Evaluating the Evidence of Aducanumab Treatment Benefit Using Standardized Test Statistics and Global Statistical Tests

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Disclosures

• SD is an employee of Pentara Corporation and SH is an employee and owner of Pentara Corporation, a company that consults for Biogen

• SB, SBH, CC-V, PH, JM, and YT are employees of Biogen and may be stockholders

• LY was an employee of Biogen at the time of this work and has since left the company

• PA is a consultant to Biogen

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• Aducanumab is approved for use in the following markets: the United States, the United Arab Emirates, and Qatar. In the rest of the world, it is an investigational drug. Its efficacy and safety have not been established in Spain
Statistical evidence in EMERGE and ENGAGE: Are the results due to a chance or real treatment effects?

- Statistical evidence, clinical meaningfulness, and safety should be considered separately
- Traditional clinical endpoints have inherent challenges and are misaligned with disease progression when used individually
- The degree of difficulty in Alzheimer’s disease clinical trials leaves little room for error
Alzheimer’s disease is a progressive and heterogeneous neurodegenerative disorder\(^1,2\)

- Disease course measurement is complex due to variability in the rate of disease progression\(^3,4\)
- Disease severity and symptom assessment are also complicated by heterogeneous disease features\(^5\)
  - Clinical phenotypes of Alzheimer’s disease involve different domains\(^1,5,6\)
- Several validated assessments are widely adopted in clinical practice to detect/monitor Alzheimer’s disease across domains\(^6\)

Phase 3 clinical trials of aducanumab

- Aducanumab is a monoclonal antibody that selectively targets aggregated soluble Aβ oligomers and insoluble Aβ fibrils\(^1,2\)

- **EMERGE (NCT02484547)** and **ENGAGE (NCT02477800)** were identically designed, randomized, double-blind, placebo-controlled Phase 3 studies of aducanumab in patients with MCI due to Alzheimer’s disease or mild Alzheimer’s disease dementia\(^3,4\)

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Aβ, amyloid beta; MCI, mild cognitive impairment.

Phase 3 clinical trials of aducanumab

Development of aducanumab using Reverse Translational Medicine Technology (2007)¹

Primary endpoint⁵ CDR-SB at Week 78
Secondary endpoints⁵ MMSE, ADAS-Cog 13, and ADCS-ADL-MCI
Other endpoints include cerebral Aβ plaques as measured by PET at Weeks 26 and 78⁵

Phase 3: ENGAGE²,³ N=1653; placebo-controlled (Months 1-18), parallel-group study in early AD, low/high dose (global) LTE

Phase 3: EMERGE²,⁴ N=1643; placebo-controlled (Months 1-18), parallel-group study in early AD, low/high dose (global) LTE

March 2019
Studies halted following futility analysis of EMERGE and ENGAGE⁶

FDA filing and acceptance of BLA for aducanumab⁶

Aducanumab was approved by FDA for the treatment of Alzheimer's disease⁷,⁸


Phase 3b: EMBARK⁸,⁹ Screened 1856 participants (1694 enrolled)⁸; open-label re-dosing study

### EMERGE and ENGAGE efficacy results

Low-dose aducanumab group from EMERGE and ENGAGE were consistent

<table>
<thead>
<tr>
<th></th>
<th>ENGAGE N=547</th>
<th>EMERGE N=543</th>
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</thead>
<tbody>
<tr>
<td>CDR-SB</td>
<td>-0.18 (-12%)</td>
<td>-0.26 (-15%)</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.2 (-6%)</td>
<td>-0.1 (3%)</td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>-0.58 (-11%)</td>
<td>-0.70 (-14%)</td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>0.7 (-18%)</td>
<td>0.7 (-16%)</td>
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</table>

High-dose aducanumab group from EMERGE and ENGAGE were partially inconsistent

<table>
<thead>
<tr>
<th></th>
<th>ENGAGE N=555</th>
<th>EMERGE N=547</th>
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</thead>
<tbody>
<tr>
<td>CDR-SB</td>
<td>0.03 (2%)</td>
<td>-0.39 (-22%)</td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.1 (3%)</td>
<td>0.6 (-18%)</td>
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<tr>
<td>ADAS-Cog 13</td>
<td>-0.59 (-11%)</td>
<td>-1.40 (-27%)</td>
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<tr>
<td>ADCS-ADL-MCI</td>
<td>0.7 (-18%)</td>
<td>1.7 (-40%)</td>
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</table>

**Diff vs placebo (%)**

- Difference vs. placebo at Week 78.
- Number of participants in ENGAGE PET substudy = 585 and EMERGE substudy = 488.

ADAS-Cog 13, Alzheimer's Disease Assessment Scale—Cognitive Subscale (13 item); ADCS-ADL-MCI, Alzheimer’s Disease Cooperative Study—Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating—Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SUVR, standardized uptake value ratio.

Clinical endpoints measure distinct, important symptoms of cognition, function, and global performance

Clinical efficacy rating scales were used in EMERGE and ENGAGE

- Validated and widely used in early Alzheimer’s disease
- Includes key perspectives:
  - Expert clinical judgment based on patient examination and caregiver input
  - Patient and caregiver reports
  - Cognitive performance tests
- Collectively they measure many distinct elements and cover the various symptoms experienced by patients with Alzheimer’s disease **with each contributing unique information**
Statistical methodologies and objectives\textsuperscript{1,2}

**Standardized test statistics** allow for a comparison of results across different endpoints by standardizing the treatment effect (t statistics).

The standardized test statistics were used to assess the results of the primary efficacy analyses across EMERGE, and ENGAGE with the goal of evaluating the totality of statistical evidence on efficacy.

## The standardized test statistics:

The divergent Phase 3 primary endpoint results are challenging if evaluated in isolation.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CDR-SB</th>
<th>MMSE</th>
<th>ADAS-Cog 13</th>
<th>ADCS-ADL-MCI</th>
<th>Standardized statistics (95% CI)</th>
<th>% Treatment difference</th>
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<tbody>
<tr>
<td>ENGAGE low dose</td>
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<td>Favors aducanumab</td>
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<td>-1.21 (-3.17 to 0.75)</td>
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<td>-0.71 (-2.67 to 1.25)</td>
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<td>-1.14 (-3.1 to 0.82)</td>
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<td>-1.55 (-3.51 to 0.41)</td>
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<td>ENGAGE high dose</td>
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<td>0.21 (-1.75 to 2.17)</td>
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<td>0.24 (-1.72 to 2.2)</td>
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<td>-1.13 (-3.09 to 0.83)</td>
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<td>-1.44 (-3.4 to 0.52)</td>
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<tr>
<td>EMERGE low dose</td>
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<td></td>
<td>0.31 (-1.65 to 2.27)</td>
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<td>-2.52 (-4.48 to -0.56)</td>
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<td>-1.97 (-3.93 to -0.01)</td>
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<td></td>
<td>-2.59 (-4.55 to -0.63)</td>
<td>-27</td>
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<td></td>
<td></td>
<td>-3.44 (-5.4 to -1.48)</td>
<td>-40</td>
</tr>
</tbody>
</table>

Results for CDR-SB were based on an MMRM, with change from baseline CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. The change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI scores were also analyzed using MMRM.

AD, Alzheimer’s disease; ADAS-Cog 13, Alzheimer’s Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer’s Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination.
The standardized test statistics:
Demonstrated consistency in the totality of statistical evidence from aducanumab clinical studies

A correlation of 0.3 to 0.5 was observed between endpoints.

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A correlation of 0.3 to 0.5 was observed between endpoints.
The **global statistical test (GST)**\(^3\) assesses the totality of the evidence of multiple scales by standardizing all endpoints and combining them into a single univariate scale.

The GST assesses **the overall treatment effect of aducanumab in EMERGE and ENGAGE** across 3 clinical endpoints (CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI) by averaging the standardized \(z\) scores.
Global statistical test (GST)

- To capture heterogeneous clinical manifestations of Alzheimer’s disease, 3 clinical endpoints were chosen for the present analysis (post hoc)
  - Primary endpoint and 2 secondary endpoints
  - MMSE was excluded to avoid double-counting cognition
- These endpoints measure distinct elements with very little overlap
- The GST is a clinically meaningful approach to demonstrate an overall drug effect on Alzheimer’s disease progression
  - The GST combines outcomes to assess the overall impact of treatments in AD, highlighting the consistency of the different assessments (e.g., ADCS-ADL, ADAS-Cog, and CDR-SB)\(^1,2\)

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### Results for CDR-SB were based on an MMRM, with change from baseline CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. The change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI scores were also analyzed using MMRM.

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- MMSE: 0.24 (-1.72 to 2.2)
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- ADCS-ADL-MCI: -1.44 (-3.4 to 0.52)

#### EMERGE low dose
- CDR-SB: -1.7 (-3.66 to 0.26)
- MMSE: 0.31 (-1.65 to 2.27)
- ADAS-Cog 13: -1.29 (-3.25 to 0.67)
- ADCS-ADL-MCI: -1.44 (-3.4 to 0.52)

#### EMERGE high dose
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- MMSE: -1.97 (-3.93 to -0.01)
- ADAS-Cog 13: -2.59 (-4.55 to -0.63)
- ADCS-ADL-MCI: -3.44 (-5.4 to -1.48)

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## The global statistical test (GST):
**CDR-SB, ADAS-Cog 13, and ADCS-ADL-MCI**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference vs. placebo (%)</th>
<th>Treatment difference from placebo group in GST composite scores (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENGAGE low dose</td>
<td>-0.16 (-16)</td>
<td>-0.16 (-16)</td>
</tr>
<tr>
<td>ENGAGE high dose</td>
<td>-0.07 (-7)</td>
<td>-0.07 (-7)</td>
</tr>
<tr>
<td>EMERGE low dose</td>
<td>-0.17 (-16)</td>
<td>-0.17 (-16)</td>
</tr>
<tr>
<td>EMERGE high dose</td>
<td>-0.31 (-28)</td>
<td>-0.31 (-28)</td>
</tr>
<tr>
<td>Pooled low dose</td>
<td>-0.16 (-15)</td>
<td>-0.16 (-15)</td>
</tr>
<tr>
<td>Pooled high dose</td>
<td>-0.19 (-18)</td>
<td>-0.19 (-18)</td>
</tr>
</tbody>
</table>

-1.0 -0.5 0.0 0.5 1.0

Favors aducanumab

Results were based on an MMRM, with change from baseline in z score as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline z score, baseline z score by visit interaction, baseline MMSE z score, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

AD, Alzheimer’s disease; ADAS-Cog 13, Alzheimer’s Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer’s Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; GST, global statistical test; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination.
Standardized test statistics and GSTs demonstrate consistency in the totality of statistical evidence from aducanumab across efficacy endpoints in EMERGE and ENGAGE

• Statistical approaches further demonstrated a treatment benefit with aducanumab in early Alzheimer's disease
  o Standardized test statistics demonstrated a positive treatment effect with aducanumab across efficacy endpoints in EMERGE and ENGAGE
  o The GST supported positive overall effects of aducanumab across cognition, function, and global performance
    – EMERGE had a statistically significant overall treatment effect over placebo
    – ENGAGE had a numeric advantage over placebo
    – Low-dose groups also showed a numeric advantage over placebo
• Overall statistical evidence supports an aducanumab treatment effect in patients with early Alzheimer's disease
EMERGE and ENGAGE results are not due to chance

- Statistical evidence is strong across phase 3 studies and both doses
- Clinical meaningfulness and safety should be considered separately
- Alzheimer’s disease clinical trials leave little room for error and benefit from assessing the totality of statistical evidence
- Dismissing the totality of statistical evidence of effect in EMERGE and ENGAGE sets a bad precedent for the field
Acknowledgments

We thank the Alzheimer’s disease community, all the patients and their family members participating in the aducanumab studies, and the investigators and their staff conducting these studies.