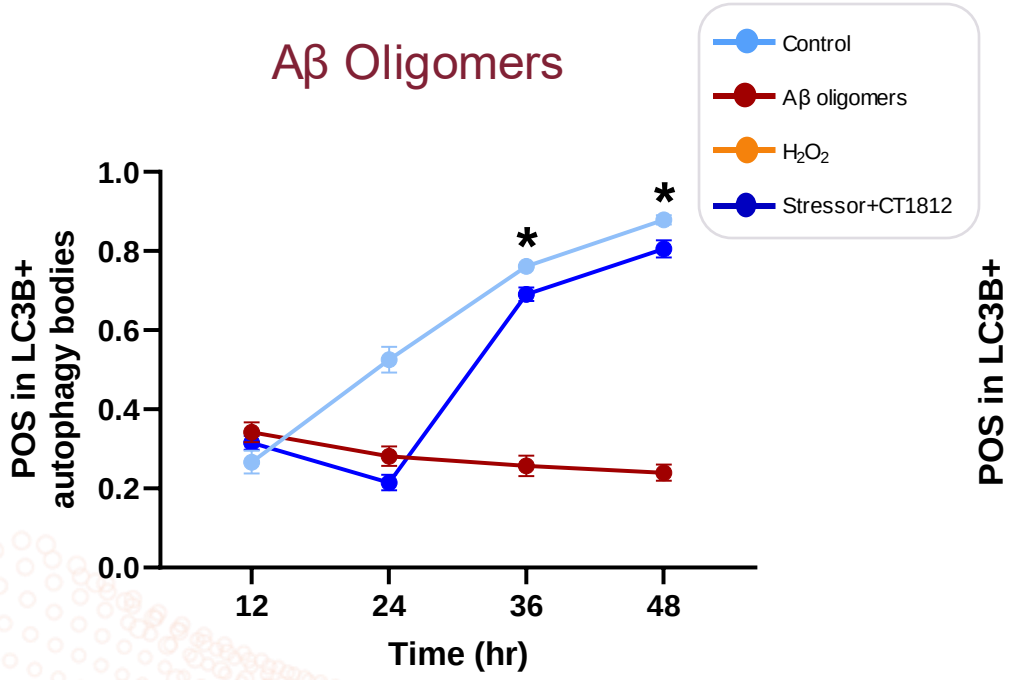
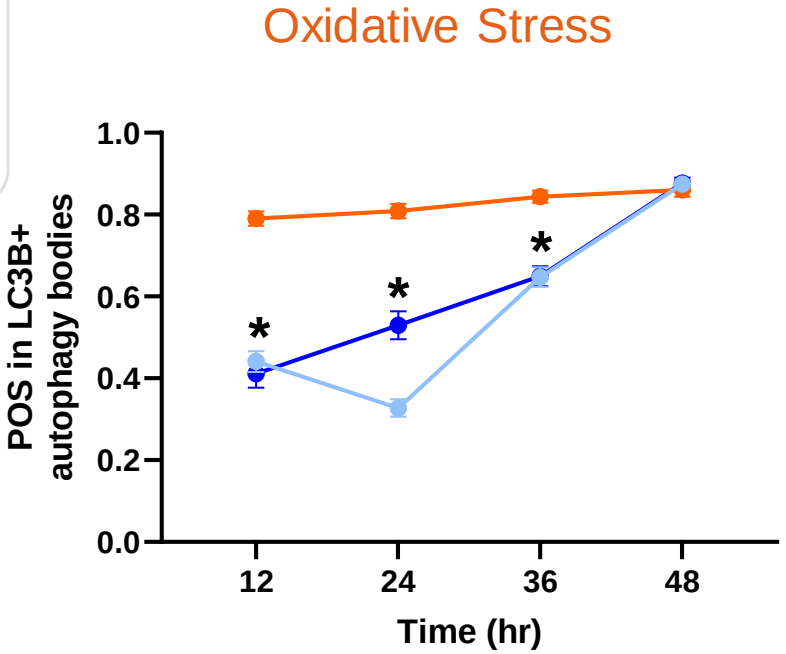
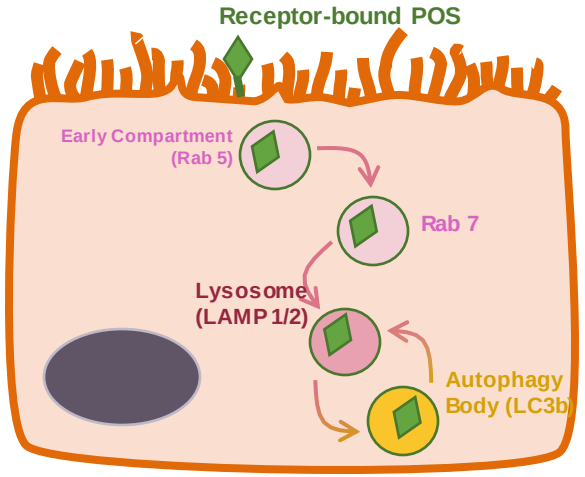
σ-2 Receptor Modulators Rescue RPE Lysosomal Trafficking Deficits

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





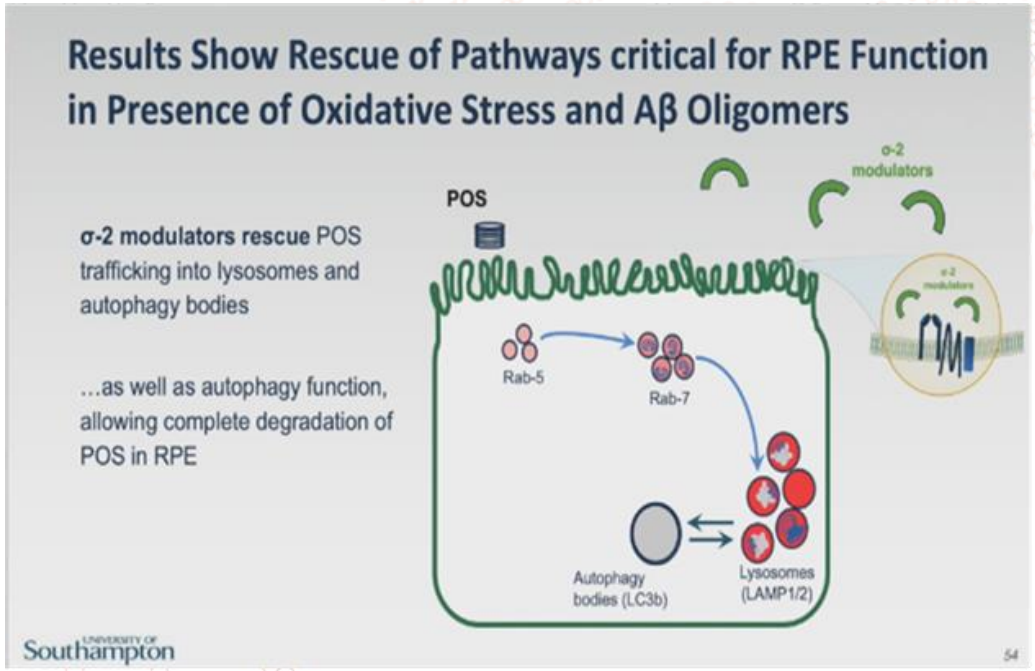


Malagise E et al. Sigma-2 receptor modulators rescue POS trafficking deficits in RPE cell-based models of dry AMD. Poster presented at: 2022 ARVO

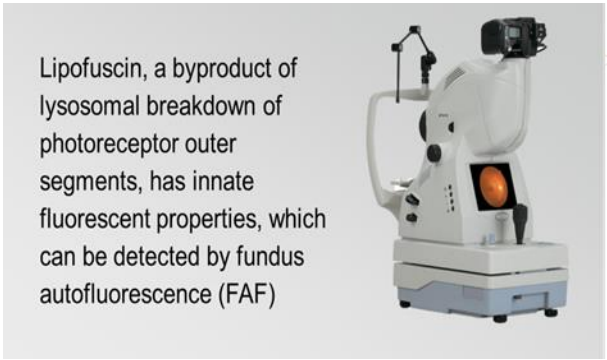
COGNITION™ Therapeutics

Dry AMD Endpoints: GA

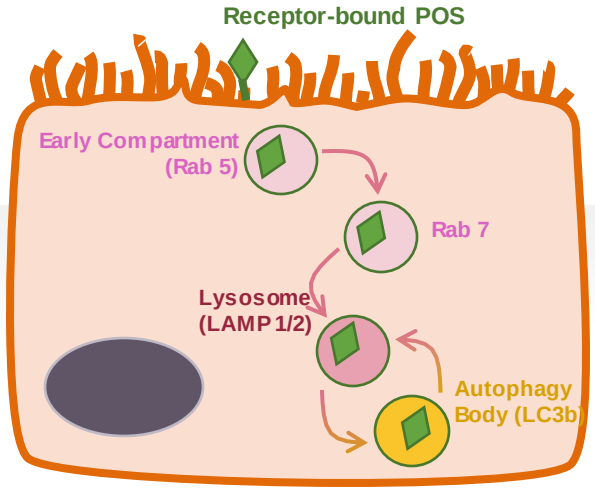
- A fundus camera records images of the interior surface of the eye, providing visual detail of the retina, optic disc and macula
- Fundus photography is used to determine the presence of drusen and GA lesions
- In dry AMD, GA lesions are correlated with death of RPE cells and often precede noticeable vision loss



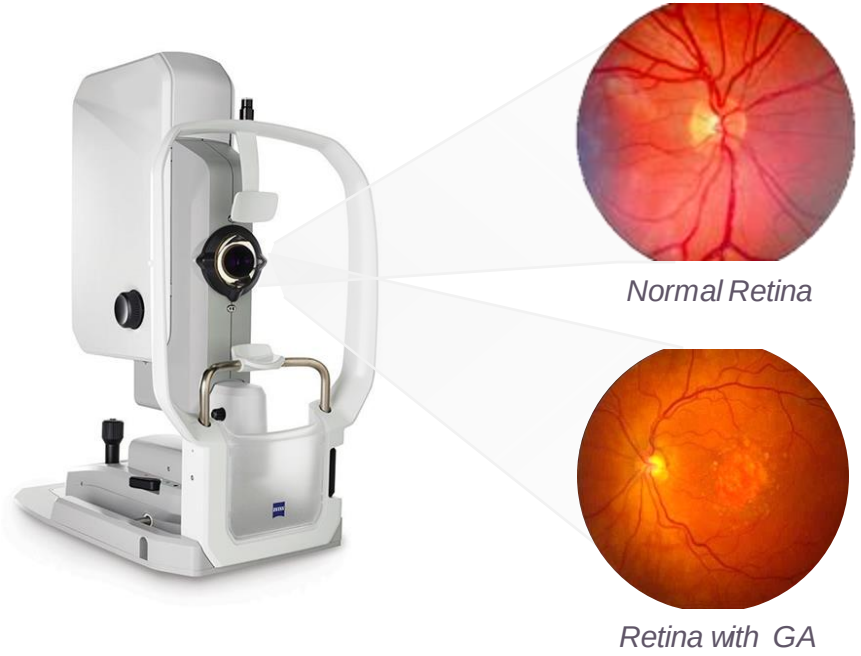
Dr. Arjuna Ratnayaka
University of Southampton
Clinical and Experimental Sciences



Dry AMD Clinical Development



- Genetic, biomarker and preclinical data demonstrate the potential of σ-2 modulation to improve outcomes in GA associated with dry AMD
- GA is a large unmet medical need where recent successes have demonstrated a clear and objective path to regulatory approval
- Coming soon: a phase 2 clinical trial

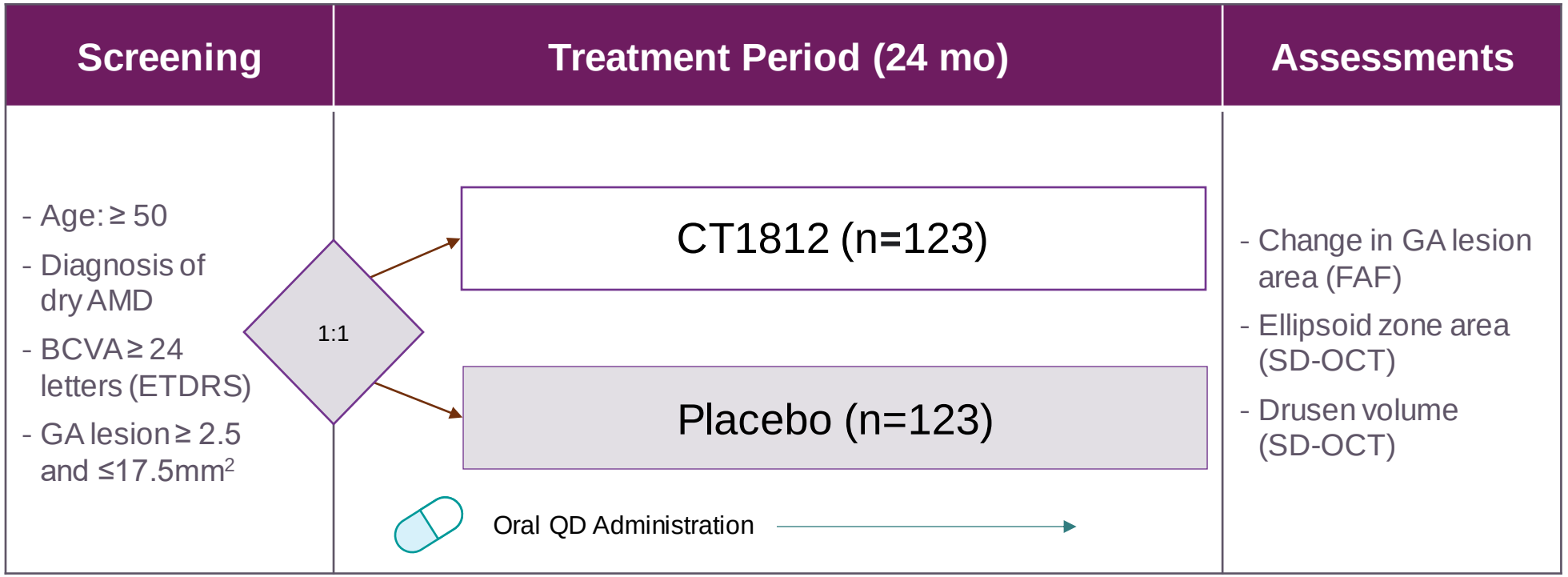


Normal Retina

Retina with GA

COGNITION™ Therapeutics

Phase 2 will Assess CT1812 in GA Secondary to Dry AMD



Finances and Conclusions

Andrew Einhorn
Interim Chief Financial Officer

COGNITION™ Therapeutics

Significant Grant Support from NIH

Provides validation of scientific approach

Grant funding for CT1812 studies as of Dec 31, 2022

- Cumulative grant awards: appx $171.0 million
  - Approximate funding used: ($81.7 million)
  - *Remaining grant funding:* **$89.3 million**

Clinical Study	Total Award	NIA Grant Number
START (early Alzheimer's disease)	$ 81 million	AG065248
SHINE (mild-moderate Alzheimer's)	$ 30 million	AG058660
SHIMMER (mild-moderate DLB)	$ 29 million	AG071643
SEQUEL (qEEG in Alzheimer's)	$ 5.4 million	AG058710

Financial Position

Financials as of December 31, 2022

- Cash and Cash Equivalents: $41.6 million
- Expected cash runway into the second half of 2024

Recent Financings

- ATM initiated
- Committed Equity Facility
- Reverse inquiry November 2022

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Thank You

Lisa Ricciardi
President & CEO
917-658-5789
lricciardi@cogrx.com

Tony Caggiano, MD, PhD
CMO and Head of R&D
914-221-6730
acaggiano@cogrx.com

Andy Einhorn
Chief Financial Officer
973-879-8240
aeinhorn@cogrx.com

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