The Anti-Aβ Oligomer Drug CT1812 for Alzheimer's: Phase 1b/2a Safety Trial Outcomes

Lon S Schneider, MD[1], Michael Grundman, MD, MPH[3,2], MS, Steven DeKosky, MD[4], Roger Morgan, MD[5], Robert Guttendorf[6], Michelle Higgin, PhD[7], Julie Pribyl[7], Kelsie Mozzoni[3], Nicholas J Izzo, PhD[3], Hank Safferstein, PhD[3], Celine Houser, RN[3], Michael Woodward, MD[8] Susan M Catalano, PhD[3]

(1) Keck School of Medicine of USC, Los Angeles (2) Global R&D Partners, LLC, San Diego (3) Cognition Therapeutics, Inc., Pittsburgh (4) McKnight Brain Institute, University of Florida, Gainesville (5) MedSurgPI, LLC, Raleigh, NC (6) Aclairo Pharmaceutical Development Group, Inc., Vienna, VA (7) PharmaDirections, Cary, NC (8) Austin Health, Melbourne, Australia

10th Clinical Trials on Alzheimer's Disease Meeting
Boston, MA
November 4, 2017

CXGRX

Keck School of Medicine of USC

The Anti-Aβ Oligomer Drug CT1812 for Alzheimer's Disease: Phase 1b/2a Safety Trial Outcomes

Disclosures

Lon S. Schneider, MD:

- Grant or research support: NIH, USC ADRC, ADNI, UCSD ADCS, phytoSERMs, AD trials simulations, allopreganolone, in silico screening for AD medications; P50 AG05142, R01 AG033288, R01 AG037561, UF1 AG046148, R01 AG057684, Banner Alzheimer Prevention Initiative, DIAN-TU/Washington Univ; State of California AD Program (CADC), California Institute for Regenerative Medicine (CIRM); Biogen, Roche/Genentech, Eli Lilly (ADCS), Merck, Novartis, Tau Rx
- Consultant (past 3 years): AC Immune, Avraham, Axovant, Boehringer Ingelheim, Cerespir, Clintara, Cognition, Corium, Eli Lilly, Impel, Insys, GE, Kyowa Kirin, Medavante, Merck, Neurim, Novartis, Roche, Samus, Stemedica, Takeda, Tau Rx, Tonix, Toyama/FujiFilm, vTv
- Editorial boards other (past 3 years): *The Lancet Neurology* (editorial board), *Cochrane Collaboration* (editor base), *Alzheimer's and Dementia: Translational Research and Clinical Intervention* (editor-in-chief emeritus), *Alzheimer's & Dementia* (senior associate editor), *Current Alzheimer Research* (associate editor); guidelines committee for the World Federation of Societies of Biological Psychiatry

Clinical Studies:

- National Institute on Aging AG051593, AG054176

Preclinical Studies:

- National Institute on Aging AG037337, AG047059, AG054176, AG052249, AG033670
- National Institute on Neurological Diseases and Stroke NS083175
- Alzheimer's Research UK

Overview of CT1812

- Preclinical Studies
- Early Clinical Development
- Phase 1b/2a Study of CT1812 in Mild to Moderate AD (COG0102)
- Future Clinical Development

CT1812:

- Orally-administered lipophilic isoindoline as a fumarate; rapidly absorbed, highly brain penetrant
- Sigma-2/PGRMC1* receptor complex allosteric antagonist, destabilizes the Aβ oligomer binding site, increases off-rate of oligomers from synaptic receptors, Aβ oligomers then cleared into CSF

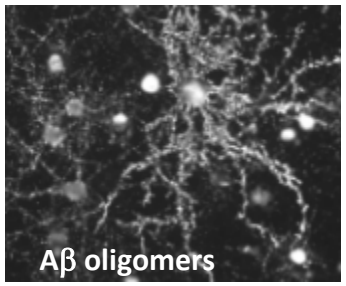
*progesterone receptor membrane component 1

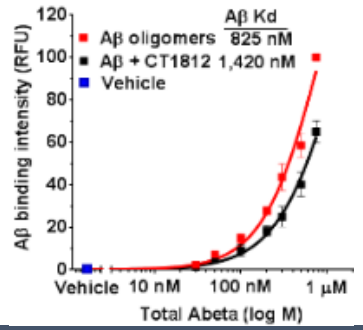
CT1812 Preclinical Studies

- Displaces Aβ oligomers from neurons, AD neocortex and living transgenic AD mouse brain
- Clears oligomers into CSF
- Restores synapses
- Restores performance in transgenic AD mice

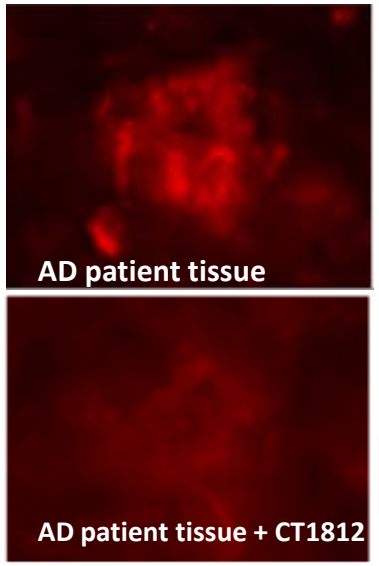
Displaces Aβ oligomers…

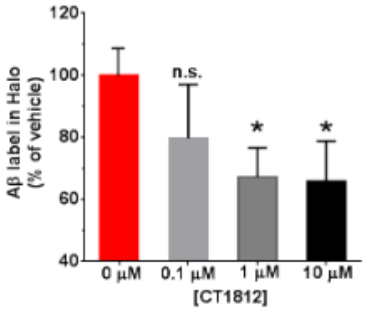
…from neurons



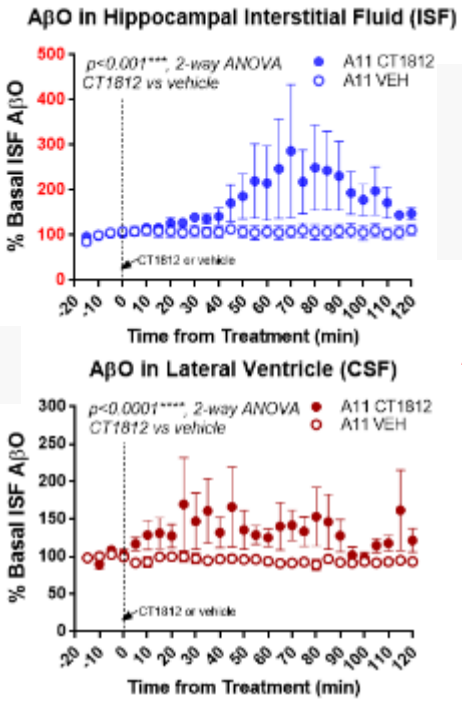


…from AD patient neocortical tissue





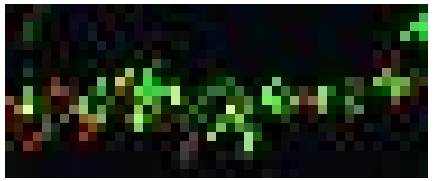
…from hippocampus of living transgenic APP/PS1 mice; clears Aβ oligos into CSF without affecting monomer concentrations



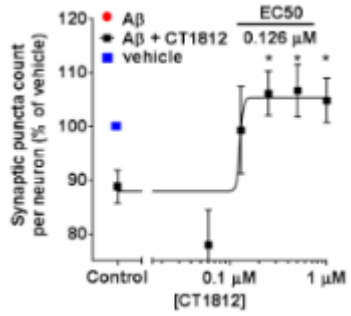
Restores…

…synapse number to normal

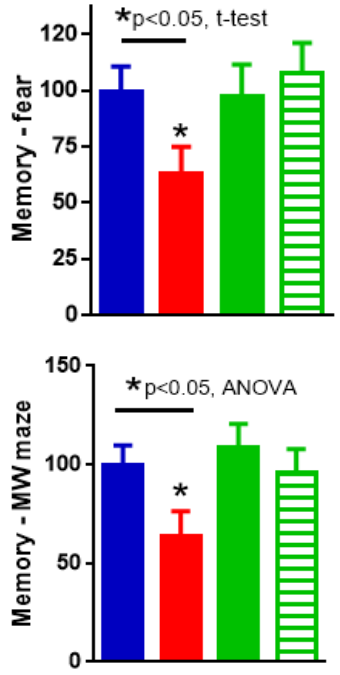
Aβ oligomers and synapses



Aβ oligomers and synapses + CT1812



…memory in transgenic AD mice at concentrations > 80% receptor occupancy



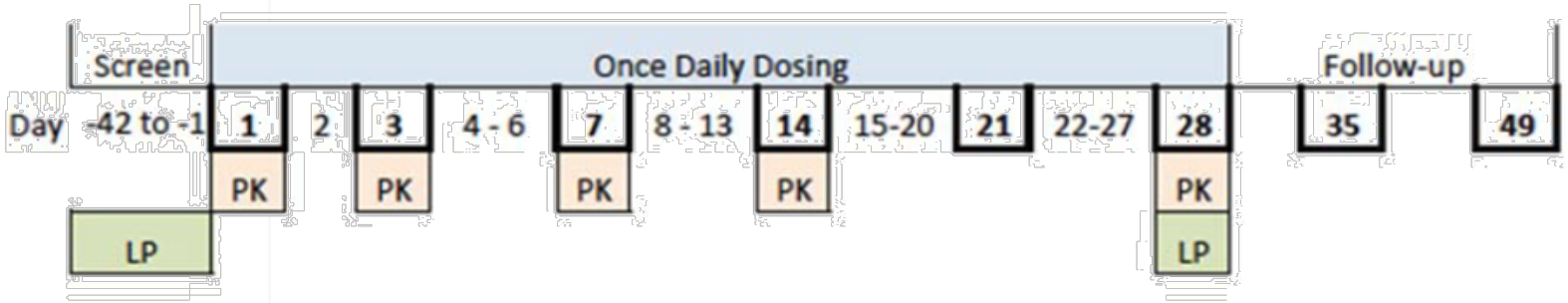
CT1812 Early Clinical Development Program

- Healthy volunteers (n = 74)
  - Ascending single dose: safe and well tolerated to 1120 mg
  - 14-day multiple dose (QD): safe and well tolerated up to 840 mg in young and 560 mg in elderly (aged 65-75)

- Drug-drug interaction study (n = 15)
  - Suggested minor interactions with CYP isoenzymes

COG0102: A Phase 1b/2a Randomized Double Blind Placebo Controlled Trial of CT1812 in Mild to Moderate AD

Population	19 participants, 50 – 80 years, mild/ moderate AD MMSE 18 – 26
N Per Dose Group	Placebo (n=5), 90mg (n=4), 280mg (n=5), 560mg (n=5)
Dosing	1x daily for 28 days
Primary Objectives	Safety and tolerability
Secondary Objectives	Pharmacokinetics
Exploratory Objectives	• ADAS-Cog, COWAT, CFT, and composite • CSF concentrations of CT1812 and CSF biomarkers



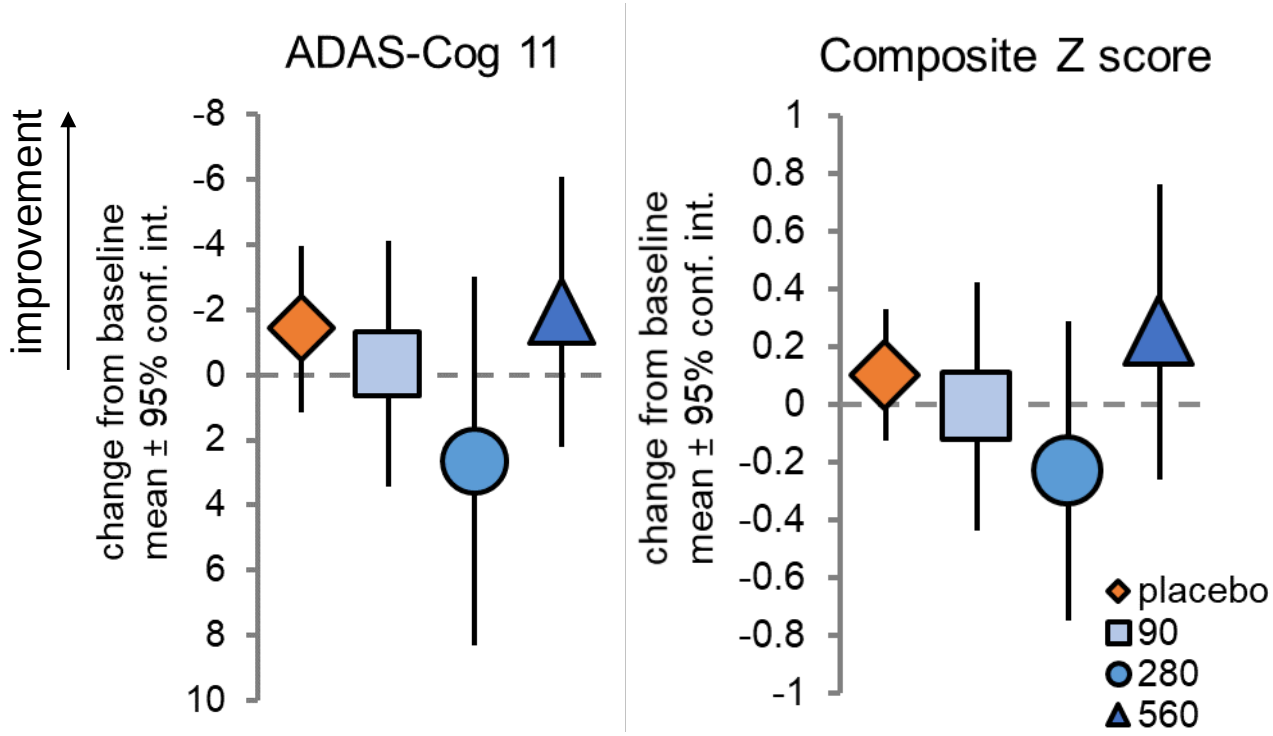
	Placebo	90 mg	280 mg	560 mg
Age	64.4 ± 8.9	71.8 ± 7.7	71.8 ± 12.4	73 ± 6.8
Sex M/F	2/3	3/1	3/2	1/4
MMSE	21.2 ± 3.1	24 ± 3.4	21.4 ± 2.6	21.8 ± 3

Treatment-Emergent Adverse Events and Exploratory Cognitive Outcomes

	Placebo (n=5)	90 mg (n=4)	280 mg (n=5)	560 mg (n=5)
TEAEs - n (%)	3 (60%)	3 (75%)	4 (80%)	5 (100%)
Mild TEAEs – n (%)	3 (60%)	4 (100%)	3 (60%)	5 (100%)
Moderate TEAEs – n (%)	1 (20%)	0 (0%)	1 (20%)	3 (60%)
Severe TEAEs – n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAEs – n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Adverse Events Occurring in More Than 1 Participant				
Lymphocytopenia – n (%)	0 (0%)	0 (0%)	0 (0%)	3 (60%)*
Headache – n (%)	0 (0%)	1 (25%)	0 (0%)	2 (40%)
Nausea – n (%)	1 (20%)	0 (0%)	0 (0%)	2 (40%)
Vomiting – n (%)	1 (20%)	0 (0%)	0 (0%)	2 (40%)

*transient



- Change from baseline similar across groups

Composite: ADAS-Cog word recall, recognition, ADAS-Cog orientation; Controlled Oral Word Association Test; Category Fluency Test

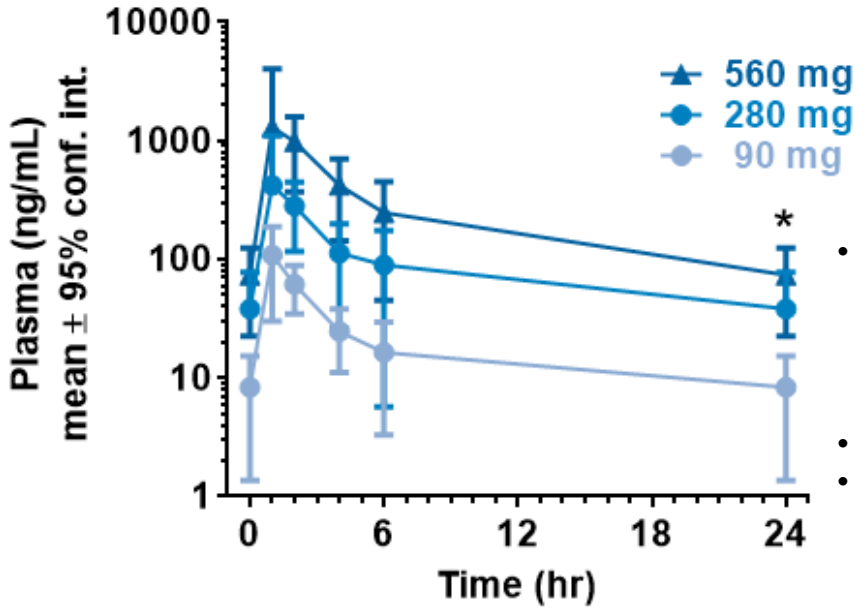
Safety and Cognitive Data Summary

- Generally safe and well tolerated at all doses
  - No severe AEs or SAEs
  - All AEs were mild or moderate
    - 1 participant showed ALT ~ 4.7x ULN at 560 mg; resolved by end of study; no associated increase in bilirubin
    - Lymphocytopenia resolved by end of study

- Cognitive outcomes were similar across the treatment groups

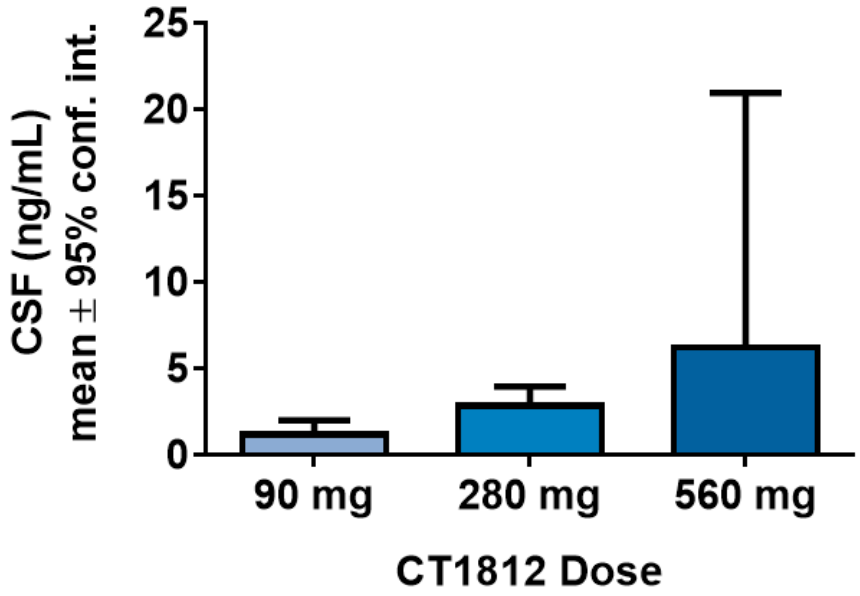
Pharmacokinetics

Plasma CT1812 (day 28)



- *24 hr timepoint estimated from pre-dose blood draw on day 28
- $T_{1/2}$ = 12 hr
- T_{max} = 1-2 hr

CSF CT1812 (day 22-30)

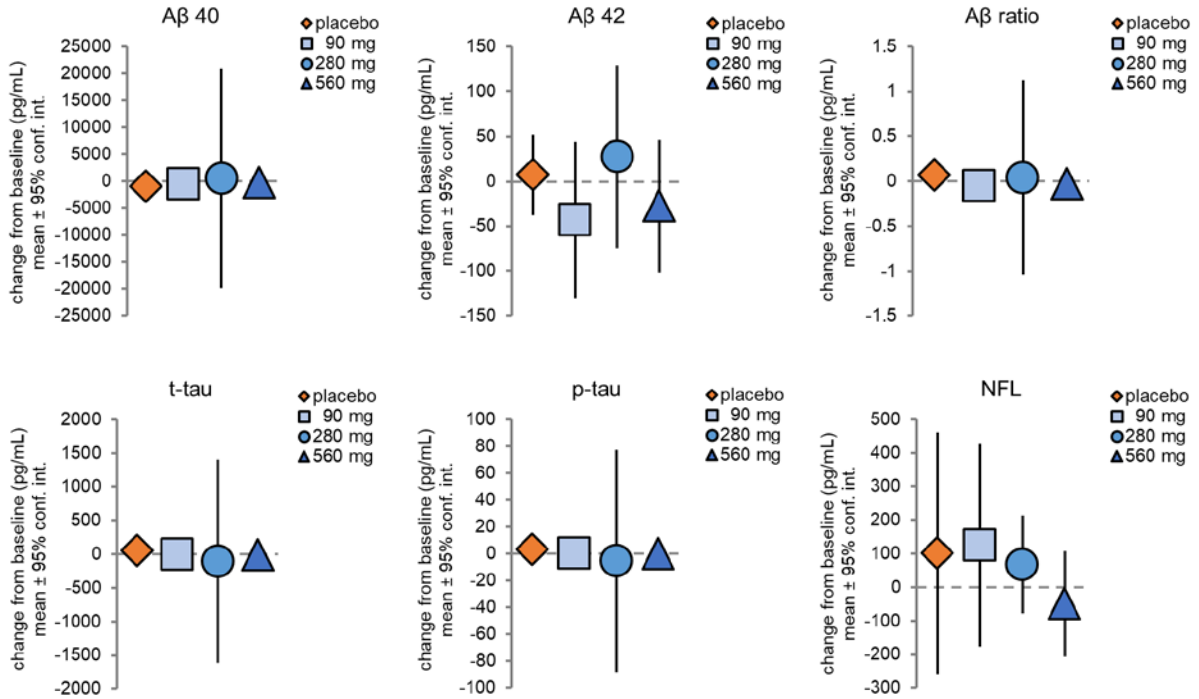


- Samples drawn 24 hr post dose, at trough plasma levels

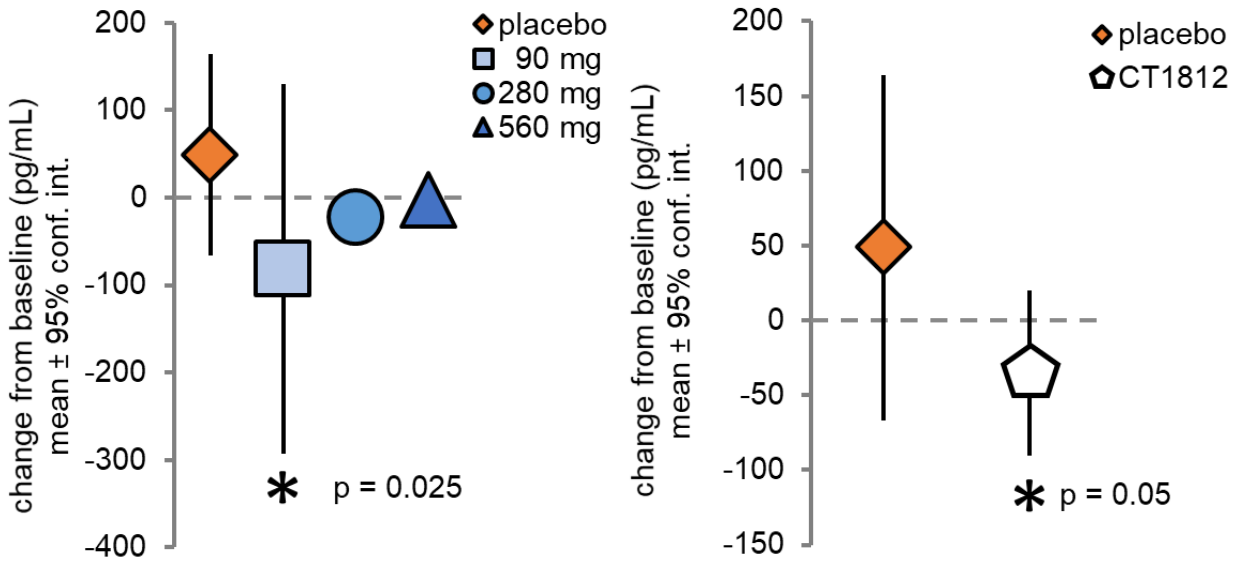
- Plasma CT1812 concentration increased approximately dose proportionally
- Dose dependent increase in CSF concentration
- All CSF concentrations > 80% estimated brain receptor occupancy (threshold needed to demonstrate efficacy in preclinical studies)

CSF AD Biomarkers

Aβ, tau, and NfL



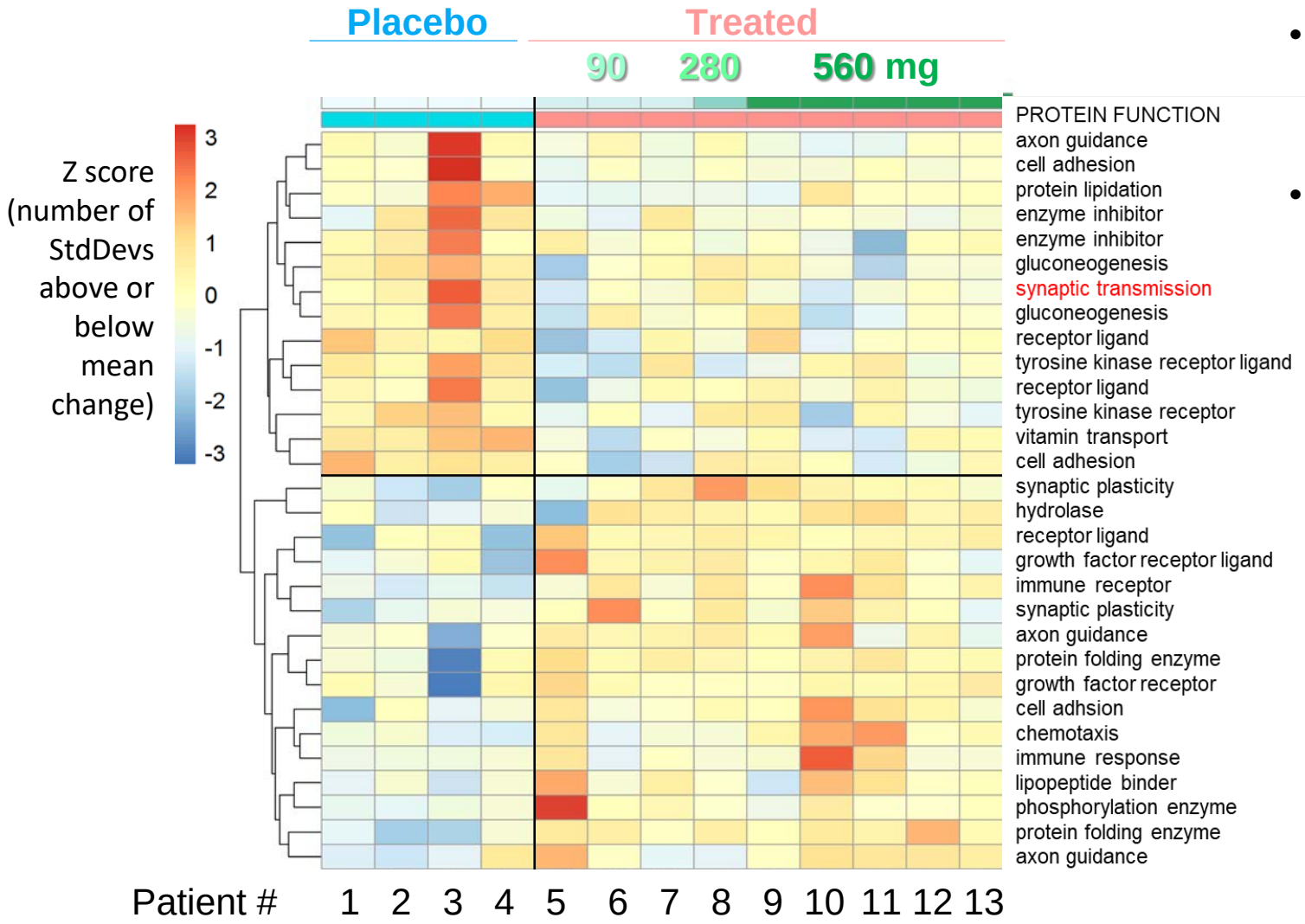
Neurogranin



*ANCOVA (baseline coV)

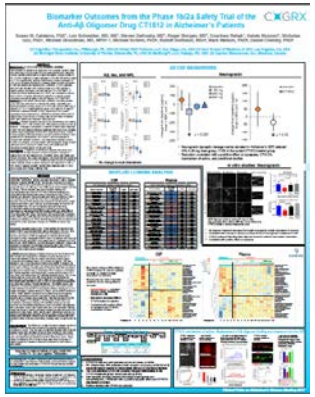
- Neurogranin (synaptic damage marker elevated in Alzheimer's CSF) reduced 33% at 90 mg, 17.6% pooled
- Consistent with a positive effect on synapses, CT1812's mechanism of action, and preclinical studies

CSF LC/MSMS Analysis: Consistent Protein Response to CT1812 Treatment in AD Patients



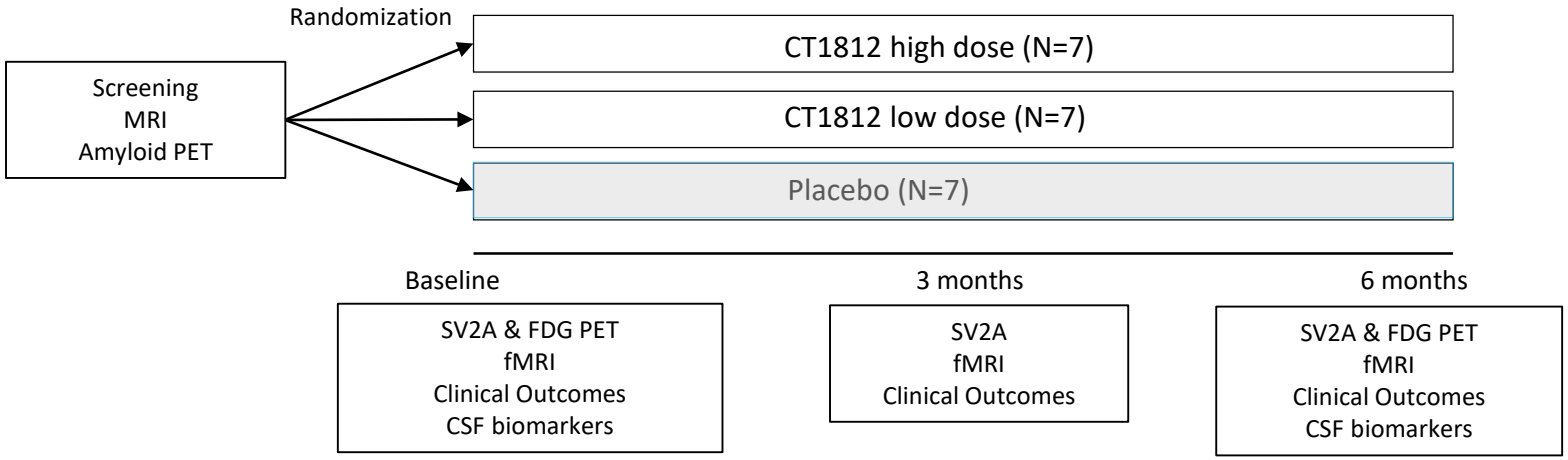
- 30 proteins changed differentially in CT1812-treated vs. placebo patients ($p \leq 0.05$, i.e., higher or lower expression vs. placebo)
- Several play key roles in synaptic plasticity and are dysregulated in AD brain:
  - Synaptotagmin-1, a synaptic damage marker, elevated in Alzheimer's CSF
  - Expression decreased 63% in CT1812-treated vs. placebo
  - Consistent with positive effect on synapses and CT1812's mechanism of action

(See poster LBP28)



Planned Clinical Studies in AD patients

1. Single dose administration followed by hourly sampling of lumbar CSF via indwelling catheter for 24 hours (NIA AG057780, PI Sheline)
2. Measurement of rapid changes in synaptic number and function via SV2A expression, FDG-PET and fMRI (NIA AG057553, PIs van Dyck and Carson)



3. Measurement of rapid changes in synaptic function via quantitative EEG (PI Scheltens)
4. Longer term Phase 2 efficacy trial – 6 months, 160 patients, 3 doses + placebo

Conclusions: COG0102 Phase 1b/2a 28-day Trial Outcomes

- CT1812 safe and well tolerated across all doses, no SAEs
- Greater than 80% estimated brain receptor occupancy at all doses (threshold needed to demonstrate efficacy in preclinical studies)
- After 4 weeks of treatment, CSF synaptic damage markers decreased (neurogranin and synaptotagmin), consistent with a positive synaptic effect and CT1812's mechanism of action
- Further studies with CT1812 are planned

Acknowledgements

Cognition Therapeutics, Inc.

Kelsie Mozzoni
Colleen Silky
Gilbert Rishton
Ray Yurko
Courtney Rehak
Gary Look
Hank Safferstein
Nicholas Izzo
Thomas Walko III
Nicole Knezovich
Susan Catalano

Medical Advisory Board

Lon Schneider
Steven DeKosky
Michael Grundman

Clinical Consultants

Roger Morgan
Manfred Windisch

Scientific Advisory Board

Cynthia Lemere
Robert Malenka
Harry LeVine III
Dominic Walsh
John Cirrito
Alison Goate
Rolf Craven
Mike Cahill

Spires-Jones Lab

Tara Spires-Jones
Molly J. Kirk
Chris Henstridge

Cirrito Lab

John Cirrito
Carla Yuede

Stanford Neurobehavioral Lab

Mehrdad Shamloo
Lilly To
Marie Monbureau

Carlos Cruchaga, Wash U.
Elizabeth Head, U. Kentucky

Neuroscience Trials Australia and the Alzheimer's patients and their families who participated in COG0102

Supported by

Clinical: National Institute on Aging AG051593, AG054176

Preclinical: National Institute on Aging AG037337, AG047059, AG054176, AG052249, AG033670, National Institute on Neurological Diseases and Stroke NS083175, Alzheimer's Research UK

Thank you!