Aducanumab for the Treatment of Alzheimer’s Disease: Clinical Overview of Efficacy

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Center for Drug Evaluation and Research
Aducanumab

• Molecular characteristics of aducanumab
  – Selectivity for aggregated forms of Aβ
  – Derived from B-cells collected from elderly subjects who appear phenotypically resistant to cognitive deterioration

• Clinical development features
  – Targets patients at earlier stages of the disease
  – Inclusion of subjects with evidence of Aβ pathology
  – Confirmed target engagement and reduction of Aβ plaque burden
Clinical Studies Relevant to Evaluation of Efficacy

• Studies 301 and 302
  – Multicenter, global, randomized, double-blind, placebo-controlled studies of identical design
  – Primary objectives: efficacy and safety

• Study 103
  – Multicenter, randomized, double-blind, placebo-controlled, dose-ranging, staggered study conducted in the United States
  – Primary objectives: safety, tolerability and proof of concept
# Study 301/302 Protocol Design

| Study Population | • Mild cognitive impairment (MCI) due to Alzheimer’s disease and mild Alzheimer’s disease dementia (Stage 3 and 4)  
• Positive amyloid PET scan |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Study Duration</td>
<td>78 week placebo-controlled period</td>
</tr>
</tbody>
</table>
| Dosing           | • Two dose levels (low and high)  
• Dosing based on ApoE ε4 status                                                                                   |
| Key Endpoints    | Primary: CDR-SB  
Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI                                                                     |

Special Protocol Assessment (SPA) agreements, indicating concurrence by FDA with adequacy and acceptability of protocol design, were granted in 2015

CDR-SB – Clinical Dementia Rating-Sum of Boxes; MMSE – Mini-Mental State Examination; ADAS-Cog 13 – Alzheimer’s Disease Assessment Scale – Cognitive 13-Item Scale; ADCS-ADL-MCI – Alzheimer’s Disease Cooperative Study Activities of Daily Living-Mild Cognitive Impairment; ApoE – apolipoprotein E; PET – positron emission tomography
Termination of Studies 301 and 302 (March 2019)

• Interim futility data cutoff date of December 26, 2018
• Conditional power: chance the primary efficacy endpoint analysis will be statistically significant in favor of aducanumab given interim data
  – Assumption 1: Treatment effect is similar in the two studies
  – Assumption 2: Treatment effect does not change over time
• Prespecified futility criteria met: <20% conditional power for both high dose and low dose treatment arms
Futility Decision Was Not an Accurate Reflection of Individual Studies

Conditional power calculation assumes future unobserved effect would be similar to pooled interim data

<table>
<thead>
<tr>
<th></th>
<th>Study 301 Futility Data</th>
<th>Study 302 Futility Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 78 Difference vs. placebo (%)</td>
<td>Conditional Power</td>
</tr>
<tr>
<td>Low Dose (N=320)</td>
<td>-0.15 (-10%)</td>
<td>0.22 (15%)</td>
</tr>
<tr>
<td>High Dose (N=301)</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>CDR-SB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

※ Treatment effect for the high dose was not similar in the two studies
Study 302 Had Reasonable Likelihood of Success at Interim Futility Analysis

Conditional power re-calculated for each study independently

<table>
<thead>
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<tr>
<td>CDR-SB</td>
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<td>0.22 (15%)</td>
</tr>
<tr>
<td></td>
<td>11%</td>
<td>0%</td>
</tr>
</tbody>
</table>

✓ Using non-pooled analysis, Study 302 would not have met futility criteria
Analysis of Final Dataset

- Per-protocol collection of blinded data continued between data cutoff (December 2018) and futility announcement (March 2019)
- Primary analysis performed using all data collected up to March 20, 2019
  - On face, Study 302 was positive with high-dose treatment effect changing from -18% (futility dataset) to -22% (final dataset) on CDR-SB
  - Study 301 was negative with treatment difference favoring placebo changing from 15% to 2% on CDR-SB

⚠️ Treatment effect for the high dose changed over time
June 14, 2019 Type C Meeting

- Applicant presented data and asked FDA for advice on next steps
- FDA comments:
  - It would have been more appropriate if futility had not been declared
  - It is possible...Study 302 might not only be interpreted as being supportive of the efficacy...but might also be considered exceptionally persuasive...
  - It is imperative that extensive resources be brought to bear on achieving a maximum understanding of the existing data
  - The effect of early termination of the studies on the interpretability of the observed efficacy data and associated analyses is a matter for further detailed consideration
Interpretability of Observed Efficacy Data

• “Virtual completion” of studies to explore range of plausible outcomes had studies been run to completion
  – Supplement observed data with simulated outcomes for data that was censored because of early termination
  – Fully simulate clinical trials to explore range of plausible results

• Simulation results were highly consistent with the primary analysis of the data

October 2019 Type C Meeting: We agree that the results of Studies 301 and 302 are interpretable and suitable for additional consideration
## Study 302 Met Primary and Secondary Objectives

### Study 302 Final Data

<table>
<thead>
<tr>
<th></th>
<th>Week 78 Placebo decline (N=548)</th>
<th>Week 78 Difference vs. placebo (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Dose (N=543)</td>
<td>High Dose (N=547)</td>
<td></td>
</tr>
<tr>
<td>CDR-SB</td>
<td>n=288 1.74</td>
<td>n=290 -0.26 (-15%)</td>
<td>0.0901</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=299 -0.39 (-22%)</td>
<td>0.0120</td>
</tr>
<tr>
<td>MMSE</td>
<td>n=288 -3.3</td>
<td>n=293 -0.1 (3%)</td>
<td>0.7578</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=299 0.6 (-18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0493</td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>n=287 5.162</td>
<td>n=289 -0.701 (-14%)</td>
<td>0.1962</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=293 -1.400 (-27%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0097</td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>n=283 -4.3</td>
<td>n=286 0.7 (-16%)</td>
<td>0.1515</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=295 1.7 (-40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0006</td>
</tr>
</tbody>
</table>

- Positive results on multiple distinct and important clinical measures
- Positive results on tertiary endpoint (NPI-10): 87% less decline vs. placebo (nominal p=0.0215)
- Numerically favorable results for the low dose for primary endpoint (p=0.0901) and two secondary endpoints
- Low dose results suggestive of dose-response relationship

NPI-10 – Neuropsychiatric Inventory-10

**ITT population excluding data collected after March 20, 2019**

Negative % means less progression in the treated arm

n: number of randomized and dosed subjects with endpoint assessment at Week 78

[www.fda.gov](http://www.fda.gov)
# Study 302 Encompasses Two Acceptable Approaches to Establish Effectiveness

<table>
<thead>
<tr>
<th></th>
<th>Study 302 Final Data</th>
<th>Week 78 Difference vs. placebo (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low Dose (N=543)</td>
<td>High Dose (N=547)</td>
</tr>
<tr>
<td>Week 78 Placebo decline (N=548)</td>
<td></td>
<td>n=290</td>
<td>n=299</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>1.74</td>
<td>-0.26 (-15%)</td>
<td>-0.39 (-22%)</td>
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<td>-4.3</td>
<td>0.7 (-16%)</td>
<td>1.7 (-40%)</td>
</tr>
</tbody>
</table>

FDA accepts a statistically significant change on an inherently meaningful instrument (CDR-SB) as evidence of a clinically meaningful effect.

ADAS-Cog 13 and ADCS-ADL-MCI independently assess cognition and daily function and are accepted as co-primary endpoints.

ITT population excluding data collected after March 20, 2019
Negative % means less progression in the treated arm
n: number of randomized and dosed subjects with endpoint assessment at Week 78

[www.fda.gov](http://www.fda.gov)
Study 302: Longitudinal Change from Baseline in CDR-SB
Longitudinal Change in PET SUVR For Target Dosing Regimens

SUVR – standard uptake value ratio

www.fda.gov
Study 302 Provides Primary Evidence of Effectiveness

• Findings are robust to numerous sensitivity analyses
  – Statistical significance on all 4 endpoints in opportunity to complete population
• Positive findings on secondary endpoints reinforce persuasiveness of the findings on the primary endpoint
• Favorable results for primary and secondary endpoints across 79/80 prespecified subgroups of interest
• Biomarkers support observations on clinical outcomes
  – Target engagement (brain Aβ reduction and CSF Aβ_{1-42} levels)
  – Downstream Alzheimer’s tau pathology (p-tau and tau PET)
  – Neurodegeneration (t-tau)
• Relationship between aducanumab exposure and clinical endpoints identified
• Dose- and concentration-dependent relationships for biomarkers support apparent dose- and concentration response relationships observed for clinical endpoints
Study 301 is a Negative Study

<table>
<thead>
<tr>
<th></th>
<th>Week 78 Placebo decline (N=545)</th>
<th>Week 78 Difference vs. placebo (%) p-value</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low Dose (N=547)</td>
<td>High Dose (N=555)</td>
<td></td>
</tr>
<tr>
<td>CDR-SB</td>
<td>n=333 1.56</td>
<td>n=331 -0.18 (-12%) 0.2250</td>
<td>n=295 0.03 (2%) 0.8330</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>n=332 -3.5</td>
<td>n=334 0.2 (-6%) 0.4795</td>
<td>n=297 -0.1 (3%) 0.8106</td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>n=331 5.140</td>
<td>n=332 -0.583 (-11%) 0.2536</td>
<td>n=294 -0.588 (-11%) 0.2578</td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>n=331 -3.8</td>
<td>n=330 0.7 (-18%) 0.1225</td>
<td>n=298 0.7 (-18%) 0.1506</td>
<td></td>
</tr>
</tbody>
</table>

- Does not contribute to the evidence of effectiveness
- Negative results on tertiary endpoint (NPI-10)
- Numerically favorable results for the low dose for primary endpoint and all secondary endpoints
- High dose arm had lower effect on biomarkers than Study 302

ITT population excluding data collected after March 20, 2019
Negative % means less progression in the treated arm
n: number of randomized and dosed subjects with endpoint assessment at Week 78

www.fda.gov
# Partially Discordant Results in Studies 301 and 302

<table>
<thead>
<tr>
<th>Study</th>
<th>Study 301 Final Data</th>
<th>Study 302 Final Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 78 Placebo decline (N=545)</td>
<td>Week 78 Difference vs. placebo (%) p-value</td>
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<td>n=331 -3.8</td>
<td>n=330 0.7 (-18%) 0.1225</td>
</tr>
</tbody>
</table>

**ITT population excluding data collected after March 20, 2019**

Negative % means less progression in the treated arm

n: number of randomized and dosed subjects with endpoint assessment at Week 78

www.fda.gov
Analysis of Discordant Results in Studies 301 and 302

• June 2019 Type C Meeting: agreement that extensive resources be brought to bear on achieving a maximum understanding of existing data
• Analyses were not aimed at obtaining independent support from Study 301
• Framework for exploratory analyses
  – Based on well-defined hypotheses
  – Limited in scope
  – Rigorous and prespecified to the maximum degree possible
• Does understanding preclude independent consideration of Study 302?
Areas of Further Investigation

1. Demographics and baseline disease characteristics
2. Influence of ARIA and ARIA management
3. Influence of study participants with rapid disease progression
4. Influence of dosing

ARIA – amyloid-related imaging abnormalities

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Influence of ARIA and ARIA Management

• Motivation – potential for functional unblinding
  – ARIA is associated with aducanumab treatment in a dose-dependent manner
  – ARIA prompts differential management of patients
  – ARIA management evolved over the course of the studies

• Mitigation: Raters were independent of patient care and were to remain blinded to dosing and adverse events

• Protocols were subject to SPA agreements
Systematic Bias Due to ARIA Is Not Apparent

- Incidence and radiographic severity of ARIA was similar between Studies 301 and 302
- Exclusion of assessments after occurrence of ARIA does not change results

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th></th>
<th>Study 302</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 78 Placebo decline (N=545)</td>
<td>Week 78 Placebo decline (N=548)</td>
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<td>Week 78 Placebo decline (N=548)</td>
</tr>
<tr>
<td></td>
<td>n=333 1.56</td>
<td>n=331 1.56</td>
<td>n=295 0.03</td>
<td>n=288 1.74</td>
</tr>
<tr>
<td></td>
<td>Low Dose (N=547)</td>
<td>Low Dose (N=543)</td>
<td>Low Dose (N=548)</td>
<td>Low Dose (N=548)</td>
</tr>
<tr>
<td></td>
<td>n=240 1.55</td>
<td>n=240 1.55</td>
<td>n=194 1.55</td>
<td>n=194 1.55</td>
</tr>
<tr>
<td></td>
<td>High Dose (N=555)</td>
<td>High Dose (N=557)</td>
<td>High Dose (N=548)</td>
<td>High Dose (N=548)</td>
</tr>
<tr>
<td></td>
<td>n=181 0.0</td>
<td>n=181 0.0</td>
<td>n=194 0.0</td>
<td>n=194 0.0</td>
</tr>
<tr>
<td></td>
<td>Week 78 Difference vs. placebo (%) p-value</td>
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<td>Week 78 Difference vs. placebo (%) p-value</td>
<td>Week 78 Difference vs. placebo (%) p-value</td>
</tr>
<tr>
<td>CDR-SB (all observations)</td>
<td>-0.18 (-12%)</td>
<td>0.03 (2%)</td>
<td>-0.26 (-15%)</td>
<td>-0.39 (-22%)</td>
</tr>
<tr>
<td>CDR-SB (post-ARIA observations excluded)</td>
<td>-0.11 (-7%)</td>
<td>0.0 (0%)</td>
<td>-0.19 (-11%)</td>
<td>-0.57 (-33%)</td>
</tr>
</tbody>
</table>
Motivation

• Distribution of change from baseline in CDR-SB was skewed
• Futility analysis dataset indicated patients treated with high dose in Study 301 had greater cognitive decline than patients receiving placebo
Number of patients with CDR-SB change from baseline of >8 at Week 78

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th>Study 302</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Low Dose</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>High Dose</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>13</td>
</tr>
</tbody>
</table>

- Results for primary and secondary endpoints for Study 301 high dose were sensitive to rapid progressors.
- Exclusion of rapid progressors changes primary endpoint from 0.03 (2%) to -0.09 (-6%) in Study 301.
- Results from Study 302 were not sensitive to rapid progressors.
Influence of Rapid Disease Progressors In Studies 301 and 302

• Individual baseline factors do not predict rapid progression
• Aducanumab treatment does not appear to be associated with rapid cognitive decline
• Exploratory analyses suggest:
  – Small imbalances in the number of rapid progressors can have relatively large impact on magnitude of clinical endpoints
  – High dose arm in Study 301 was disproportionately affected by such an imbalance
Influence of Dosing

• Motivation
  – Prior experience with other amyloid-targeting therapies
  – Dose-dependent relationships for aducanumab observed in Study 103
  – Protocol amendments during Studies 301 and 302
    • Modification of ARIA management so that patients were more likely to continue dosing or achieve target dose levels
    • Increase the target dose for ApoE ε4 carriers from 6 mg/kg to 10 mg/kg

• Challenges
  – Identification of appropriate dosing metric
  – Randomized dose does not fully capture level of aducanumab exposure
  – Confounding by other factors (ARIA, ApoE ε4 carrier status)
Dosing Patterns in Studies 301 and 302

- Patients enrolled later in the studies were more likely to achieve higher aducanumab exposure
- Patients in Study 302 were more likely to benefit from changes to the protocol than patients in Study 301

Figure 17 in briefing document
Patients in Study 301 with Higher Exposure to 10 mg/kg Dose Had Effect Similar to Patients in Study 302

Study 302 had more patients with high ≥8 doses of 10 mg/kg (35%) than Study 301 (29%) 
Study 301 had more patient with 0 doses of 10 mg/kg (29%) than Study 302 (24%)
Rapid Progressors Account for Some of the Discrepancy in Middle Exposure Group

<table>
<thead>
<tr>
<th>0 Doses of 10 mg/kg</th>
<th>1-7 Doses of 10 mg/kg</th>
<th>≥8 Doses of 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>← Favors high dose</td>
<td>← Favors high dose</td>
<td>← Favors high dose</td>
</tr>
<tr>
<td>Favors placebo</td>
<td>Favors placebo</td>
<td>Favors placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference from placebo (95% CI)</th>
<th>Difference from placebo (95% CI)</th>
<th>Difference from placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>-0.5</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 22 in briefing document

OTC population excluding data collected after March 20, 2019
Placebo patients were matched on ApoE ε4 status, age, sex, clinical stage, baseline CDR-SB, MMSE, ADAS-Cog13, and ADCS-ADL-MCI years of education, years since first symptom, medication use at baseline, US/non-US, enrollment window
Contribution of Dosing to Results of Studies 301 and 302

- Dosing is an important consideration for interpretation of the efficacy results in Studies 301 and 302.
- In general, consistent exposure to 10 mg/kg was associated with better clinical outcome.
- Patients in Study 301 with higher exposure to the 10 mg/kg dose demonstrated treatment effects similar to patients in Study 302.
- Lower exposure to the target dose of 10 mg/kg in Study 301 was likely a small but contributing factor to discordant results.
Areas of Further Investigation

1. Demographics and baseline disease characteristics
   – Not a contributing factor

2. Influence of ARIA and ARIA management
   – Systematic bias due to ARIA not apparent

3. Influence of study participants with rapid disease progression
   – Small imbalances in the number of rapid progressors can have relatively large impact on magnitude of clinical endpoints
   – High dose arm in Study 301 was disproportionately affected by such an imbalance

4. Influence of dosing
   – Patients in Study 301 with higher exposure to the 10 mg/kg dose demonstrated treatment effects similar to patients in Study 302

Understanding of discordant results for high dose arms, while not complete, is sufficient to allow for independent consideration of Study 302
## Study 103 Protocol Design

<table>
<thead>
<tr>
<th>Design</th>
<th>• Randomized, double-blind, placebo-controlled, staggered, parallel-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>• 3:1 active:placebo within each cohort</td>
</tr>
<tr>
<td>Study Population</td>
<td>• Prodromal Alzheimer’s disease and mild Alzheimer’s disease dementia (Stage 3 and 4)</td>
</tr>
<tr>
<td></td>
<td>• Positive amyloid PET scan</td>
</tr>
<tr>
<td>Study Duration</td>
<td>54 week placebo-controlled period</td>
</tr>
<tr>
<td>Dosing</td>
<td>• Fixed doses (1 mg/kg, 3 mg/kg, 6 mg/kg, and 10 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>• Titration (44-week period)</td>
</tr>
<tr>
<td>Key Objectives</td>
<td>Primary: Safety and tolerability</td>
</tr>
<tr>
<td></td>
<td>Secondary: PK, change in amyloid PET</td>
</tr>
<tr>
<td>Clinical Outcomes</td>
<td>Blinded assessment of CDR-SB and MMSE</td>
</tr>
</tbody>
</table>
10 mg/kg is appropriate dose for comparison to high dose in Study 302

<table>
<thead>
<tr>
<th></th>
<th>Study 302 High Dose</th>
<th>Study 103 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td># 10 mg/kg doses</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>SUVR Difference from placebo</td>
<td><strong>-0.278</strong> (Week 78)</td>
<td><strong>-0.277</strong> (Week 54)</td>
</tr>
</tbody>
</table>
# Dose-Response on Clinical Outcomes with Nominal Significance for 10 mg/kg Dose

<table>
<thead>
<tr>
<th>Placebo decline (N=48)</th>
<th>Study 103 Final Data</th>
<th>Difference vs. placebo (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mg/kg (N=31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg/kg (N=32)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>6 mg/kg (N=30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Titration (N=23)</td>
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<td></td>
<td></td>
<td>10 mg/kg (N=32)</td>
<td></td>
</tr>
<tr>
<td>CDR-SB</td>
<td>n=39  1.88</td>
<td>n=23 -0.06 (-3%) 0.9136</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=27 -0.45 (-24%) 0.3869</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=26 -0.68 (-36%) 0.2035</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=21 -0.73 (-39%) 0.2047</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=23 -1.08 (-57%) 0.0464</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>n=40 -2.5</td>
<td>n=25  0.3 (-12%) 0.7708</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=26 1.3 (-52%) 0.1615</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=26 0.4 (-16%) 0.6366</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=21 1.4 (-56%) 0.1680</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=25 1.9 (-76%) 0.0356</td>
<td></td>
</tr>
</tbody>
</table>

Pooled placebo group
Negative % means less progression in the treated arm
n: number of randomized and dosed subjects with endpoint assessment at Week 54 (CDR-SB) or Week 52 (MMSE)
MMRM model with same covariates as primary ANCOVA model specified in SAP
10 mg/kg dose was able to achieve nominal statistical significance according to the prespecified plan

Dose-response relationship for brain amyloid reduction supports finding in 10 mg/kg arm and is consistent with dose-response for clinical endpoints

Limitations of Study 103
- Placebo group is pooled across cohorts and not entirely contemporaneous with 10 mg/kg treatment arm
- Statistical significance was not robust to sensitivity analyses
- There was no control for multiplicity
Evidence of Effectiveness

- Study 302 provides primary evidence of effectiveness
- Results of Study 103 are appropriately viewed as supportive evidence of the effectiveness of aducanumab
- Study 301 does not contribute to the evidence of effectiveness
  - Analyses allow for independent consideration of Study 302 and do not represent evidence that aducanumab is ineffective
Aducanumab for the Treatment of Alzheimer’s Disease: Clinical Overview of Safety

Natalie Branagan, MD
Medical Officer/Safety Team
Division of Neurology 1

Brian Trummer, MD, PhD
Medical Officer
Division of Neurology 1
Overview

• Deaths
• Serious adverse events
• Most common adverse events
• Amyloid related imaging abnormality
# Deaths in Study 302

<table>
<thead>
<tr>
<th></th>
<th>Aducanumab (N=1090)</th>
<th>Placebo (N=548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>0.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>
### SAEs in Study 302

<table>
<thead>
<tr>
<th>SAEs</th>
<th>ADU 10 mg/kg N=547 %</th>
<th>Placebo N=548 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>13.3</td>
<td>14.8</td>
</tr>
<tr>
<td>Amyloid related imaging abnormality-edema/effusion</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Inguinal Hernia</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Superficial Siderosis of Central Nervous System</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>
# AEs in Study 302 with Incidence in the Aducanumab 10 mg/kg Arm at Least 2% Higher Than Placebo

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ADU 10 mg/kg N=547</th>
<th>Placebo N=548</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid related imaging abnormality-edema/effusion</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Superficial siderosis of central nervous system</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Dizziness, Vertigo</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Confusion, Delirium, Altered Mental Status, Disorientation</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Nausea, Vomiting</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Visual Disturbance</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
ARIA-related Events
### Subjects with Serious Adverse Events of ARIA in Study 302

<table>
<thead>
<tr>
<th>Subjects with SAEs</th>
<th>Aducanumab 10 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=547</td>
<td>N=548</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>ARIA</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>ARIA-H (microhemorrhage)</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>ARIA-H (superficial siderosis)</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>ARIA-H (cerebral hemorrhage)</td>
<td>0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Frequency of ARIA in the placebo controlled period of Study 302

<table>
<thead>
<tr>
<th>Term</th>
<th>Aducanumab 10 mg/kg N=547 %</th>
<th>Placebo N=548 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ARIA Events</td>
<td>41.7</td>
<td>10.2</td>
</tr>
<tr>
<td>Subjects with symptomatic ARIA</td>
<td>7.5</td>
<td>0.4</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>34.4</td>
<td>2.4</td>
</tr>
<tr>
<td>ARIA-H (microhemorrhage)</td>
<td>19.7</td>
<td>6.8</td>
</tr>
<tr>
<td>ARIA-H (superficial siderosis)</td>
<td>13.3</td>
<td>2.6</td>
</tr>
<tr>
<td>ARIA-H (cerebral hemorrhage)</td>
<td>0.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Conclusion

• The safety profile of aducanumab is acceptable for the proposed indication.
• ARIA can be managed by appropriate labeling language, which would include a warning for ARIA.
• Prescriber and patient education regarding ARIA is important.
• Appropriate methods to communicate and educate healthcare providers and patients about the risk of ARIA are under consideration.
BLA 761178 Statistical Review
Aducanumab in Alzheimer’s

Tristan Massie, Ph.D.
Mathematical Statistician
Division of Biometrics I,
Office of Biostatistics/OTS/CDER, FDA
Acronyms

APOE: Apolipoprotein E carrier status, a randomization stratification factor used in the phase 3 trials

PV4: Protocol Version 4 which was finalized in March 2017. In the slides PV4 or Post-PV4 refers to the subset that provided consent to this protocol amendment by day 113 of their study participation, which would allow those APOE carriers assigned to the high dose to have the maximum number of 10 mg/kg doses (14) allowed by the PV4-modified titration regimen
High Level Summary and Issues

- Both Phase 3 Trials (301,302) futility stopped
  - Increased placebo worsening later entangled with a possible effect of late mid-study dose increase in APOE carriers
  - Positive 302 has Consistently smaller effects in non-carriers who had higher exposure from study start (interaction significant for first key secondary MMSE)
- Study 103 small, staggered cohorts safety study
  - Randomization does not back sponsors analysis, which is also non-robust
- Week 78 High Dose changes in CDRSB and PET Aβ plaque SUVR uncorrelated
  - No evidence of disease slowing (lack of biomarker correlation, delayed start, only single significant timepoint for primary clinical endpoint)
- Lack of Substantial Evidence
  - no replication, highly conflicting results in two studies, conflicting subgroup results
- Less Long Term Safety Data at 10 mg/kg for High Dose Carriers due to futility stop and mid-study dose increase
Phase 3 Titration Regimens and Mid-Study Dose Increase in High Dose APOE carriers

301 and 302 78 week parallel group trials: placebo: low:high 1:1:1 stratified by APOE and Site
N=545 / group

Dose Increase Mid-Study in APOE+ High Dose APOE+ (2/3 of population)

Source: page 14 of summary-clin-efficacy-ii.pdf in BLA/0003/M2
## Two Phase 3 Primary Week 78 Results

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th>Study 302</th>
<th>Studies 301+302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diff vs PBO</td>
<td>Diff vs PBO</td>
<td>Diff vs PBO</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>p-value</td>
<td>(%)</td>
</tr>
<tr>
<td><strong>PBO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>decline</strong></td>
<td>N=545</td>
<td>Low dose</td>
<td>N=547</td>
</tr>
<tr>
<td><strong>CDR-SB</strong></td>
<td>1.55</td>
<td>-0.18</td>
<td>(12%)</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>-3.5</td>
<td>0.2</td>
<td>(-6%)</td>
</tr>
<tr>
<td><strong>ADAS-Cog13</strong></td>
<td>5.171</td>
<td>-0.590</td>
<td>(-11%)</td>
</tr>
<tr>
<td><strong>ADCS-ADL-MCI</strong></td>
<td>-3.8</td>
<td>0.7</td>
<td>(-18%)</td>
</tr>
</tbody>
</table>

*: difference vs placebo at week 78. Negative percentage means less progression in the treated arm.

N: numbers of all randomized and dosed subjects that were included in the ITT analysis.

Primary Pbo/High LSMeans : 1.55 (.15) 1.58 (.15) p=0.83; 1.74 (.15) 1.34 (.15) p=.01

multiplicity plan favored testing primary for low dose over including secondary endpoints in label

Technically, because low did not win on primary, secondaries could not be tested for high dose

Source: page 152 of correspondence_type c mingle Minor 24-20190614.pdf in DLA/0003/M1
Phase 3 Trials Futility Stopped

- Conditional power (CP) <20% futility decision used interim treatment effect from pooled studies
- Study 302 high dose CP was only 58.63% at the interim for 302 interim effect:
  High dose interim effect size: -.28 (19), p=0.139.
  At interim N=782: Placebo LS Mean= 1.53 (.16) (Week 78 is 8% missing)
- In remaining N=798 ITT patients (Only 156 have Week 78 = 80% missing)
  Placebo LS Mean: 1.77 (.24) (worse placebo after interim)
  Low effect: -.57 (.34) p=.094 (better than dose-increased-high)
  High effect: -.50 (.33) p=.126

Bigger effect after interim a concern (potential operational bias)
- Opportunity To Complete Population: N=953 Hi -.362 (.172), p=.0368 (Week 78 is 8% missing)

- Less long term safety information (including rare potential events) about 10 mg/kg in carriers due to futility stop and protocol version 4 (PV4) mid-study dose increase
  - only fully available to post-PV4 population: their average placebo controlled follow up is about 50 weeks
Collaborative Workstream in Q3 of 2019

• Wave 1 work: Simulate Completed Trials as if had not stopped for futility using Multiple Imputation
  – Multiple Simulated Completed Study Results agree with Final ITT Results (note: >40% missing Week 78)
• Wave 2 work: Explore Differences between 301 and 302 and see if there are 302-like patients in 301
  – A Lack of 302-like Patients Could Possibly Explain the Failure of 301 while existence might render some support for 302
Study 302 Primary Endpoint

- No effect before Week 78
- ITT >45% missing Wk 78 due to futility stopping
“Rapid Progressors” in Early Alzheimer’s Study 301?

- A Rare disease terminology- post-hoc definition, explanation for 301 failure here
- Dominantly inherited Alzheimer’s Platform Trial (DIAN) doesn’t adjust for rapid progressors despite << sample size
- Blinded sample size increase from 450 to 535 should have helped, if real
- Subgroup analysis suggests more 302 effect in Mild AD than MCI (Prodromal AD)
  - Aducanumab described as disease slowing contraindicated in Mild-Rapid?
  - Low dose still numerically better than high in 301 after excluding “rapid progressors”
  - Exclusion of worst 3 outliers in 301 high dose still shows no effect compared to placebo and numerically worse than low dose
  - Robust regression: legitimate, more resistant to outlier analysis of 301, still shows no effect of high dose compared to placebo and numerically worse than low dose
  - Trimmed mean analysis removing these shows no significant high dose effect: -.15

- May actually be a systemic lack of efficacy
APOE+ Pre-PV4 vs. Post PV4 CDRSB Profiles by Treatment Group and Study

**Placebo**
- 302 Low 302 APOE+
- High 302 APOE+

**301**
- Placebo 301 APOE+
- Low 301 APOE+
- High 301 APOE+

Effect of Dose Increase is entangled with Simultaneous Placebo Worsening

*Overall:*
- Post-PV4 1.75 1.37 1.25 1.84 1.42 1.35
- Pre-PV4 1.51 1.42 1.17 1.41 1.30 1.71
High Dose APOE Non-carriers: earlier 10mg/kg dosing, but less effect

- If intermediate dosing (less 10 mg/kg doses) in APOE carriers was really what stopped 301 and APOE carriers and non-carriers have the same effects as the sponsor claims then there should be more effect in the non-carriers
- APOE- high dose: had 10 mg/kg whether pre-PV4 or post-PV4
  - Non-carriers comprise 1/3 of study population
- more 10mg/kg doses = less intermediate dosing
- also less ARIA adverse events for APOE-, so less dose reductions (less unblinding too)
- However, results show less effect in this randomization stratified subgroup
  - Even pooling studies, no effect in high non-carriers, consistent across studies
  - Consistent across all 4 primary and key secondary endpoints in 302
    - numerically worse for first key secondary MMSE which shows significant treatment by APOE interaction test p=0.0065
    - 302 APOE+ may be the outlier: positive in 302, wrong direction in 301
    - major amendment mid-study, more ARIA in carriers=more unblinding
302 High Dose Higher Avg. Dose for Non-carriers but Less Effect Trend on all 4 Key Endpoints

Key Outcomes(Higher Better*)

CDRSB high APOE interaction p=.15

MMSE: Numerically Worse for high dose: interaction p=0.0065 across both doses p=0.07 for high only interaction

ADCS-ADL p=0.07 for high interaction only

Avg. Dose

Group with highest dose throughout study and less ARIA, numerically worse than placebo on first key secondary and numerically less effect than carriers on all 4 endpoints

* Note: The signs of CDRSB and ADASCOG were changed without loss of generality for this analysis so that the same sign of the difference reflects benefit for all 4 endpoints.
302 Low Dose Has APOE by Treatment Interaction Trend in Same Direction As High Dose on all 4 Key Endpoints

Key Outcomes (Higher Better)  Avg. Dose

MMSE: Nominally → Significantly Worse for Low Non-carriers
APOE Interaction
p=0.0065 across both doses

Low dose non-carriers: higher dose than carriers but numerically worse than placebo all 4 eps Interaction on first key secondary and numerically less effect than carriers on all 4 endpoints (eps)
More Unblinding in APOE+ who drive 302

- up to 35% of high dose patients had dose titration modifications due to treatment related ARIA adverse events.

- The primary outcome assessment in this study a physician rating could potentially be susceptible to bias if the treatment was revealed.

![Graph showing percent dose titration modification for different conditions and dose levels](https://www.fda.gov)
Phase 1B Study 103 Staggered Design

Sponsor compares Arm 4 to pooled Arms 3, 5, 7, and 9.
Study 103 Exploratory Phase 1B
54 Week Safety Study (N=179)

• Staggered Multiple Arm/Cohort Randomizations design for dosing arms
  – Not all Placebo arms concurrent with 10 mg/kg (more females and APOE+ in pooled placebo) sponsor analysis not backed by overall randomization

• 10 mg/kg Week 54 p=.0436 overall, not significant after excluding data post baseline starting of concomitant AD meds: .90 (.53), p= .0954
  – Not significant against concurrent placebo : 1.13 ( .70), p=.12 or excluding titration placebo arm (all APOE+)

• Unlike study 302 here bigger 10 mg/kg effect in APOE- than APOE+ (not reproduced in phase 3)
  – Carrier -0.88 (.64) p=.172
  – Non-carrier -1.63 (.96) p=.091 (in 302 -0.07 p=0.80 at Week 78)

• No suggestion of any 10 mg/kg or titration group effects at Week 26
Sponsor’s Post Randomization High Dose Actual Dosing Subgroups Confounded by Unequal Placebo Response

301: 32% with opportunity had 14 10 mg/kg doses

302: 43% with opportunity had 14 10 mg/kg doses

61% of non-carriers had 14 10 mg/kg doses

301 appears to show a dosing trend but **there is simultaneous confounding placebo worsening** trend in placebo progression rate as dosing increases

This is post-hoc, not supported by randomization: matching is imperfect and cannot restore or recreate randomization
Country Differences between 301 and 302

• Different countries enrolled and significant Country by Visit by Treatment interactions (different country progression profiles)
  – 6 countries unique to 302 and 6 others unique to 301
  – US 46.4% in 301 vs. 39.6% in 302

• Changing distribution of countries after Protocol Amendment 4
  – In 302 Poland with a negative high dose effect decreased enrollment post-PV4 (19% to 6%) while Japan with positive country effect increased enrollment post-PV4 (2% to 12%)
  – Changing demographics in later enrolled also confound the effect of raising the dose (different regions favored later, more MCI vs. Prodromal, more use of AD meds at baseline, etc.)
302 Week 78 CDRSB High Dose effect
Forest Plot for Subgroups

- Effect Modifiers?
  - Age Group
- Mild BL Diagnosis
- APOE
- Country
- USA 301 vs. 302
  - APOE+ 301 vs. 302
Lack of Correlation between Week 78 CDRSB changes and cerebellum PET Aβ SUVR Week 78 changes for High Dose 301 and 302 High Dose Week 78 CDRSB (y) vs. Week 78 SUVR (x) 302 full 10 mg/kg doses subgroup

In the absence of such a correlation worse placebo explanation for 302 seems more likely

There is very little to support disease slowing (only one + timepoint, no correlation with SUVR, no delayed start design, second failed study)

Note: Lower is better on both CDRSB and SUVR: Positive slope required for biologic linkage
Sponsor Exploratory Tau Medial Temporal SUVR Biomarker Change vs. Dose Collected After Futility Press Release

Wk 78 Change in Tau (y) vs Avg Dose (x)

Low dose has stronger slope than High

Very Small sample with baseline group differences
The baseline CDRSB was 2.75 for the 12 placebo and 2.27 for the 11 high,

this is mostly 301 data: 92% vs. 100%

Wk 78 CDRSB Change (y) vs. Tau Change (x)

Correlation between CDRSB and Tau Changes
Note: Positive slope required for biologic linkage
A Benefit Risk assessment

- Futility Stop and Mid-Study Increase to 10 mg/kg for APOE carriers means less long term safety data at 10 mg/kg in carriers who drive efficacy
  - 10 mg/kg only fully available post-PV4: their average follow up is about 50 weeks
- Incidence of Falls and Time to first Fall appear significantly worse for high dose and seem important for the intended population

Falls Hazard Ratio 1.33  p=.016

www.fda.gov
2019 Substantial Evidence Draft Guidance

• “poor execution can render a trial of any design to be not adequate or not well-controlled and, therefore, unable to provide substantial evidence of effectiveness. Examples of this include a randomized, double-blind, placebo-controlled trial in which unblinding is common due to an effect of the test drug, and where a modest treatment effect is found on a primary endpoint that is subject to bias when drug assignment is known (e.g., a physician global impression). In these cases, the trials might not be considered adequate and well-controlled.”

• “Findings from other trials that are not consistent with the findings of the single positive trial would need to be considered collectively, and could weaken the overall strength of evidence.”
Reproducibility?

• INCONSISTENCY: It’s not like we have one strong study in isolation

• We have an equally-sized and identically designed study 301 that directly contradicts 302, 301 high dose is numerically worse than placebo, p=.8252

• Under null, .0975 chance of falsely rejecting the null across 2 studies

• If you have two and you take the best and pretend like it’s the only one, your estimate is likely biased as in publication bias
Lack of Substantial Evidence and Implications for Drug Development

• At best evidence is from 302 only and there exists conflicting adequate well controlled evidence

• Impact on Ongoing and future Trials for other candidates
  – Noninferiority would be questionable with mixed divergent results
  – Create Recruitment challenges for ongoing trials

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Backup Slides
Correlations among Primary and Key Secondary endpoints

• Moderate correlations between .40 and .64
  – Considerably larger than CDRSB correlation w/ SUVR

• The 4 endpoints joint information can be explained well with a simple sum of the 4: only 1 dimension or factor (at most 2) needed rather than 4
Study 301 Forest Plot of Subgroup Effects for High Dose
Study 302 Correlation between Week 78 Changes in CDRSB and Aβ SUVR is small, driven by Low Dose and still very weak.
Study 103 Weak High Dose Correlation between $\alpha$B SUVR and CDRSB change at Week 54

Exploratory Exclusion of the outlier patient increases primary CDRSB p-value to .89 (.54), p=0.10
Some Subgroup High Dose Effect orderings differ between Aβ SUVR and CDRSB change

- APOE⁻ – bigger effect in SUVR for APOE⁻ but smaller in CDRSB, APOE⁺ (bigger for CDRSB)
- Prodromal – bigger effect in SUVR for Prodromal but smaller in CDRSB (bigger for Mild)

Source: pages 95 and 98 of ise.pdf

Note: Farther to the left is better for both CDRSB and SUVR
• Study effects don’t have equal variance and correlated within study due to sharing same placebo
• 103 effects have more uncertainty and effects much larger than phase 3 and comparison to pooled placebo not randomization supported

Source: page 242 of sponsor’s ise.pdf
Study 302 Post PV4 dose modified due to ARIA High subgroup
LS Mean numerically better than non-modified full-dosed subgroup

Numbers shown are Avg #10mg/kg doses

dc=dose change or modification of titration
Two Phase 3 Primary Week 78 Results

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th>Study 302</th>
<th>Studies 301+302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diff vs PBO (%)</td>
<td>p-value</td>
<td>Diff vs PBO (%)</td>
</tr>
<tr>
<td></td>
<td>PBO decline (n=545)</td>
<td>Low dose (N=547)</td>
<td>High dose (N=555)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>1.55</td>
<td>-0.18</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>(-12%)</td>
<td>(-2%)</td>
<td>(2%)</td>
</tr>
<tr>
<td></td>
<td>0.2362</td>
<td>0.8252</td>
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</tr>
<tr>
<td>MMSE</td>
<td>-3.5</td>
<td>0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td></td>
<td>(-6%)</td>
<td>(3%)</td>
<td>(-3%)</td>
</tr>
<tr>
<td></td>
<td>0.4875</td>
<td>0.7961</td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog13</td>
<td>5.171</td>
<td>-0.500</td>
<td>-0.605</td>
</tr>
<tr>
<td></td>
<td>(-11%)</td>
<td>(-12%)</td>
<td>(-12%)</td>
</tr>
<tr>
<td></td>
<td>0.2475</td>
<td>0.2446</td>
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<tr>
<td>ADCS-DAE-MCI</td>
<td>-3.8</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>(-18%)</td>
<td>(-18%)</td>
<td>(-18%)</td>
</tr>
<tr>
<td></td>
<td>0.1345</td>
<td>0.1520</td>
<td></td>
</tr>
</tbody>
</table>

*: difference vs placebo at week 78. Negative percentage means less progression in the treated arm.

Prespecified Closed testing for each endpoint multiplicity tradeoff: two doses for primary vs. secondaries for high

High correlations (range .40 to .64 all p<0.0001) between each pair of the four endpoints. Significance-wise They all go the same way in both studies.
First linear combination explains 64% of the variance next adds only 17%