10TH ANNUAL CHAIR SUMMIT
Master Class for Neuroscience Professional Development

November 16 - 18, 2017 | Hotel Monteleone | New Orleans, LA

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Treatment Targets in Alzheimer’s Disease

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Disclosures

- **Research/Grants:** MECTA Corporation; Merck & Co. Inc.

- **Consultant:** Multiple Energy Technologies; Anthem Insurance
Explore treatment targets in AD and agents in development that target these pathways.
Mechanisms of Action of Agents for AD in Phase 3 Development

### Agents in Development for AD

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Type</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adacanumab</td>
<td>Aβ</td>
<td>Fully human IgG1mAb</td>
<td>Passive immunotherapy</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>Aβ</td>
<td>Humanized mAb</td>
<td>Passive immunotherapy</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Aβ</td>
<td>Humanized mAb</td>
<td>Passive immunotherapy</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Aβ</td>
<td>Humanized mAb</td>
<td>Passive immunotherapy</td>
</tr>
<tr>
<td>ALZT-OP1</td>
<td>Aβ</td>
<td>Small molecule</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>AZD3293</td>
<td>Aβ</td>
<td>Small molecule</td>
<td>BACE inhibitor</td>
</tr>
<tr>
<td>CNP520</td>
<td>Aβ</td>
<td>Small molecule</td>
<td>BACE inhibitor</td>
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</table>

### Agents in Development for AD (cont’d)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Type</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elenbecestat</td>
<td>Aβ</td>
<td>Small molecule</td>
<td>BACE inhibitor</td>
</tr>
<tr>
<td>Lananbecestat</td>
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<td>BACE inhibitor</td>
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<tr>
<td>Verubecestat</td>
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<td>BACE inhibitor</td>
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<tr>
<td>AGB101</td>
<td>Aβ</td>
<td>Small molecule</td>
<td>Anti-epileptic drug</td>
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<tr>
<td>Azeliragon</td>
<td>Aβ</td>
<td>Small molecule</td>
<td>RAGE inhibitor</td>
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<tr>
<td>RVT-101</td>
<td>Other</td>
<td>Small molecule</td>
<td>5HT$_6$ receptor antagonist</td>
</tr>
<tr>
<td>LMTM</td>
<td>Tau</td>
<td>Small molecule</td>
<td>Tau aggregation inhibitor</td>
</tr>
</tbody>
</table>

LMTM = Leuco-methylthioninium, RAGE = receptor for advanced glycation end products.
Proposed Biology of AD: Amyloid Cascade

Proposed Biology of AD: Downstream Pathophysiology

Combined EXPEDITION 1 and 2 Data for Solanezumab in Mild and Moderate AD

Pooled data from EXPEDITION 1 and 2 show less decline from baseline in ADAD-Cog scores

MODELED MEAN GROUP DIFFERENCE (95% CI): 1.141 (0.35, 2.47)  
P = 0.009

Placebo (n = 663)  
Solanezumab (n = 659)

Worsening

ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognition.  
EXPEDITION 3

● Randomized, double-blind, placebo-controlled, phase 3, 80-week trial + open label extension

● 2129 patients with mild AD
  - Aged 55 to 90 years
  - Probable AD
  - Amyloid positive
  - MMSE score 20 to 26

● Intervention
  - Solanezumab 400 mg IV q4w OR Placebo

● Patients treated with solanezumab did not experience a statistically significant slowing in cognitive decline compared with patients treated with placebo ($p = 0.095$), as measured by the ADAS-cog14

MMSE = mini mental state exam.
PRIME CDB-SB Data for Aducanumab

- Change from baseline on the CDR-SB
  - Demonstrated dose-dependent slowing of clinical progression with aducanumab treatment at one year
  - Dose-response, $p < 0.05$, with the greatest slowing for 10 mg kg$^{-1}$ ($p < 0.05$ versus placebo)

CDR-SB = clinical dementia rating scale-sum of boxes.
PRIME Study Design and Results

- Randomized, double-blind, placebo-controlled, phase 1b trial

- Participants
  - 165 adults
  - Aged 50 to 90 years
  - Mild/prodromal AD

- Intervention, q4W for 1 year
  - Fixed dose of IV aducanumab
    - 1 mg/kg
    - 3 mg/kg
    - 6 mg/kg
    - 10 mg/kg
  - Placebo

- Results
  - Clinical assessments were exploratory as the study was not powered to detect clinical change
  - Aducanumab penetrates the brain and decreases Aβ in a time- and dose dependent manner
  - Aducanumab-treated patients with had decreased SUVR scores after 1 year of treatment experienced a stabilization of clinical decline on both CDR-SB and MMSE scores
  - Patients with a smaller or no decrease experienced clinical decline similar to patients receiving placebo

SUVR = standardized uptake value ratio.
**PRIME: 12-Month Interim Analysis of Titration Dosing**

- Added 31 APOE-ε4 carriers
- Randomized to placebo or titrated aducanumab: 1mg/kg for 2 doses, 3 mg/kg for 4 doses, 6 mg/kg for 5 doses, and 10 mg/kg thereafter
- Week 52 average expected dose: 5.3 mg/kg
- Results
  - Significant decreases in brain Aβ with titrated aducanumab in mean PET SUVR ($p < .001$)
    - Aducanumab: -0.171
    - Placebo: 0.014
  - Similar results for titration-dose cohort and fixed-dose cohort in slowing of clinical decline (CDR-SB and MMSE)
  - ARIA incidence lower with titrated dosing vs higher fixed dosing of aducanumab in APOE-ε4

LMTM in Mild AD

- Double-blind, placebo-controlled, phase 3, 15-month trial
- Patients (N = 891) with mild-to-moderate AD randomized to
  - LMTM: 75 mg or 125 mg BID
  - Control: LMTM, 4 mg BID

- Co-primary endpoints assessed at week 65 in ITT population
  - ADAS-COG
  - ADCS-ADL

- Results
  - Primary analysis was negative
  - No benefit of LMTM as add-on treatment for patients with mild-to-moderate AD was observed

Drugs Recently Granted Fast-Track Approval

- **ALZ-801**
  - Optimized prodrug of tramiprosate
  - Phase 3 program will focus initially on a genetically defined group of high-risk patients (APOE4/4 homozygote)

- **CT1812**
  - First in class, orally administered small molecule
  - Inhibits binding of beta amyloid (Aβ) oligomers to neuronal receptors and facilitates clearance of Aβ oligomers into the cerebrospinal fluid
  - Recently completed Phase 1b/2 in patients with mild-to-moderate AD
Call to Action

● Be aware of emerging agents for AD and their mechanisms of action
● Be up-to-date on evidence regarding patient populations and efficacy of agents in clinical trials
Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.