Disease-modifying medicines for neurodegenerative disorders
The “New” Cognition: CNS Disease Expertise with Compelling Neurodegenerative and Neuro-Ophthalmology Opportunities

The science of σ-2 biology led us to first pursue Alzheimer’s disease and now dry AMD/GA - indications with significant unmet need and large market potential. Other indications to follow

<table>
<thead>
<tr>
<th>Neurodegenerative Diseases</th>
<th>Neuro-ophthalmic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alzheimer’s disease</td>
<td>• Dry age-related macular degeneration</td>
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<tr>
<td>• Parkinson’s disease</td>
<td>• Geography atrophy</td>
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<tr>
<td>• Multiple system atrophy</td>
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<tr>
<td>• Huntington’s disease</td>
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σ-2 Receptor Complex:
Cellular Damage Response Regulator

PGRMC1 is involved in vesicle trafficking, cell cycle regulation, autophagy

TMEM97 is involved in cholesterol transport

σ-2 receptor regulates cellular stress response

Receptor complex is upregulated in disease

PGRMC1

TMEM97

Other
Cellular Damage Response Disrupted in Multiple Conditions

- PGRMC1 and TMEM97 (σ-2 proteins) regulate damage response processes:
  - Autophagy
  - Cholesterol synthesis
  - Lipid membrane-bound protein trafficking

- These pathways are impaired by the build-up of age-related stressors such as:
  - Aβ oligomers in Alzheimer’s disease
  - Protein aggregates, oxidative stress and inflammation in dry AMD/GA
  - α-synuclein oligomers in Parkinson’s disease, DLB and MSA
  - Oxidative stress and inflammation in ALS and other neurodegenerative diseases

- Cognition’s candidates target PGRMC1 and TMEM97 proteins with aim to return pathways to normal function

- Expected to be synergistic with other therapies
Cognition Pipeline: Preclinical & Clinical Data in Neurodegenerative Diseases
## Alzheimer’s Clinical Program
### What We’ve Learned

<table>
<thead>
<tr>
<th>Study</th>
<th>COG0101 SAD/MAD (n=74)</th>
<th>COG0102 DDI (n=19)</th>
<th>COG0103 SNAP (n=18)</th>
<th>COG0104 SPARC (n=21)</th>
<th>COG0201 SHINE (n=62)</th>
<th>COG0202 SEQUEL (n=16)</th>
<th>COG0203 (n=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Healthy Volunteers</td>
<td>Mild-Moderate Alzheimer’s</td>
<td>Healthy Volunteers</td>
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<td>Mild-Moderate Alzheimer’s</td>
<td>Mild-Moderate Alzheimer’s</td>
<td>Early Alzheimer’s</td>
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<tr>
<td>Phase</td>
<td>Phase 1</td>
<td>Phase 1b/2a</td>
<td>Phase 1</td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 2</td>
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<tr>
<td>Objective</td>
<td>Safety &amp; drug-food interaction</td>
<td>Safety &amp; drug-food interaction</td>
<td>Safety &amp; drug-food interaction</td>
<td>Improvement in synapse numbers would be evidence of disease modification</td>
<td>Safety &amp; biomarker evidence of disease modification</td>
<td>Changes in synapse function would be evidence of disease modification</td>
<td>Improvement in cognition</td>
</tr>
<tr>
<td>Status</td>
<td>Completed 2015</td>
<td>Completed 2018</td>
<td>Completed 2016</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Cohort A Complete</td>
<td>Cohort A Complete</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Cohort B Ongoing</td>
<td>Commencing enrollment in 2020</td>
</tr>
<tr>
<td>Results</td>
<td>Safe &amp; well tolerated</td>
<td>Safe &amp; well tolerated</td>
<td>No clinically significant DDI</td>
<td>Topline YE2021</td>
<td>Topline 1H2021</td>
<td>SHINE A: trend for cognitive improvement</td>
<td>SHINE B: 1H 2021</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Topline ~2H 2022</td>
</tr>
</tbody>
</table>
Phase 2 SHINE Interim Analysis: Promising Evidence of CT1812 Impact on Cognitive and Biological Outcomes in First 24 pts

- Three-point difference (ADAS-COG) between treated and untreated patients at day 185
- Clinically meaningful magnitude of change
- Compares favorably with aducanumab results

- Statistically significantly lower Aβ protein (p=0.017) in treated versus placebo patients
- Additional therapeutic impact on p-tau, synaptic and AD-related proteins
ACTC $80M Grant Drives Program Through Phase 2

- COG0203: Phase 2 efficacy study, powered to show change in cognition: slowing or halting cognitive decline
- Enrollment: 540 individuals with early Alzheimer’s disease
- Conducted in collaboration with premier NIA-funded Alzheimer’s clinical trial organization
- 35 U.S. sites with potential for expansion and acceleration
Cognition Study of A673T “Icelandic” Mutation Supports CT1812 MoA

- Carriers of the A673T “Icelandic” mutation of the Aβ protein are 4 times less likely to get Alzheimer’s disease than non-carriers
- Cognition study demonstrates that mutant Aβ oligomers bind with 4-fold lower affinity to brain cell synapses than normal protein
- CT1812 is the only drug that mimics the effects of this protective mutation

Alzheimer’s Protection Effect of A673T Mutation May Be Driven by Lower Aβ Oligomer Binding Affinity*

Colleen S. Limegrover, Harry LeVine III, Nicholas J. Izzo, Raymond Yurko, Kelsie Mozzoni, Courtney Rehak, Kelsey Sadlek, Hank Safferstein, Susan M. Catalano

Cognition Pipeline: Neuro-ophthalmic Diseases
Dry AMD / Geographic Atrophy are Compelling Markets

Leading Cause of Severe Vision Loss in People over 50 (AAO)*

- Unlike wet AMD, there are no approved drugs
  - Dietary supplements are current standard of care
- Disease progression is measured in part by magnitude of geographic atrophy (GA)
  - GA is a progressive degeneration of the macula
  - Regions of atrophy result in a blind spot in the visual field

* American Academy of Ophthalmology

15 million people in North America have AMD

Wet AMD, 15% 3M People

Dry AMD, 85% 12M People

geographic atrophy
Dry AMD / Geographic Atrophy:

**Goal: Treat Biological Defects that Lead to Retinal Cell Degeneration**

- Geographic atrophy (GA) size
- Best-corrected visual acuity (BCVA)
- Low-luminance visual acuity (LLVA)

**Validated Endpoints**

- Autophagy, protein trafficking, lipid metabolism dysregulated in AMD
- Regulated by σ-2
- TMEM97 protective against cellular stress
- Aβ oligomer-induced toxicity posited in AMD; toxicity blocked by σ-2 drug candidates
In Vivo Pharmacokinetics Show Ample Distribution to Eye

- In vivo study using $^{14}$C-labeled CT1812 achieves levels\(^\dagger\) in the retina (orange) at least as great as those in the brain (green)

\[^\dagger\] >80% occupancy is target dose associated with positive effects in animal models of Alzheimer’s disease

* Sprague Dawley rats
AMD – Evidence of Preclinical Proof of Concept of CT1812

Preclinical in vitro PoC

- Does CT1812 rescue AMD-relevant cellular dysfunction and cell death?
- How does CT1812 alter the transcriptome of AMD-relevant stressor stimulated cells?

Preclinical in vivo PoC

- Does CT1812 mimic the TMEM97 knockdown-triggered rescue of cell death?
- Does CT1812 rescue on-mechanism AMD pathophysiology in vivo?

In vivo PoC

- Define the key mechanisms of action by which CT1812 may confer benefit in AMD
- Confirm that pharmacological manipulation of TMEM97 mirrors the genetic evidence that TMEM97 lowering confers benefit in AMD
CT1812 may Restore Downstream Processes

- CT1812 may remove toxic proteins from the sites where they damage retinal cells
- Objective is to restore downstream processes
- On track to complete proof-of-concept trial in 2022
- Pipeline molecules also being assessed as potential candidates for dry AMD
## Financial Update

<table>
<thead>
<tr>
<th></th>
<th>Year ended December 31, 2019 (Audited)</th>
<th>Nine-month ended September 30, 2020 (Unaudited)</th>
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</thead>
<tbody>
<tr>
<td>Cash</td>
<td>$2,889,670</td>
<td>$5,193,100</td>
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<tr>
<td>Convertible Notes Outstanding</td>
<td>$7,626,055</td>
<td>$13,000,000</td>
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<tr>
<td>Grant Revenue</td>
<td>$13,164,335</td>
<td>$10,958,200</td>
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<tr>
<td>Research &amp; Development Expenses</td>
<td>$14,379,145</td>
<td>$13,434,700</td>
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<tr>
<td>Loss from Operations</td>
<td>$4,666,425</td>
<td>$6,562,600</td>
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<tr>
<td>Fully Diluted Shares Outstanding</td>
<td>56,171,147</td>
<td>58,270,700</td>
</tr>
</tbody>
</table>

*Scored grant applications for DLB ($30M) and SHINE B ($13M) via NIA*
Use of Proceeds 2021-2022

- Dry AMD - CT1812: $17M
- Alzheimer’s disease - CT1812: $3 M
- Pipeline/Discovery: $3 M
- G&A Support: $7 M

Total: $30 M

Alzheimer’s (ACTC) FUNDDED with $80M Grant
Thank You

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