EXPEDITION3: A Phase 3 Trial of Solanezumab in Mild Dementia due to Alzheimer’s Disease

Lawrence S. Honig, MD, PhD
On behalf of the EXPEDITION3 Study Team
Disclosure Statement

♦ I will discuss investigational use only.

♦ Dr. Honig has received support as a consultant/steering committee member from Forum, Fujirebio, Lundbeck, and Eli Lilly.

♦ Dr. Honig has received research funding as an investigator for AstraZeneca, Bristol-Myer Squibb, Forum, Genentech, Janssen, Eli Lilly, Lundbeck, Pfizer, Roche, TauRx, vTv.

♦ EXPEDITION3 is funded by Eli Lilly and Company.
EXPEDITION3: Solanezumab Initiated in Mild AD Dementia

Patient Disposition

Patients Randomized
N=2129

Discontinued
N=164 (15.3%)
- Adverse Event 39 (3.6%)
- Death 16 (1.5%)
- Subject Decision 45 (4.2%)
- Caregiver Decision 41 (3.8%)
- Physician Decision 7 (0.7%)
- Protocol Violation 7 (0.7%)
- Lost to Follow Up 0 (0.0%)
- Entry Criteria Not Met 9 (0.8%)

Completed
N=908 (84.7%)

Placebo
N=1072

Discontinued
N=143 (13.5%)
- Adverse Event 48 (4.5%)
- Death 9 (0.9%)
- Subject Decision 33 (3.1%)
- Caregiver Decision 33 (3.1%)
- Physician Decision 11 (1.0%)
- Protocol Violation 7 (0.7%)
- Lost to Follow Up 3 (0.3%)
- Entry Criteria Not Met 5 (0.5%)

Completed
N=914 (86.5%)

Solanezumab
N=1057

Abbreviations: AD=Alzheimer's disease; ECG=electrocardiogram; N=number.

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Study Design for EXPEDITION3

♦ Study LZAX (NCT01900665): double-blind, Phase 3, randomized to solanezumab (400 mg per dose) or placebo every 4 weeks for 80 weeks; optional open-label extension
♦ Age 55 to 90 years
♦ Probable AD by NINCDS/ADRDA criteria¹
♦ Amyloid positive by F18 florbetapir PET or CSF Aβ₁₋₄₂
♦ MMSE score 20-26 inclusive
♦ On stable standard of care therapy (drug and non-drug)
  • Acetylcholinesterase inhibitors and/or memantine
  • Continued concomitant medication use allowed throughout study
♦ Conducted in 11 countries at 210 sites

Abbreviations: NINCDS/ADRDA=National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; PET=positron emission tomography; CSF=cerebrospinal fluid; MMSE=Mini Mental State Exam.

¹. McKhann et al. Neurology, 1984; 34(7):939-944

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## Baseline Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Placebo N=1072</th>
<th>Solanezumab N=1057</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>73.3 (8.0)</td>
<td>72.7 (7.8)</td>
<td>.073</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>631 (58.9%)</td>
<td>600 (56.8%)</td>
<td>.335</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td>.758</td>
</tr>
<tr>
<td>White</td>
<td>894 (90.7%)</td>
<td>878 (90.5%)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>19 (1.9%)</td>
<td>14 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>71 (7.2%)</td>
<td>75 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>APOE ε4 carriers, n (%)*</td>
<td>685 (66.3%)</td>
<td>712 (69.3%)</td>
<td>.144</td>
</tr>
<tr>
<td>Education, years, mean (SD)</td>
<td>13.7 (3.8)</td>
<td>13.7 (3.7)</td>
<td>.906</td>
</tr>
<tr>
<td>Symptom onset, years, mean (SD)</td>
<td>4.3 (2.6)</td>
<td>4.2 (2.5)</td>
<td>.413</td>
</tr>
<tr>
<td>Diagnosis, years, mean (SD)</td>
<td>1.6 (1.7)</td>
<td>1.5 (1.6)</td>
<td>.132</td>
</tr>
<tr>
<td>AChEI and/or memantine use, n (%)</td>
<td>856 (79.9%)</td>
<td>822 (77.8%)</td>
<td>.244</td>
</tr>
</tbody>
</table>

*Based on number of patients with available APOE status (placebo N=1033; solanezumab N=1027).

Abbreviations: AD=Alzheimer’s disease; n=number; SD=standard deviation; APOE=apolipoprotein E.
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Change in Cognition - ADAS-Cog$_{14}$ (Primary)

Abbreviations: AD=Alzheimer’s disease; ADAS-Cog$_{14}$=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=standard error.

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Change in Cognition - MMSE

Abbreviations: AD=Alzheimer’s disease; LS=least squares; MMSE=Mini–Mental State Examination; n=number; SE=standard error.
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Change in Complex ADLs - ADCS-iADL

Abbreviations: AD=Alzheimer’s disease; ADL=Activities of Daily Living; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; SE=standard error.

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Change in Complex ADLs - FAQ

Abbreviations: AD=Alzheimer’s disease; ADL=Activities of Daily Living; FAQ=Functional Activities Questionnaire; LS=least squares; n=number; SE=standard error.

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Change in Composite Scale - CDR-SB

Abbreviations: AD=Alzheimer’s disease; CDR-SB=Clinical Dementia Rating Sum of Boxes; LS=least squares; n=number; SE=standard error.
## EXPEDITION3: Solanezumab Initiated in Mild AD Dementia

### Change in Cognition and ADLs at 80 Weeks

<table>
<thead>
<tr>
<th></th>
<th>LS Mean Change (SE) at 80 Weeks</th>
<th>Less Decline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Solanezumab</td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog(_{14})</td>
<td>7.44 (0.36)</td>
<td>6.65 (0.36)</td>
<td>11%</td>
</tr>
<tr>
<td>MMSE</td>
<td>-3.66 (0.16)</td>
<td>-3.17 (0.15)</td>
<td>13%</td>
</tr>
<tr>
<td>ADCS-iADL</td>
<td>-7.17 (0.32)</td>
<td>-6.17 (0.32)</td>
<td>14%</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>-8.77 (0.39)</td>
<td>-7.42 (0.39)</td>
<td>15%</td>
</tr>
<tr>
<td>FAQ</td>
<td>5.57 (0.21)</td>
<td>5.17 (0.21)</td>
<td>7%</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>2.21 (0.11)</td>
<td>1.87 (0.10)</td>
<td>15%</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease; ADL=Activities of Daily Living; ADAS-Cog\(_{14}\)=AD Assessment Scale-Cognitive 14-item Subscale; ADCS-ADL=AD Cooperative Study-Activities of Daily Living; CDR-SB=Clinical Dementia Rating Sum of Boxes; FAQ=Function Activities Questionnaire; iADRS=Integrated AD Rating Scale; LS=least squares; n=number of patients with evaluable 80-Week scale data; N/A=not applicable; MMSE=Mini–Mental State Examination; SE=standard error.

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Plasma Changes in $A\beta_{1-40}$ and $A\beta_{1-42}$

Abbreviations: AD=Alzheimer's disease; LS=least squares; n=number.
The cortical SUV is a composite summary that consists of the following 6 regions: medial orbital frontal, anterior cingulate, parietal, temporal, posterior cingulate, and precuneus.

Abbreviations: AD=Alzheimer's disease; PET=positron emission tomography; LS=least squares; n=number; SUVr=Standard Uptake Value ratio; SE=standard error; SSWM=subject-specific white matter.
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CSF Changes in Total Tau and p-Tau

Abbreviations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; LS=least squares; n=number, p-tau=phosphorylated tau; SE=standard error.
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Flortaucipir PET Changes in Tau Deposition

Abbreviations: AD=Alzheimer’s disease; LS=least squares; n=number; PET=positron emission tomography; SE=standard error.
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MRI Whole Brain Atrophy/Ventricular Enlargement

Abbreviations: AD=Alzheimer’s disease; LS=least squares; n=number; SE=standard error.
### Adverse Events Overview

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>Placebo N=1067</th>
<th>Solanezumab N=1054</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>202 (18.9%)</td>
<td>175 (16.6%)</td>
<td>.173</td>
</tr>
<tr>
<td>Death</td>
<td>16 (1.5%)</td>
<td>9 (0.9%)</td>
<td>.227</td>
</tr>
<tr>
<td>TEAE</td>
<td>890 (83.4%)</td>
<td>891 (84.5%)</td>
<td>.515</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>39 (3.6%)</td>
<td>48 (4.5%)</td>
<td>.325</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease; AE=adverse event; n=number; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
### Treatment Emergent AE Differences (p≤.05)

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Placebo N=1067</th>
<th>Solanezumab N=1054</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE (≥1)</td>
<td>890 (83.4%)</td>
<td>891 (84.5%)</td>
<td>.515</td>
</tr>
<tr>
<td><strong>Events more frequent in solanezumab treatment group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D Deficiency</td>
<td>6 (0.6%)</td>
<td>15 (1.4%)</td>
<td>.050</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>4 (0.4%)</td>
<td>13 (1.2%)</td>
<td>.029</td>
</tr>
<tr>
<td>Spinal Osteoarthritis</td>
<td>4 (0.4%)</td>
<td>12 (1.1%)</td>
<td>.047</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2 (0.2%)</td>
<td>9 (0.9%)</td>
<td>.037</td>
</tr>
<tr>
<td><strong>Events more frequent in placebo treatment group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait Disturbance</td>
<td>18 (1.7%)</td>
<td>4 (0.4%)</td>
<td>.004</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (1.2%)</td>
<td>2 (0.2%)</td>
<td>.007</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease; AE=adverse event; n=number; TEAE=treatment-emergent adverse event.
EXPEDITION3 Conclusions

♦ Did not meet primary endpoint of decreasing cognitive decline

♦ Several secondary clinical endpoints directionally favored solanezumab, but the magnitudes of treatment differences were small

♦ Amyloid PET and CSF tau did not show significant treatment differences

♦ Factors possibly relevant to interpretation of study results include drug target, disease stage studied, and dosage of drug delivered
Many thanks to the patients and their families, and the investigators and clinical trial staff, for their time and commitment to the EXPEDITION3 study

Thank you to the EXPEDITION3 Steering Committee and Study Team
Panel Discussion

Lawrence S. Honig, MD, PhD, Columbia University Medical Center, New York, NY
Paul Aisen, MD, University of Southern California, San Diego, CA
Maria Carrillo, PhD, Alzheimer’s Association, Chicago, IL
Bruno Vellas, MD, PhD, University Hospital of Toulouse, France
Eric Siemers, MD, Eli Lilly and Company, Indianapolis, IN
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Change in Cognition - ADAS-Cog\textsubscript{14}

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