CTAD Presentation
New Exploratory Alzheimer’s Drug ANAVEX 2-73: Assessment of Safety and Cognitive Performance in a Phase 2a Study in mild-to-moderate Alzheimer’s Patients
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Relevant Disclosures: Nil
ANAVEX 2-73

- ANAVEX 2-73 is an orally available small molecule with a favorable safety profile in Phase 1

- **ANAVEX 2-73 activates the Sigma-1 Receptor, a key upstream cellular modulator mediating clearance of misfolded proteins including Aβ and Tau**

- As such, may have potential to modify protein misfolding common in many neurodegenerative diseases (e.g. Parkinson’s disease, Huntington’s disease)

- Potential for prevention, disease-modification, reversal of memory loss and neuroprotection displayed in Alzheimer’s disease models
ANAVEX 2-73 Significantly Improves Memory in Transgenic Alzheimer's Disease Mouse Model (Tg2576)

- 10 month-old Tg2576 and WT male mice administered p.o. (oral) with tap water or ANAVEX 2-73 (3 mg/kg/day); After 2 months, tested for place learning in the water-maze; N = 6-12 per group

Presented at SfN Neuroscience Meeting 2013
Protocol Summary ANAVEX 2-73

- Phase 2a study of 32 patients with mild-moderate AD
- 5 weeks’ duration, randomized, open label, with main inclusion criteria
  - MMSE 16-28,
  - CT or MRI within 12 months consistent with AD
  - Either AChEI-naïve ($n = 7$), or on a stable AChEI dose for at least 3 months ($n = 25$)
- Maximum-tolerated dose population pharmacokinetic study with primary endpoints of safety, tolerability and bioavailability
- Optional PART B open-label extension with daily oral dosing (26 weeks, now extended to 52 weeks at patient/caregiver request)
- All PART A completers volunteered to continue in PART B
- Whilst **NOT** powered to assess cognitive outcomes, several exploratory items were included: MMSE, Cogstate, EEG P300, ERP task performance and ADCS-ADL
**ANAVEX 2-73: Phase 2a with Adaptive Trial Design**

**Mild-Mod AD patients**

- ANAVEX 2-73 starting dose 30mg/50mg (oral) or 3mg, 5mg (IV)
- ANAVEX 2-73 starting dose 30mg/50mg (oral) or 3mg, 5mg (IV) + Donepezil
- Healthy control, Donepezil/ AchEI

| No. of Pts | ▪ 32 mild-moderate AD patients (MMSE 16-28), M/F = 19/13 |
| No. of Sites: | ▪ 5 |
| Allocation: | ▪ Randomized |
| Duration: | ▪ PART A: 5 weeks; PART B: 12, 26, 38 and 52-week data analyses |
| Endpoints: | ▪ **Primary:** Safety, tolerability, bioavailability (PK study)  
▪ Exploratory cognitive measures (EEG/ERP, MMSE, Cogstate) and ADCS-ADL  
▪ Exploratory add-on therapy to AD standard of care |

- Design embraces both **adaptive trial features** and **population pharmacokinetics**
- Captures all relevant information required for a larger Phase 2/3 study

# Comparison to published data (AIBL)
PART A: Bioavailability Cross-Over Design and PART B: 52-Week Open-Label Voluntary Extension

- **Screening and Randomization**
- **Part A**:
  - 1st Period: ORAL - wash out 12d
  - 2nd Period: ORAL
- **Part B**:
  - 52-week ORAL

**Dosing**

- **1st Period**: ORAL
- **2nd Period**: ORAL

**Notes**

- Once daily oral or IV dosing except during wash out period
- PART A is 5 weeks with on-off-on dosing of ANAVEX 2-73 starting dose of 30mg/50mg (oral) and 3mg, 5mg (IV)
- Dosing regimen **without** any dose optimization
# Baseline Patient Characteristics and Disposition

<table>
<thead>
<tr>
<th>Baseline Patient Characteristics</th>
<th>n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age years, mean</strong></td>
<td>71</td>
</tr>
<tr>
<td><strong>ApoE4</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>Carriers</td>
<td>17 (53%)</td>
</tr>
<tr>
<td>Non-carriers</td>
<td>15 (47%)</td>
</tr>
<tr>
<td><strong>MMSE, median, (±SD)</strong></td>
<td>20.5 (4.0)</td>
</tr>
<tr>
<td><em><em>AD Medication use,</em> n (%)</em>*</td>
<td>25 (78%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disposition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>32</td>
</tr>
<tr>
<td>Dosed</td>
<td>32</td>
</tr>
<tr>
<td>Discontinued Treatment: AE not related to study drug</td>
<td>2</td>
</tr>
</tbody>
</table>

* Donepezil
Adverse Events (AEs)

- The most common AE was dizziness (20 events in 15 patients) followed by headache (16 events in 10 patients)
  - Events were mild or moderate and reversible with 80% being grade 1
  - Most (94.4%) observed within first 8 days
- AE profile similar to that of healthy volunteer Phase 1 data
- SAE leading to discontinuation: Delirium in patient with previous history of delirium; SRC deemed likely not related to study drug
- No differences in blood pressure or resting heart rate
- Clinical laboratory parameters, vital signs, and 12-lead ECG did not show any clinically relevant or dose-dependent changes

<table>
<thead>
<tr>
<th>AEs</th>
<th>N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with an adverse event (%)</td>
<td>30 (93.8%)</td>
</tr>
<tr>
<td>Number of subjects with a serious adverse event (%) not related to study drug</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
## Adverse Events (AEs) Details

<table>
<thead>
<tr>
<th>AE Body System</th>
<th>Mild (Grade 1)</th>
<th>Moderate (Grade 2)</th>
<th>Severe (Grade 3)</th>
<th>Total N=Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders (36 of 47 dizziness and headache)</td>
<td>35 (74%)</td>
<td>12 (26%)</td>
<td>0 (0%)</td>
<td>47 (46%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>14 (88%)</td>
<td>2 (13%)</td>
<td>0 (0%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>7 (88%)</td>
<td>1 (13%)</td>
<td>0 (0%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>6 (75%)</td>
<td>2 (25%)</td>
<td>0 (0%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>3 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
<td>0 (0%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>82 (80%)</strong></td>
<td><strong>20 (20%)</strong></td>
<td><strong>0 (0%)</strong></td>
<td><strong>102 (100%)</strong></td>
</tr>
</tbody>
</table>

- There were no AEs Grade 3, 4 and 5
Efficacy Data Measurements Cognition and Function

- Exploratory cognitive measures Cogstate battery; (MMSE)
- Functional measures (ADCS-ADL)
- ERP (P300): fundamental measures of synaptic network performance
- ERP target detection task measures: direct measure of attention, speed of brain processing, and simple functional performance
ANAVEX 2-73 Increases MMSE by +1.5 Points at Week 5

- ANAVEX 2-73 improved median MMSE by +1.5 points at week 5
- n= 30 at baseline and week 5 with on-off-on ANAVEX 2-73 dosing regimen **without** any dose optimization
- # p = not significant. Trial was not designed to capture statistical significance of cognitive endpoints
ANAVEX 2-73 Significantly Improves Components of Cogstate Tasks at Week 5: Effect sizes for Change from Baseline

- ANAVEX 2-73 improved 5 of 6 Cogstate Tasks at week 5
- n= 30 at baseline and week 5 with on-off-on ANAVEX 2-73 dosing regimen **without** any dose optimization

Cognitive Decline → Cognitive Improvement

Detection: Effect size 0.33
Identification: Effect size 0.44*
One Back: Effect size 1.10**
Visual Learning: Effect size 0.10
ISLT: Effect size 0.09
ISLT-delay: Effect size -0.22

* p<0.05, ** p<0.001
ANAVEX 2-73 Significantly Improves Components of Cogstate Tasks at week 5: Data Relative to Change in AD Control Group

- Treatment with ANAVEX 2-73 is associated with improvement in psychomotor function (detection), attention (identification task) and working memory (One back task). This improvement is greater than that associated with any repeated exposure to the same tests in people with AD who are taking AChEIs.
- ANAVEX 2-73 compared to data from the AIBL-AD group who had undergone assessment with the same battery of tests over a similar retest period as part of their participation in the AIBL-rate of change study (AIBL-ROCS)##. The AIBL-ROCS cohort had been maintained on their cholinesterase inhibitor treatment throughout the study period.

### Meta-analyses indicate high dose of donepezil ~0.28 in similar patients#

* p<0.05, ** p<0.001


## Source: aibl.csiro.au/publications/
ANAVEX 2-73 Reverses Cognitive Deficits Measured by Standard ERP Methods at Week 5

<table>
<thead>
<tr>
<th></th>
<th>P300 Amplitude (µV)</th>
<th>Task Accuracy (%)</th>
<th>False Alarms (%)</th>
<th>Reaction Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5.99±0.58</td>
<td>83.8±3.9</td>
<td>3.4±1.0</td>
<td>559.0±24.0</td>
</tr>
<tr>
<td>Week 5</td>
<td>7.09±0.72</td>
<td>92.6±2.4</td>
<td>1.0±0.5</td>
<td>492.6±23.8*</td>
</tr>
<tr>
<td>Healthy Control*</td>
<td>7.36±0.39</td>
<td>94.1±1.1</td>
<td>1.1±0.2</td>
<td>458.6±11.4</td>
</tr>
</tbody>
</table>

Data are mean ± SEM *p<0.0007

Healthy Control

- Improvement
- Baseline
- Decline

- ANAVEX 2-73 improves P300 / ERP at week 5
- n= 30 at baseline and week 5 with on-off-on ANAVEX 2-73 dosing regimen without any dose optimization

*Cecchi et al, Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 2015*
Interim Data: ANAVEX 2-73 Increases ADCS-ADL by +3.21 Points at Week 12

- Interim data: ANAVEX 2-73 improved ADCS-ADL signal in 11 out of 14 (78.6%) patients
- # p = not significant. Trial was not designed to capture statistical significance
Summary

- Primary endpoints met with favorable safety and tolerability
- Despite the Phase 2a trial not being designed to demonstrate statistical significance, improvement on cognition at all doses:
  - Statistically significant improvement in Cogstate Identification Task and Cogstate One Back Task at week 5
  - Improvement of MMSE and Cogstate at week 5
  - Statistically significant improvement in ERP Reaction Time at week 5
  - Improvement of ERP (P300) at week 5
  - Improvement of ADCS-ADL at week 12
Future Development

- Phase 2a (PART A) results demonstrate an acceptable safety, bioavailability and tolerability/risk profile to continue development
- Supportive evidence (Cogstate, MMSE, ERP) indicating a cognitive benefit associated with ANAVEX 2-73 already at 5 week treatment including a washout period
- This converting supportive evidence provides sufficient confidence to start a larger randomized, double-blind Phase 2/3 study
- Phase 2a Population PK/PD, including long-term extension PART B, is ongoing
- Additional data, including updates on PART B to be presented at upcoming scientific meetings
Acknowledgments

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  John Harrison, PhD
  Ottavio Arancio, MD, PhD

- Most of all, grateful acknowledgement of the contribution of the participating AD patients and their caregivers