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

Lon S Schneider, MD¹, Michael Grundman, MD, MPH³,², MS, Steven DeKosky, MD⁴, Roger Morgan, MD⁵, Robert Guttendorf⁶, Michelle Higgin, PhD⁷, Julie Pribyl⁷, Kelsie Mozzoni³, Nicholas J Izzo, PhD³, Hank Safferstein, PhD³, Celine Houser, RN³, Michael Woodward, MD⁸, Susan M Catalano, PhD³


10th Clinical Trials on Alzheimer’s Disease Meeting
Boston, MA
November 4, 2017
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, Stemeda, 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...

- 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

...from neurons

Aβ oligomers

AD patient tissue

Aβ oligomers + CT1812

Aβ oligomers and synapses

Displaces Aβ oligomers…

...from AD patient neocortical tissue

Aβ oligomers and synapses + CT1812

Aβ oligomers and synapses + CT1812

Aβ oligomers and synapses

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

...synapse number to normal

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

Restores…
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
### Treatment-Emergent Adverse Events and Exploratory Cognitive Outcomes

#### TEAEs - n (%)  
<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=5)</th>
<th>90 mg (n=4)</th>
<th>280 mg (n=5)</th>
<th>560 mg (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>3 (60%)</td>
<td>3 (75%)</td>
<td>4 (80%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Mild TEAEs</td>
<td>3 (60%)</td>
<td>4 (100%)</td>
<td>3 (60%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Moderate TEAEs</td>
<td>1 (20%)</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Severe TEAEs</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>SAEs</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

#### Adverse Events Occurring in More Than 1 Participant  

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=5)</th>
<th>90 mg (n=4)</th>
<th>280 mg (n=5)</th>
<th>560 mg (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytopenia – n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (60%)*</td>
</tr>
<tr>
<td>Headache – n (%)</td>
<td>0 (0%)</td>
<td>1 (25%)</td>
<td>0 (0%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Nausea – n (%)</td>
<td>1 (20%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Vomiting – n (%)</td>
<td>1 (20%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (40%)</td>
</tr>
</tbody>
</table>

*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 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)

**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

Cognition Therapeutics, Inc.
- 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 ≤ 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               Courtney Rehak               Thomas Walko III
Colleen Silky                Gary Look                  Nicole Knezovich
Gilbert Rishton              Hank Safferstein          Susan Catalano
Ray Yurko                   Nicholas Izzo

Medical Advisory Board
Lon Schneider               Steven DeKosky               Michael Grundman

Clinical Consultants
Roger Morgan                 Manfred Windisch

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

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!