Alzheimer’s Disease: The current state of clinical trials

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OUTLINE

Background of AD
Background of clinical trials in AD
Current trials in AD

WHAT IS ALZHEIMER’S DISEASE?

MEMORY LOSS

WORD-FINDING DIFFICULTY
POOR NAVIGATION

PATHOLOGY OF ALZHEIMER’S DISEASE

NEURITIC (AMYLOID) PLAQUE
NEUROFIBRILLARY (TAU) TANGLES

Slide courtesy of Edward Plowey
Biomarkers develop at different times

There are no disease modifying drugs

Cholinesterase inhibitors: main treatment

Bace inhibitors have failed

<table>
<thead>
<tr>
<th>Phase</th>
<th>Population</th>
<th>Outcome</th>
<th>VERUBACESTAT (MERCK)</th>
<th>LANAOCESTAT (Lilly/AZ)</th>
<th>ATABACESTAT (JNJ)</th>
<th>LY3200206 (Lilly)</th>
<th>ELENBACESTAT (Eisai)</th>
<th>CNPS20 (Novartis)</th>
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<tbody>
<tr>
<td></td>
<td>Mild AD, MCI</td>
<td>Mild AD: no difference</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>II</td>
<td>III</td>
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<tr>
<td></td>
<td>MCI</td>
<td>MCI: worse</td>
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<td></td>
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<td>Worse</td>
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<td>Halting safety</td>
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<td>Halting futility</td>
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<td>Halted</td>
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<td>Cognitive worsening</td>
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</table>
M ost large trials have targeted amyloid

**ANTII-AMYLOID ANTIBODIES**

<table>
<thead>
<tr>
<th>Company</th>
<th>Bapineuzumab</th>
<th>Solanezumab</th>
<th>Crenezumab</th>
<th>Gantenerumab</th>
<th>Aducanumab</th>
<th>BAN2401</th>
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<tbody>
<tr>
<td>Origin</td>
<td>Humanized</td>
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<td>Humanized</td>
<td>Human</td>
<td>Human</td>
<td>Human</td>
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<tr>
<td>Target</td>
<td>All forms of Aβ</td>
<td>Soluble Aβ</td>
<td>All forms of Aβ</td>
<td>Fibrillar &amp; oligomeric forms of Aβ</td>
<td>Fibrillar &amp; oligomeric forms of Aβ</td>
<td>All proteoforms</td>
</tr>
<tr>
<td>Outcome</td>
<td>Failed</td>
<td>Failed</td>
<td>Failed</td>
<td>Failed?</td>
<td>ONGOING!</td>
<td>Failed?</td>
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</tbody>
</table>

Biogen loses $18B in value as it kills Aducanumab Alzheimer’s program

In shocking reversal, Biogen to submit

That New Alzheimer’s Drug? Don’t Get Your Hopes Up Yet

**LESS PROGRESSION**


Stanford University
CURRENT TRIALS:

**ONGOING**
- PREVENTION
  - GENERATIONS 1, 2

**MCI/MILD AD**
- Tango
- Tauriel

**MODERATE AD**
- Lauriet

**ADVANCED AD**
- PEACE AD

**UPCOMING**
- BAN2401
- GAIN

**COMPLETED**
- APECS
- PLASMA
- BLAZE
- MISSION AD
- PRIME?
- EMERGE?
- CREAD

PATHOLOGY OF ALZHEIMER'S DISEASE

NEURITIC (AMYLOID) PLAQUE  NEUROFIBRILLARY (TAU) TANGLES

TAU IS A TARGET IN AD

**Compared to Aβ, tau has a tighter relationship to symptoms and progression...**

Aβ | Tau | Symptoms
---|-----|-------
Normal Control | LBD | Alzheimer's Disease

TAU ANTIBODIES REDUCE TAU SPREADING
### PHASE 2 TAU TRIALS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SPONSOR</th>
<th>CLASS</th>
<th>POPULATION</th>
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</thead>
<tbody>
<tr>
<td>AADvac1</td>
<td>Axon Neuroscience</td>
<td>Active immunotherapy</td>
<td>Mild AD</td>
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<tr>
<td>ABBV-8E12</td>
<td>Abbvie</td>
<td>Passive immunotherapy</td>
<td>MCI, AD</td>
</tr>
<tr>
<td>ANAVEX 2-73 OLE</td>
<td>Anavex Life Sciences</td>
<td>Sigma-1 receptor &amp; musc agonist</td>
<td>Mild-mid AD</td>
</tr>
<tr>
<td>AZD0358</td>
<td>AstraZeneca</td>
<td>Sirtuins</td>
<td>Mild AD</td>
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<tr>
<td>Biib092 (TANGO)</td>
<td>Biogen</td>
<td>Immunotherapy</td>
<td>MCI, mild AD, PSP</td>
</tr>
<tr>
<td>IONIS MAPT RO</td>
<td>Ionis Biogen</td>
<td>MAPT RNA inhibitor, antisense oligonucleotide</td>
<td>Mild AD</td>
</tr>
<tr>
<td>Methylene Blue</td>
<td>Texas AD Research</td>
<td>Tau protein aggregation inhibitor</td>
<td>Healthy, MCI, mild AD</td>
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<tr>
<td>Nicotinamide (Vit B3)</td>
<td>UCI</td>
<td>Histone deacetylase inhibitor</td>
<td>MCI, AD</td>
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<tr>
<td>Nilotinib</td>
<td>Georgetown</td>
<td>Tyrosine kinase inhibitor</td>
<td>AD</td>
</tr>
<tr>
<td>ROT105705 (TAURIEL, Lauriel)</td>
<td>Roche/Genentech</td>
<td>Immunotherapy</td>
<td>MCI/AD, Mod AD</td>
</tr>
<tr>
<td>LY3303560</td>
<td>Lilly</td>
<td>Immunotherapy</td>
<td>memory &gt;6 months</td>
</tr>
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As of February 2019:
- 132 drugs
- 156 trials
- 73% DMD
- 40% Amyloid
- 18% Tau
- 11% Behavioral sx
- 14% Cognition


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**Opportunities for Aβ/β-amyloid Combination Therapies based on therapeutics currently in clinical development**

**BACE inhibitors**
- Targeting soluble Aβ by different mechanisms: BACEi, Gsm, BACEi + anti-soluble Aβ mAb
- Targeting insoluble Aβ: BACEi/Gsm + anti-Aβ mAb (plaque-specific)

**Anti-Aβ mAbs**
- Soluble Aβ
- Crossed Aβ amyloid

**Tau therapies**
- Anti-Tau mAb
- Small molecule tau
- Tau APOE

Neuronal dysfunction and cell degeneration
- Inflammation
- Excessive amyloid
- Neuroplasticity

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**STANFORD CENTER FOR MEMORY DISORDERS**

THANK YOU!