Introduction

• Aducanumab is a human, immunoglobulin (Ig) monoclonal antibody directed against amyloid-β (Aβ) and approved for treatment of Mild Cognitive Impairment (MCI) and early Alzheimer’s disease (AD). 1

• Aducanumab is the first FDA-approved Alzheimer’s disease treatment that reducess the accumulation of amyloid plaques, a defining pathophysiological feature of Alzheimer’s disease. 2

• A robust dose-dependent reduction in brain Aβ plaque levels, as measured by amyloid PET, was demonstrated across aducanumab clinical studies (PRIME, ENGAGE, MCI substudy; ENGAGE, NC3249454, and ENGAGE, NCT2477800). 3,4

• Here, we examine the association between aducanumab-induced reduction in biomarkers of Alzheimer’s disease pathophysiology and clinical measures from 3 clinical trials evaluating aducanumab in patients with early Alzheimer’s disease.

Figure 1. Therapeutic hypothesis

Results

Group-level analysis (Figure 2)

• A greater treatment effect on brain Aβ plaque levels was associated with greater treatment effect on CDR-SB, less decline in clinical measures (Figure 2A) and other recent studies of anti-Aβ monoclonal antibodies (Figure 2B). 5,6

Participant-level analysis (Figure 3)

• A greater reduction in Aβ PET SUVR was associated with lesser decline in all clinical measures at Week 78 in EMERGE (Figure 3). In ENGAGE, in which a clinical treatment effect was not observed, correlations were not apparent (not shown). In PRIME, the correlation coefficients (ρ) were 0.33 for CDR-SB and 0.32 for MMSE.

• A greater reduction in Aβ PET SUVR was associated with greater reductions in CSF tau (EMERGE: ρ = 0.52 for p-tau and ρ = 0.37 for tau t-tau; ENGAGE: ρ = 0.59 for p-tau and ρ = 0.42 for t-tau). A greater reduction in CSF t-tau was associated with lesser decline in clinical measures in EMERGE (Figure 3); a similar pattern of association was also observed in CSF p-tau (not shown).

• These results are consistent with the hypothesized direct effect of aducanumab in lowering brain Aβ pathology and the subsequent effect on reducing tau pathology (p-tau) and neurodegeneration (t-tau) and slowing of clinical decline.

CONCLUSIONS

Aducanumab-induced changes in biomarkers of Alzheimer’s disease pathophysiology were correlated with clinical measures consistent with the hypothesized mechanism of action for aducanumab (ie, a direct effect of aducanumab on lowering brain Aβ pathology with a subsequent effect on reducing tau pathology and neurodegeneration and slowing of clinical decline).

• Change from baseline in Aβ PET SUVR was correlated with all key clinical measures (CDR-SB, MMSE, ADAS-cog13, ADCS-ADL-MCI) in EMERGE.

• In PRIME, change from baseline in Aβ PET SUVR was correlated with both CDR-SB and MMSE, which is supportive of the findings from EMERGE.

• Group-level analyses based on data from EMERGE, ENGAGE, and PRIME demonstrated a positive association between aducanumab treatment effect on brain Aβ plaques and clinical measures.

• In all 3 studies, a smaller magnitude of decline across key clinical measures was observed in patients for whom Aβ plaque levels were lowered to a threshold2 considered to be amyloid negative (relative to those who did not reach this threshold).

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Table. Clinical decline by Aβ PET status at follow-up in clinical studies of aducanumab

<table>
<thead>
<tr>
<th>Phase 3 studies (by Aβ PET status at Week 78)</th>
<th>CDR-SB, median/mean (IQR)</th>
<th>MMSE, median/mean (IQR)</th>
<th>ADL-MCI, median/mean (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUVR ≤ 1.10</td>
<td>25.0/25.8</td>
<td>26.4/26.1</td>
<td>4.4/3.0</td>
</tr>
<tr>
<td>SUVR &gt; 1.10</td>
<td>26.0/26.4</td>
<td>25.8/25.6</td>
<td>4.5/3.1</td>
</tr>
</tbody>
</table>

PRIME substudy: Change at Week 50

| SUVR ≤ 1.10                                 | 2.65/2.70                 | 0.7/0.8                  | 1.7/2.0                    |
| SUVR > 1.10                                 | 2.75/2.85                 | 0.85/1.0                 | 1.8/2.1                    |

EMERGE substudy: Change at Week 78

| SUVR ≤ 1.10                                 | 2.35/2.45                 | 0.75/0.85                | 1.6/1.8                    |
| SUVR > 1.10                                 | 2.45/2.55                 | 0.85/1.0                 | 1.7/1.9                    |

ENGAGE substudy: Change at Week 78

| SUVR ≤ 1.10                                 | 2.50/2.60                 | 0.66/0.80                | 1.6/1.8                    |
| SUVR > 1.10                                 | 2.60/2.70                 | 0.75/0.85                | 1.7/1.9                    |