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# A Phase 2 Clinical Trial Of Bapineuzumab (AAB-001)

July 29, 2008



# Safe Harbor Statement

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This presentation will involve forward-looking statements that are subject to material risks and uncertainties.

Please refer to the joint press release issued by the companies earlier today describing forward-looking statements.

The companies assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

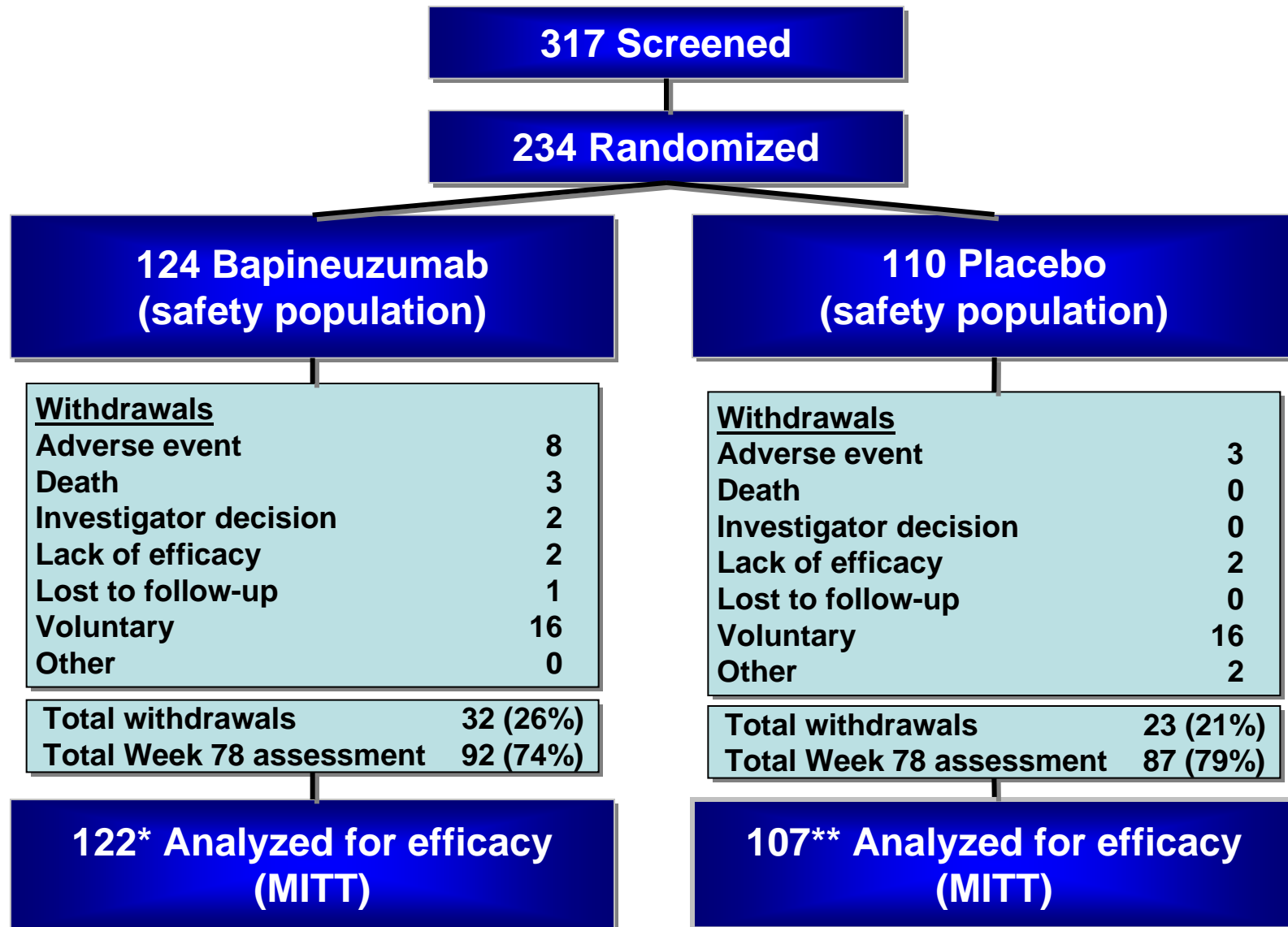
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- Ron Black, M.D., Wyeth Research, Assistant Vice President, Neuroscience
  - Sid Gilman, M.D., F.R.C.P., University of Michigan, Chair of Bapineuzumab Safety Monitoring Committee
  - Allison Hulme, Ph.D., Elan, Executive Vice President and Head of Global Development
  - Dale Schenk, Ph.D., Elan, Executive Vice President and Chief Scientific Officer
  - Gary L. Stiles, M.D., Wyeth Pharmaceuticals, Executive Vice President and Chief Medical Officer

# Bapineuzumab Phase 2: Study Objectives and Design

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- Bapineuzumab: humanized version of murine monoclonal antibody that recognizes N-terminal of A $\beta$
- Primary objective: evaluate safety and tolerability in patients with mild to moderate AD
- Secondary objective: evaluate efficacy in patients with mild to moderate AD
- Design: randomized, multicenter, placebo-controlled, parallel-group, multiple ascending-dose study
  - Enrolled 234 patients
  - Randomization: bapineuzumab or placebo (8B:7P)
  - 6 infusions, 13 weeks apart
  - 4 dose cohorts: 0.15, 0.5, 1.0, 2.0 mg/kg
  - Final assessment: Week 78

# Bapineuzumab Phase 2: Patient Disposition Through Week 78



\*2 patients – no post-baseline primary efficacy

\*\*3 patients – no post-baseline primary efficacy

# Bapineuzumab Phase 2: Demographics Total Population (MITT)

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	<b>Patient Demographics and Characteristics</b>	
	<b>All placebo (N = 107)</b>	<b>All bapineuzumab (N = 122)</b>
<b>Age, yrs</b>	<b>67.9</b>	<b>70.1</b>
<b>Gender, % female</b>	<b>59.8</b>	<b>50.0</b>
<b>Ethnicity, % Caucasian</b>	<b>95.3</b>	<b>96.7</b>
<b>Time since onset, yrs</b>	<b>3.7</b>	<b>3.5</b>
<b>ApoE4, % carrier</b>	<b>69.8</b>	<b>60.5</b>
<b>Screening MMSE Score</b>	<b>20.7</b>	<b>20.9</b>
<b>AChEI or memantine use, %</b>	<b>96.3</b>	<b>95.1</b>

## Bapineuzumab Phase 2: Safety

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- AEs generally mild to moderate, transient, not dose-related
- AEs occurring  $\geq 2$  times as often as placebo rate and seen in  $>5\%$  of bapineuzumab patients

Back pain	12.1% vs 5.5%	Weight loss	6.5% vs 1.8%
Anxiety	11.3% vs 3.6%	Paranoia	6.5% vs 0.9%
Vomiting	9.7% vs 3.6%	Skin laceration	5.6% vs 2.7%
VE (vasogenic edema)	9.7% vs 0%	Gait disturbance	5.6% vs 1.8%
Hypertension	8.1% vs 3.6%	Muscle spasms	5.6% vs 0.9%

- Excluding VE (more frequent in ApoE carriers), percentage of patients with SAEs was similar to percentage of placebo in 0.5, 1.0 and 2.0 mg/kg dose cohorts
- 3 deaths in bapineuzumab-treated patients; not considered treatment-related
- AEs of interest in  $<5\%$  of Bapineuzumab: syncope, DVT, PE, SZ, cataracts

# Vasogenic Edema: Summary

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- 12 patients with VE
  - All cases in bapineuzumab group, most after first or second dose
  - Most initially detected by MRI, with few or no clinical symptoms
  - 10 ApoE4 carriers, 2 non-carriers
    - 2.0 mg/kg (6 carriers, 2 non-carriers)
    - 1.0 mg/kg (3 carriers)
    - 0.5 mg/kg (0 carriers)
    - 0.15 mg/kg (1 carrier)
  - Resolved over weeks to months
  - 1 patient treated with steroids for lethargy, confusion
  - 6 of the 12 patients were retreated upon resolution of VE, no recurrence of VE

## Bapineuzumab Phase 2: Prespecified Efficacy Analyses

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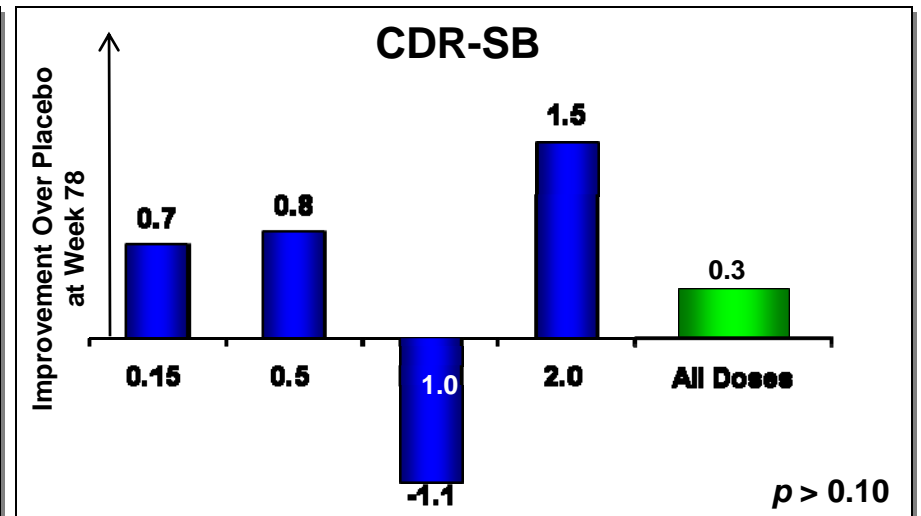
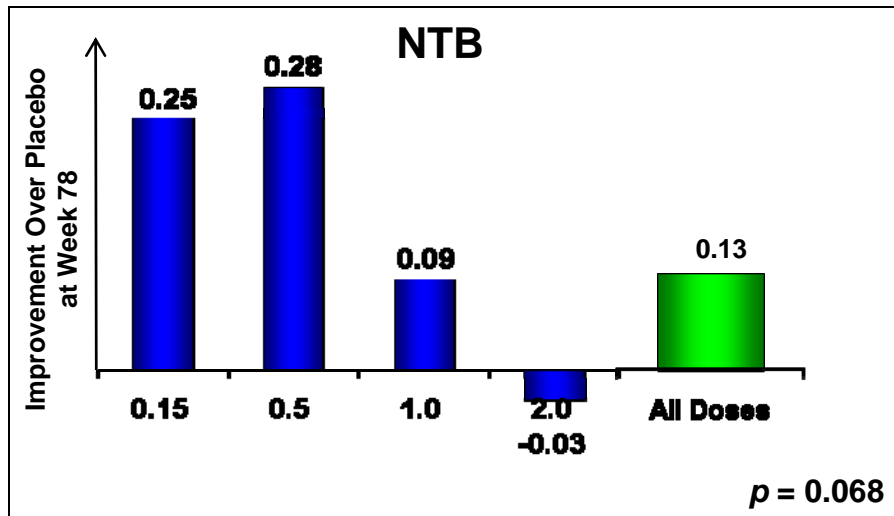
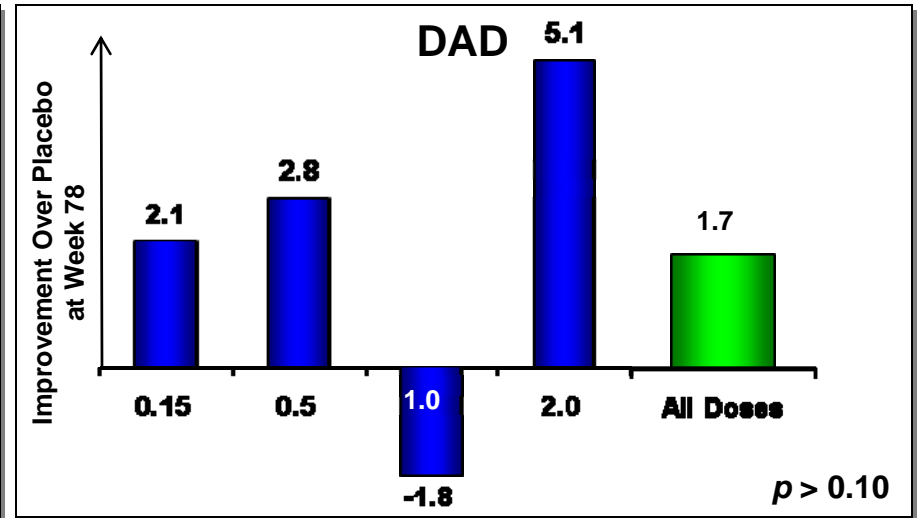
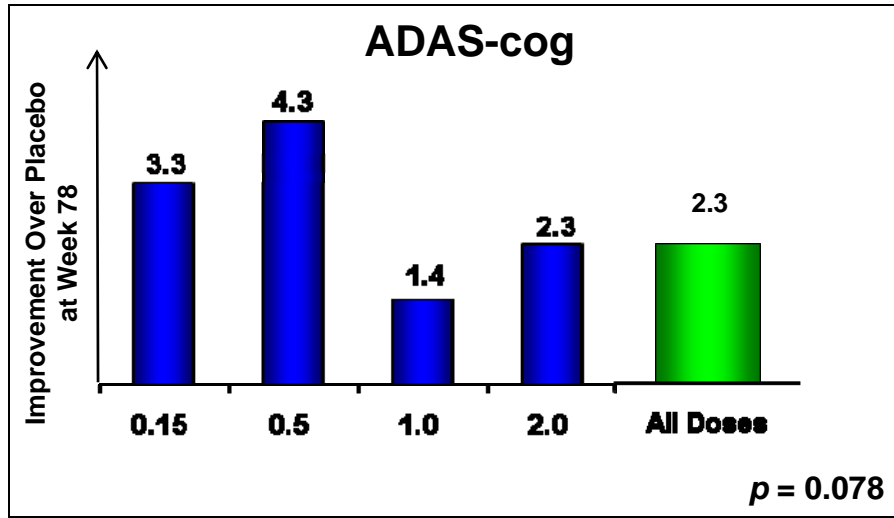
- Endpoints: within cohort treatment differences from baseline through Week 78 on ADAS-cog, NTB, DAD, CDR-SB, MMSE, CSF tau and MRI volumetrics
- MITT repeated measures (RM) model adjusted for MMSE and each baseline test score
  - Prespecified model assumed linear decline over time
- In general, decline found not to be linear over time
- Prespecified primary endpoints ADAS-cog and DAD did not achieve significance in MITT analysis

# Bapineuzumab Phase 2: Post-hoc Efficacy Analyses

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- MITT RM model without assumption of linearity
- Biological differences between ApoE4 carriers and non-carriers
  - VE more frequent in carriers
  - Higher incidence of AD in carriers
  - Greater amyloid burden in carriers
- Include adjustment for ApoE4 carrier status
  - All bapineuzumab vs all placebo patients across all doses
  - Separate analyses for ApoE4 carriers and non-carriers
- Completer analyses for patients who received all doses
  - Determine if receiving all doses influences efficacy

# Clinical Efficacy Endpoints: Total Population (MITT)

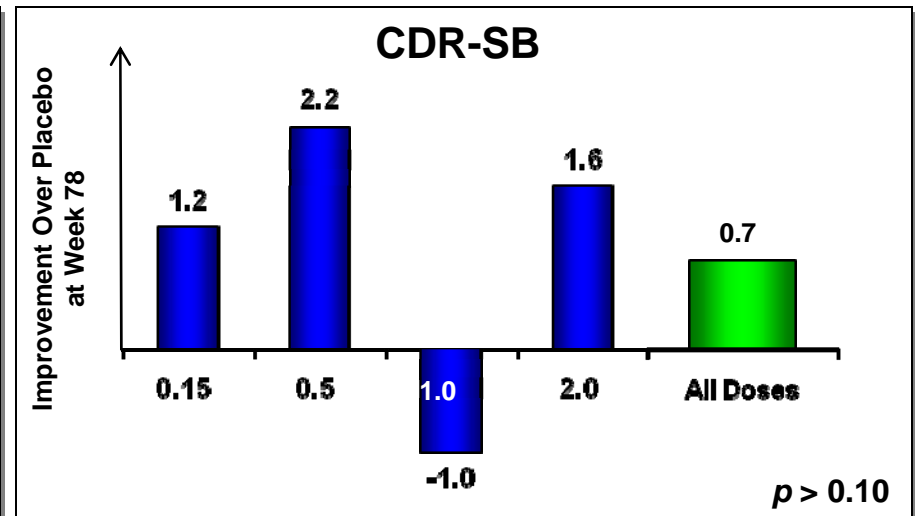
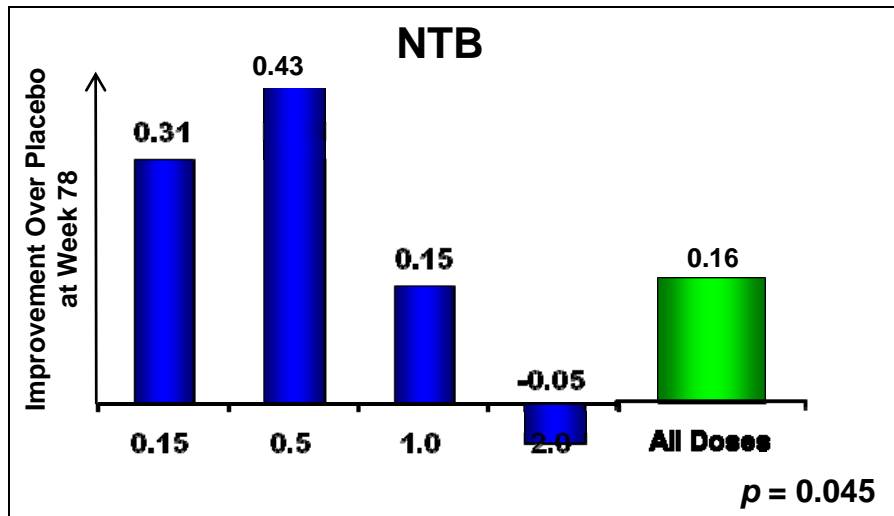
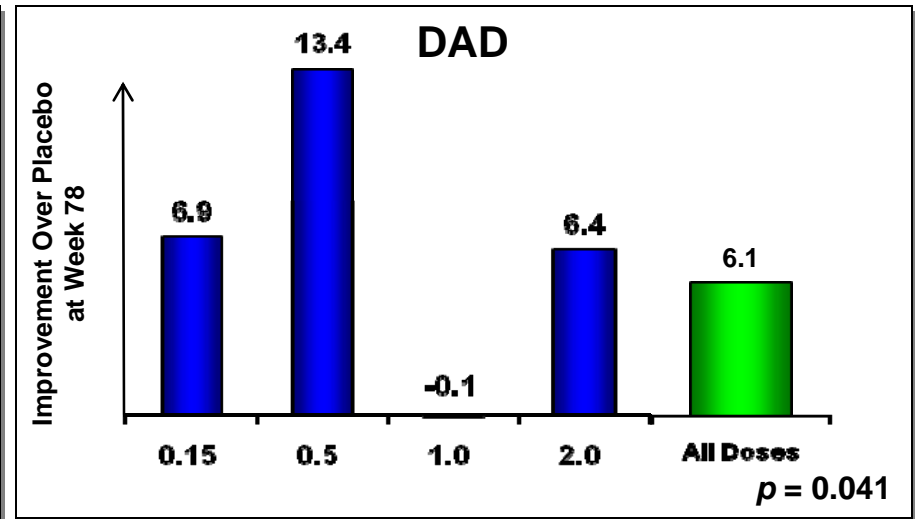
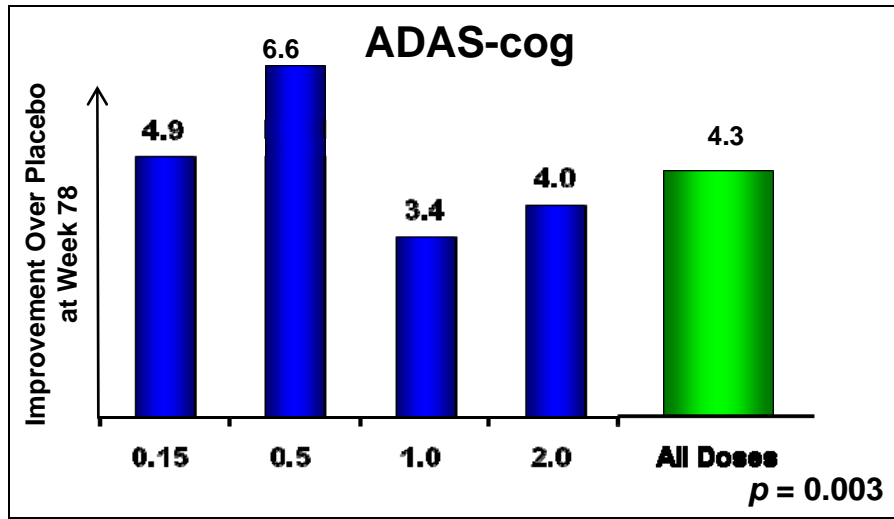


MITT analyses using repeated measures model without assumption of linearity

Bars above zero indicate improvement relative to placebo

Patient populations for "all doses" comparisons: bapineuzumab range, N = 115-119; placebo range, N = 102-106

# Clinical Efficacy Endpoints: Total Population (Completer)



Completer: patient who had all 6 infusions and an efficacy assessment at Week 78

Bars above zero indicate improvement relative to placebo

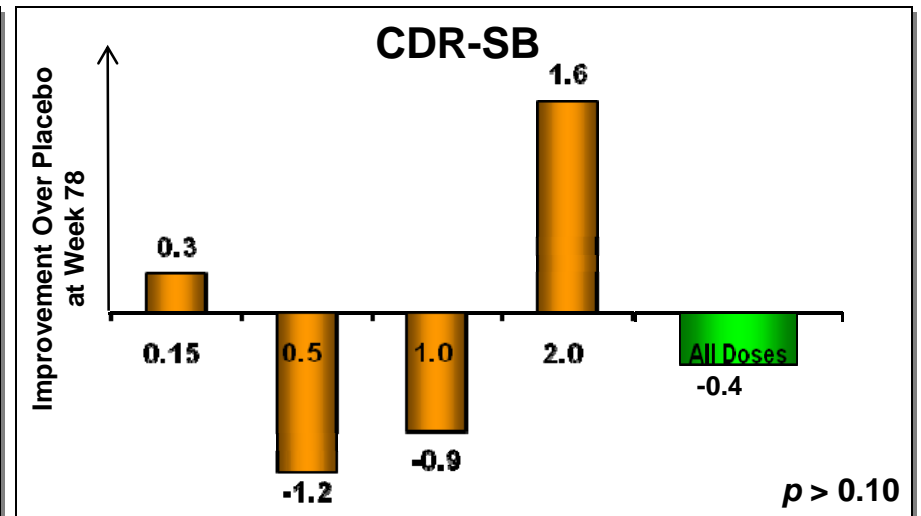
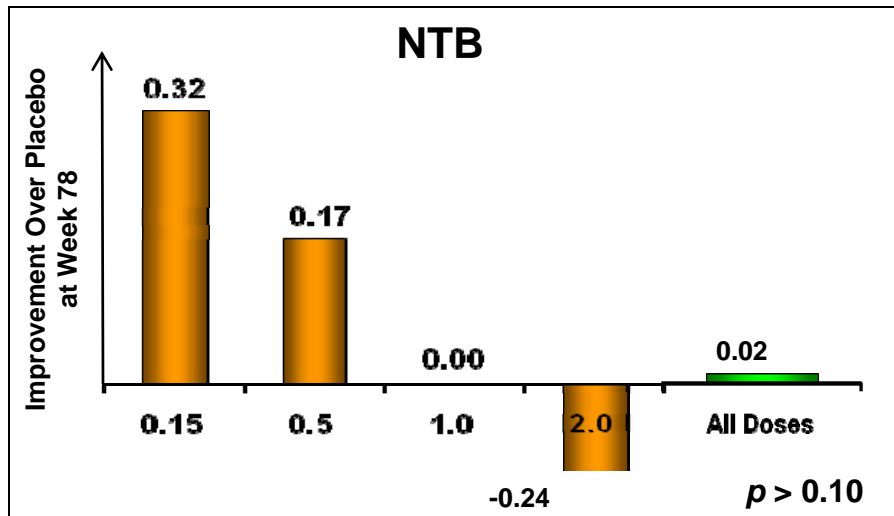
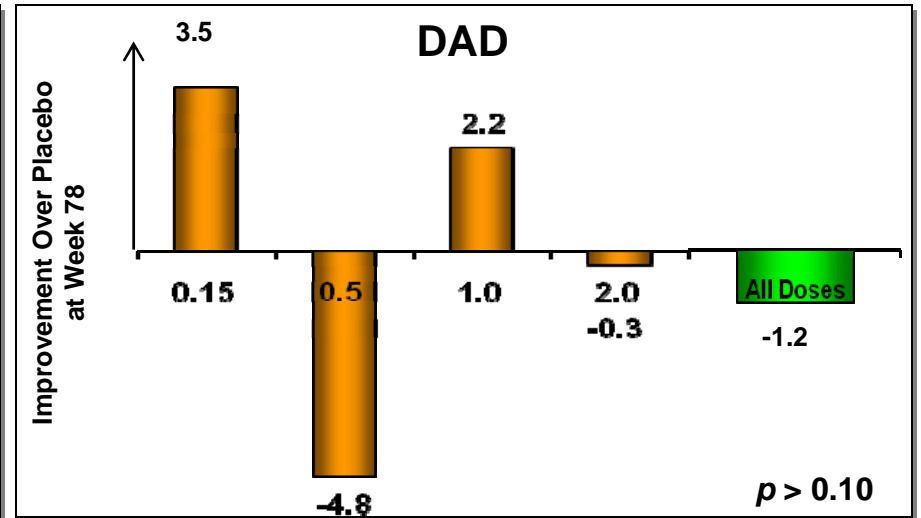
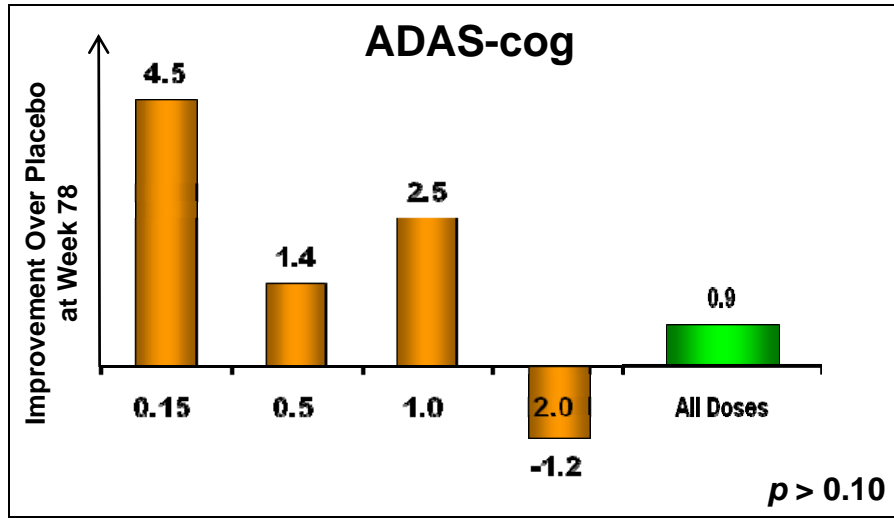
Patient populations for "all doses" comparisons: bapineuzumab, N = 78; placebo, N = 78

## Patient Demographics and Characteristics: ApoE4 Carrier and Non-carrier Populations

	ApoE4 Carrier		ApoE4 Non-carrier	
	Placebo (N = 74)	Bapineuzumab (N = 72)	Placebo (N = 32)	Bapineuzumab (N = 47)
<b>Age, yrs</b>	<b>68.6</b>	<b>71.2</b>	<b>66.1</b>	<b>69.1</b>
<b>Gender, % female</b>	<b>59.5</b>	<b>48.6</b>	<b>62.5</b>	<b>51.1</b>
<b>Ethnicity, % Caucasian</b>	<b>97.3</b>	<b>97.2</b>	<b>90.6</b>	<b>95.7</b>
<b>Time since onset, yrs</b>	<b>3.8</b>	<b>3.7</b>	<b>3.5</b>	<b>3.0</b>
<b>Screening MMSE Score</b>	<b>21.0</b>	<b>20.6</b>	<b>19.8</b>	<b>21.4</b>
<b>AChEI or memantine use, %</b>	<b>95.9</b>	<b>98.6</b>	<b>96.9</b>	<b>89.4</b>

ApoE status in 4 patients unknown

# Clinical Efficacy Endpoints: ApoE4 Carrier Population (MITT)

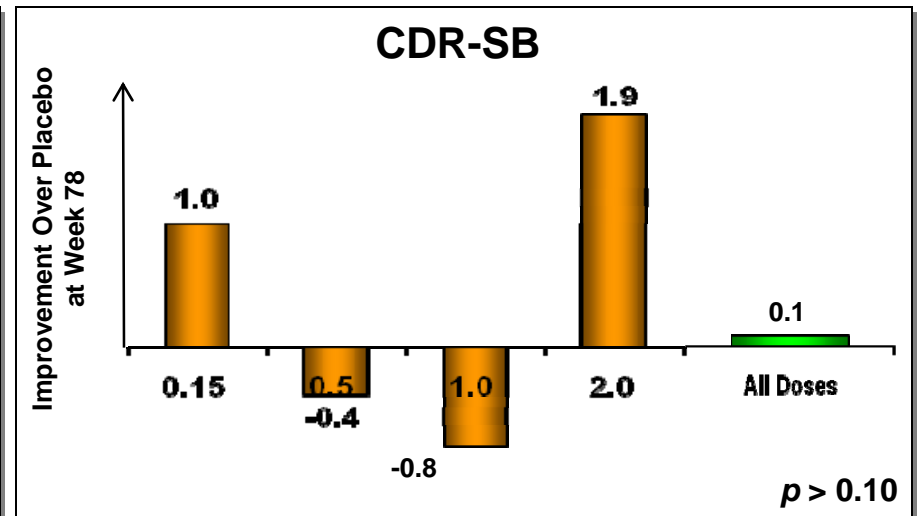
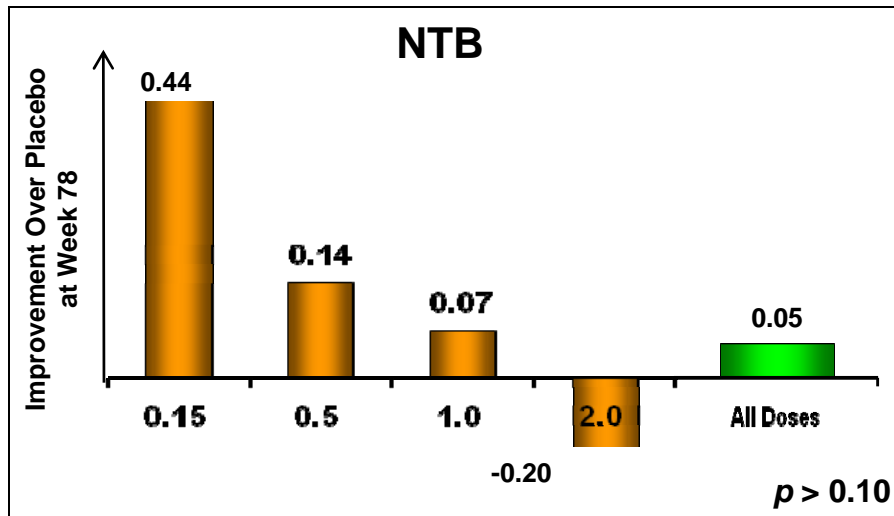
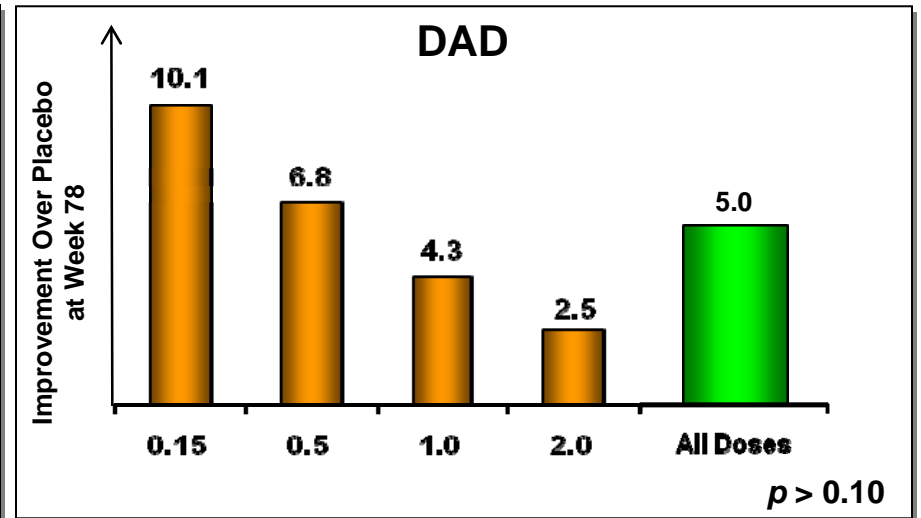
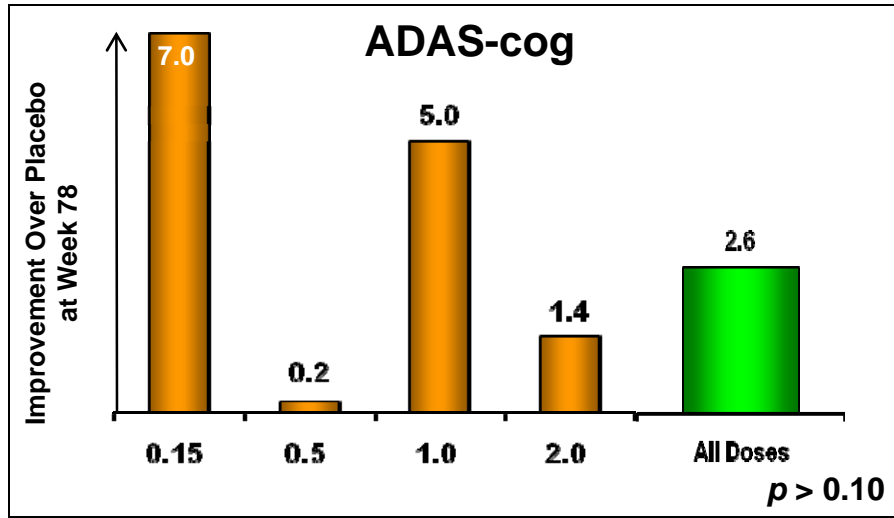


MITT analyses using RM model without assumption of linearity

Bars above zero indicate improvement relative to placebo

Patient populations for "all doses" comparisons: bapineuzumab range, N = 69-72; placebo range, N = 72-74

# Clinical Efficacy Endpoints: ApoE4 Carrier Population (Completer)

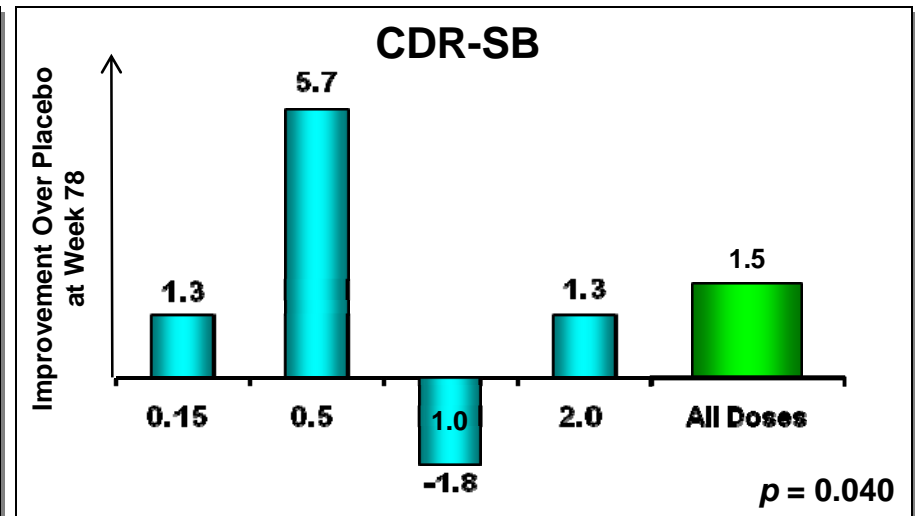
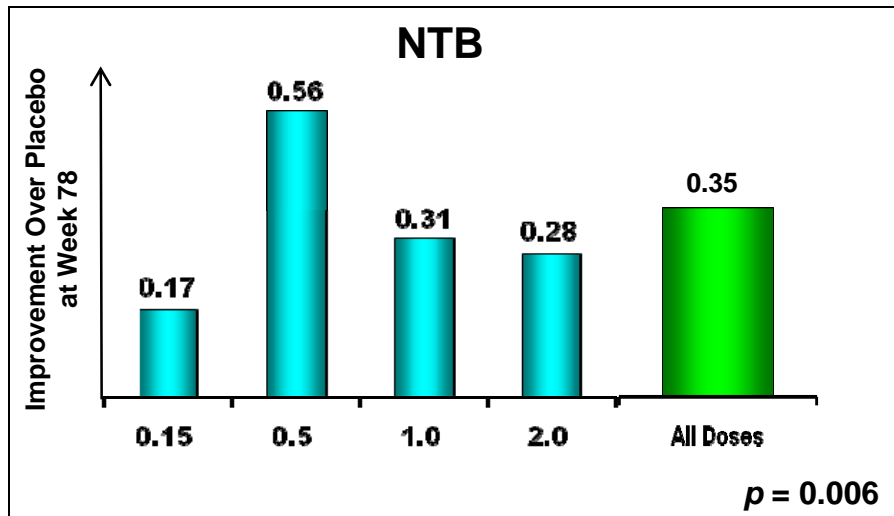
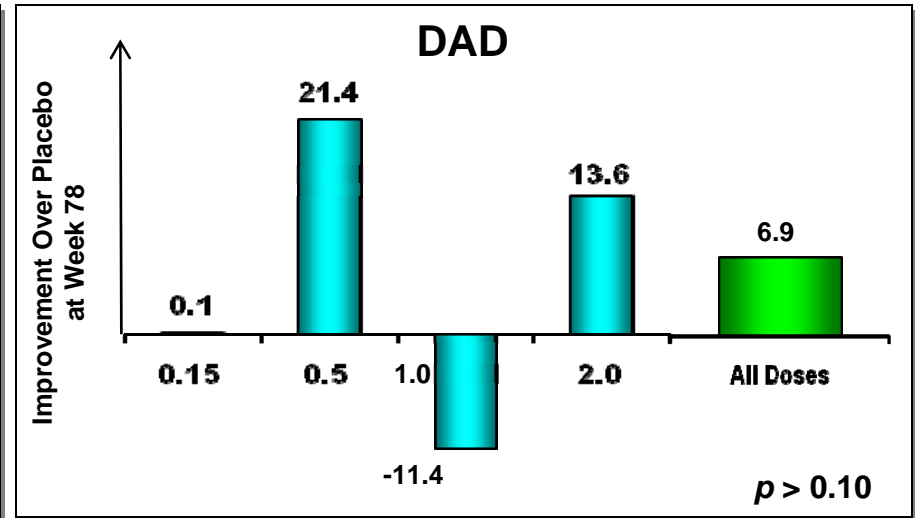
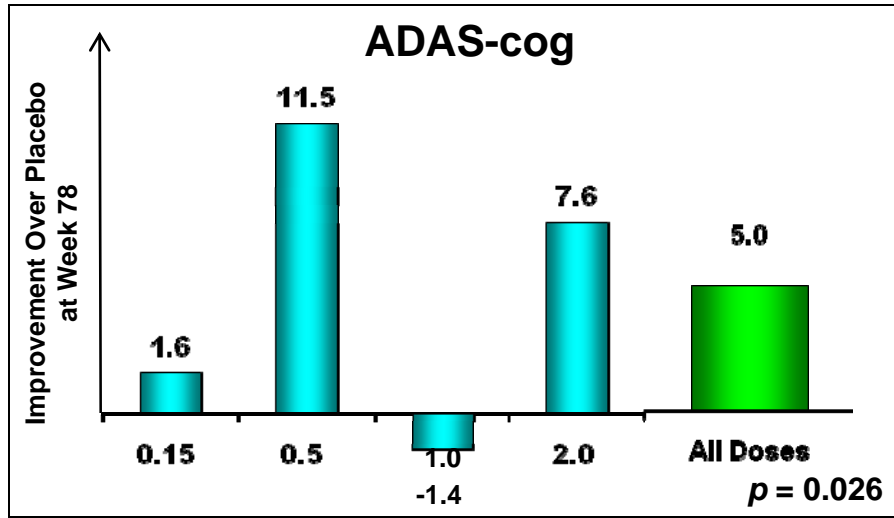


Completer: patient who had all 6 infusions and an efficacy assessment at Week 78

Bars above zero indicate improvement relative to placebo

Patient populations for "all doses" comparisons: bapineuzumab, N = 42; placebo, N = 57

# Clinical Efficacy Endpoints: ApoE4 Non-carrier Population (MITT)

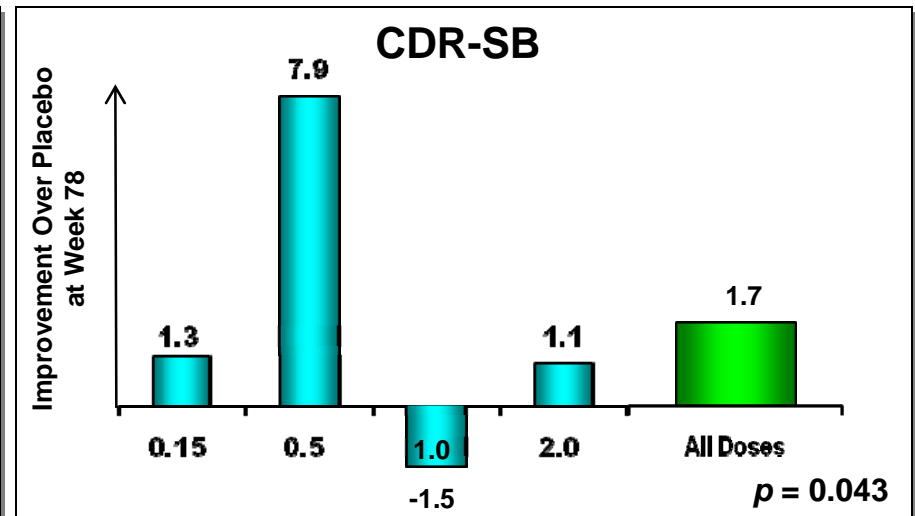
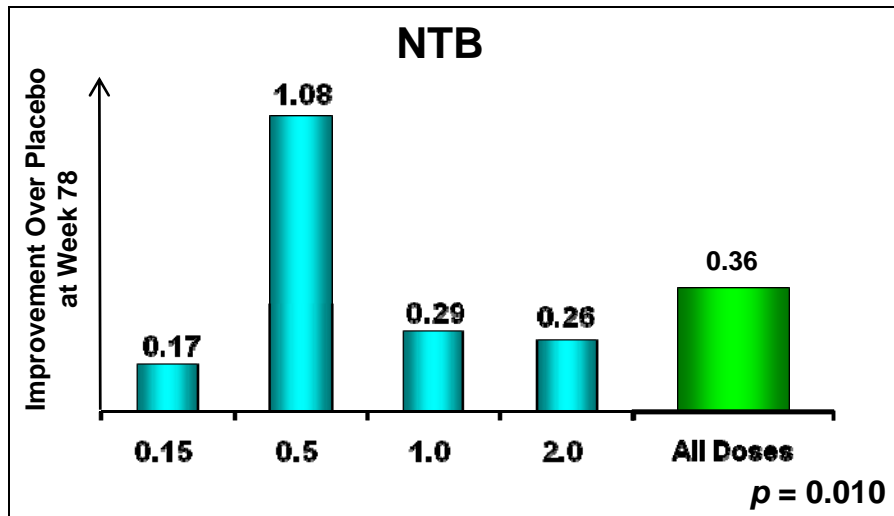
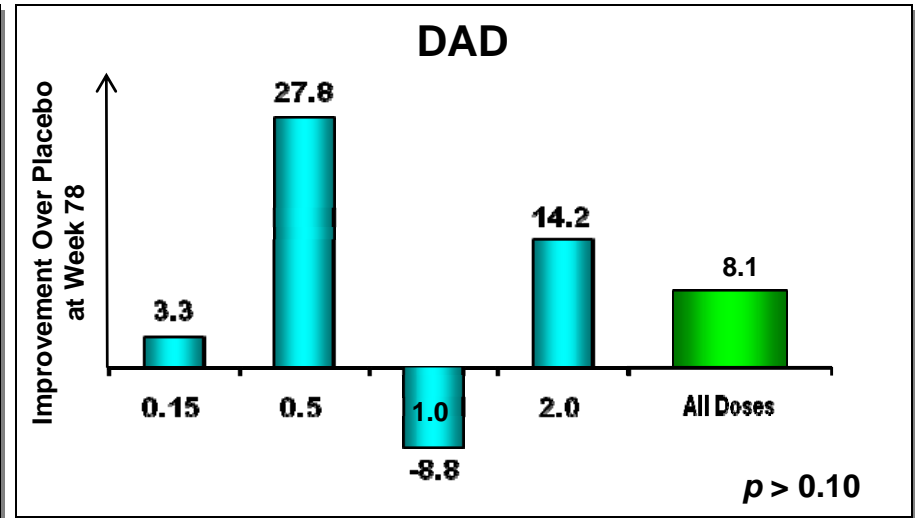
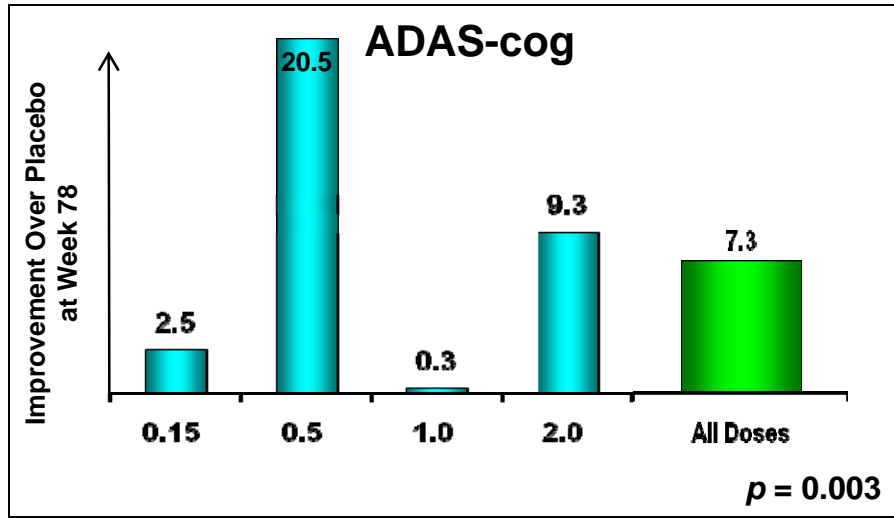


MITT analyses using repeated measures model without assumption of linearity

Bars above zero indicate improvement relative to placebo

Patient populations for "all doses" comparisons: bapineuzumab range, N = 46-47; placebo range, N = 30-32

# Clinical Efficacy Endpoints: ApoE4 Non-carrier Population (Completer)



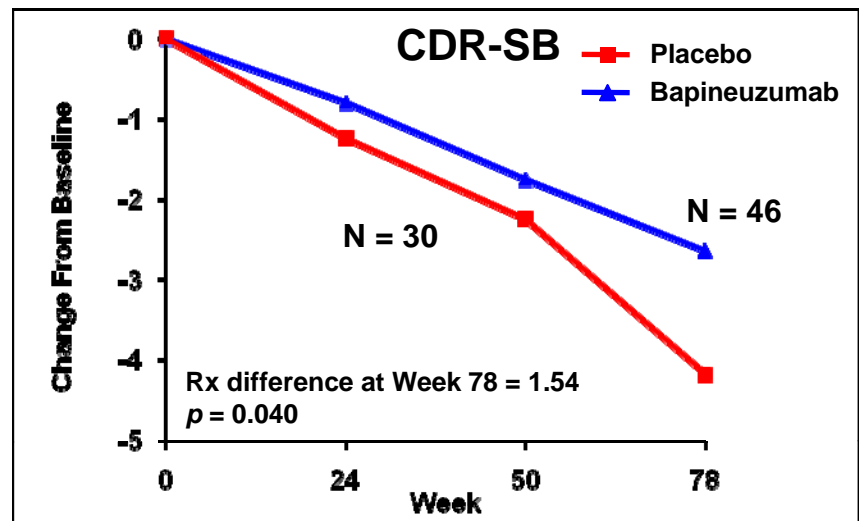
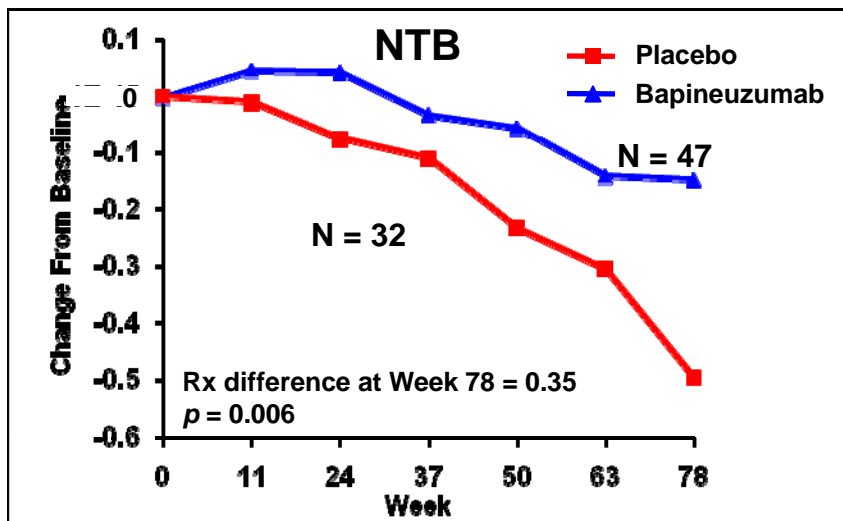
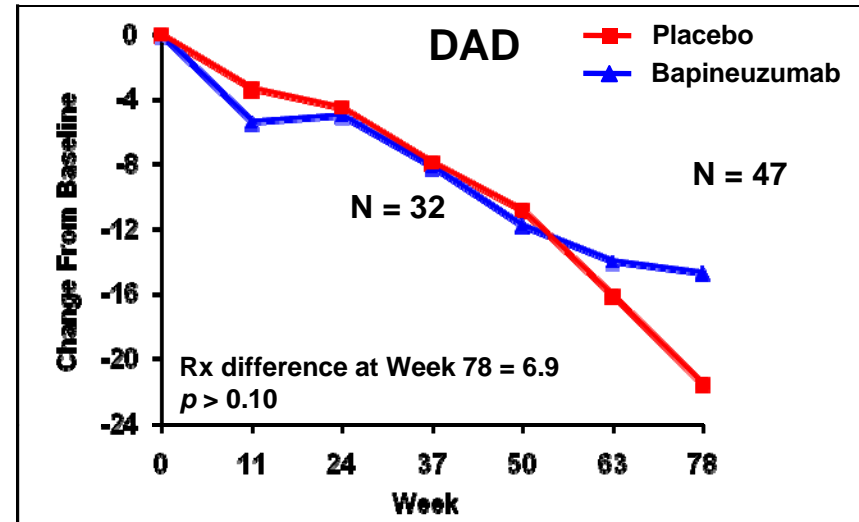
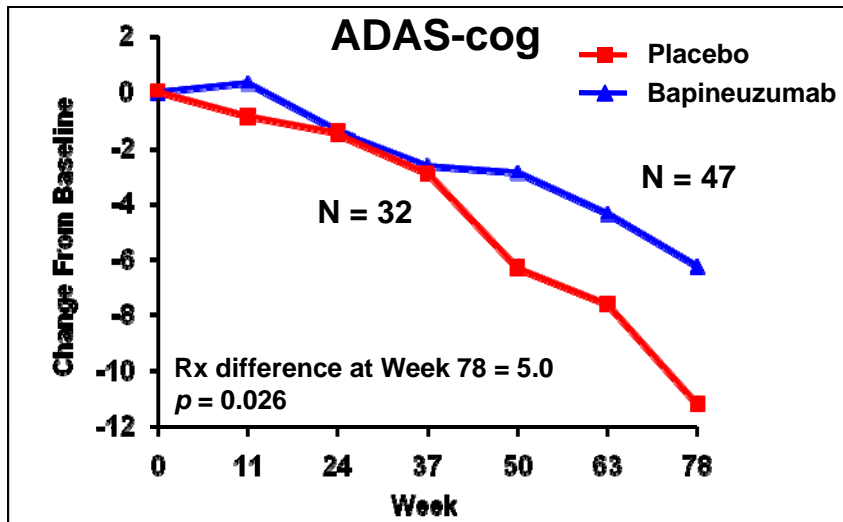
Completer: patient who had all 6 infusions and an efficacy assessment at Week 78

Bars above zero indicate improvement relative to placebo

Patient populations for "all doses" comparisons: bapineuzumab, N = 36; placebo, N = 21

# Clinical Efficacy Endpoints: ApoE4 Non-carrier Population (MITT)

MITT analysis using RM model without linearity assumption



# MRI Results Through Week 71 (MITT)

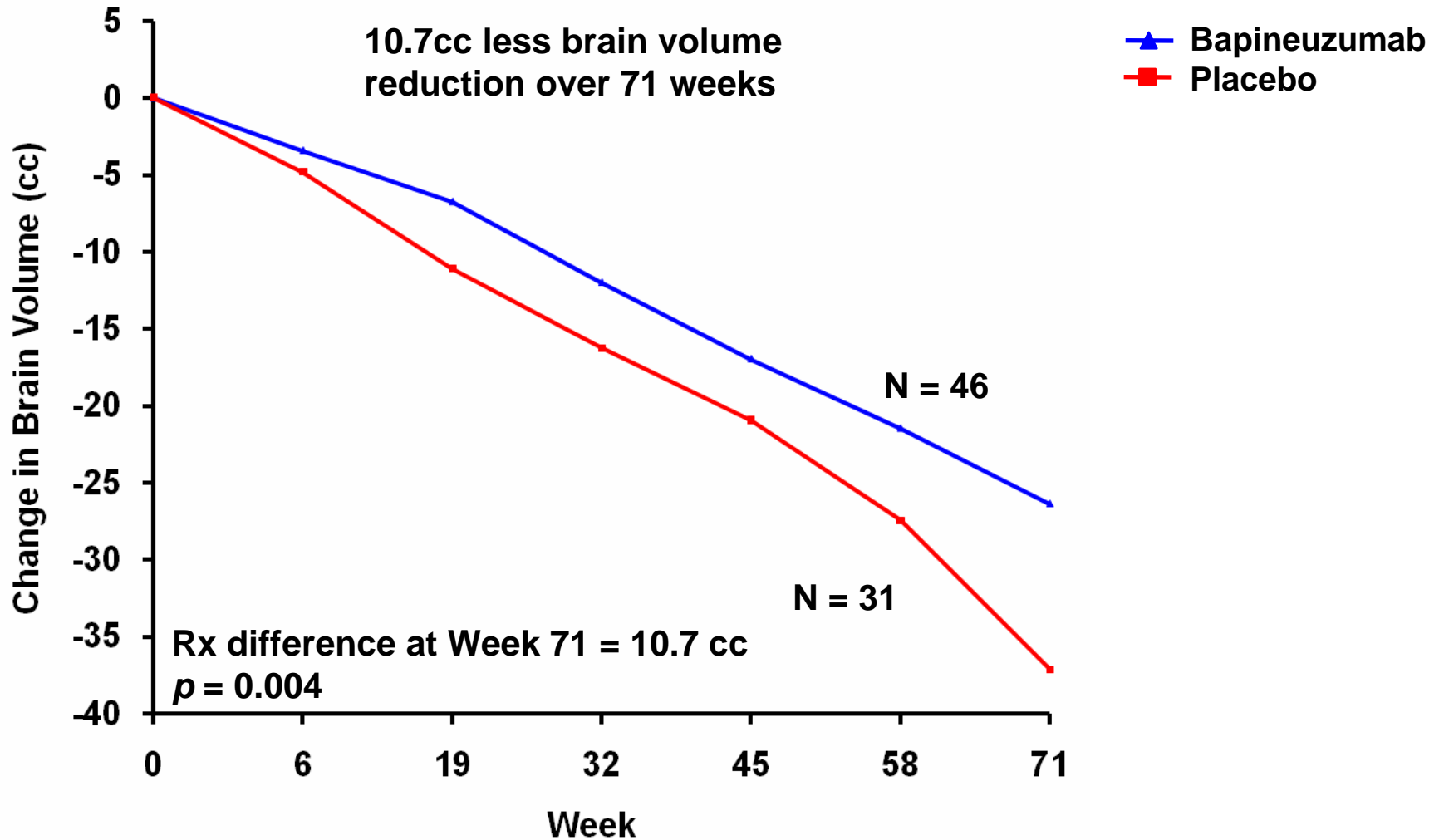
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- Total Population
  - No differences in total population in brain volume\* or ventricular volume\*\*
- Carriers
  - No significant change in brain volume
  - Significant increase in ventricular volume compared with placebo
    - Mean: 2.5 cc; 95% CI: 0.1 to 5.1 cc;  $p = 0.037$
  - Clinical relevance is unclear
- Non-carriers
  - Significantly less brain volume decline than placebo
    - Mean: 10.7 cc; 95% CI: 3.4 to 18.0 cc;  $p = 0.004$
  - Less enlargement in ventricular volume than placebo (nonsignificant)

\* Brain volume as measured by brain boundary shift integral (BBSI)

\*\* Ventricular volume as measured by ventricular boundary shift integral (VBSI)

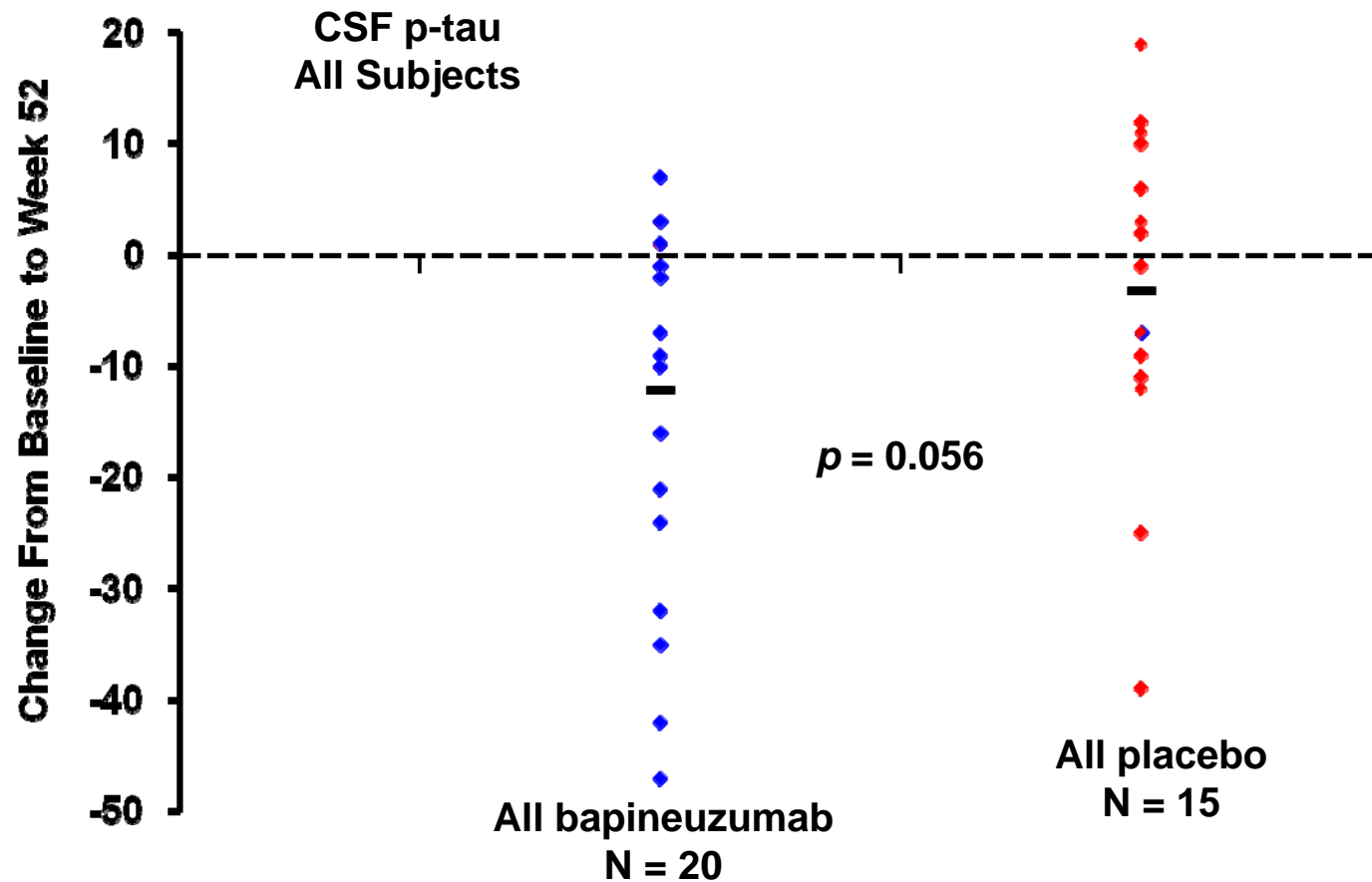
# Change in MRI Brain Volume\*: ApoE4 Non-carrier Population (MITT)



\* Brain volume as measured by brain boundary shift integral (BBSI)  
MITT analyses using RM model without assumption of linearity, adjusted for whole brain volume at baseline, MMSE at baseline and ApoE4 status

# CSF Biomarkers

- Phospho-tau (p-tau) levels trend lower at 52 weeks in bapineuzumab-treated patients versus placebo-treated patients
- No differences in CSF A $\beta$  or total tau



Based on ANCOVA; one outlier excluded in the 0.15 mg/kg placebo dose cohort

# Conclusions

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## Overall Assessment:

- Results support the design and further evaluation of bapineuzumab in the ongoing Phase 3 trials
- Bapineuzumab generally safe and well-tolerated
- VE dose related, more frequent in carriers which influenced in Phase 3 program design
- Pre-specified efficacy analysis did not reach significance in the total population

## In Post Hoc Analyses:

- Trends were observed in the cognitive endpoints ADAS-cog and NTB in the total population
- Evidence of significant efficacy in non-carriers (clinical and MRI)
- Favorable directional changes in carriers on some efficacy measures
- Potential efficacy signals over a range of doses without a clear dose response

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The logo for Elan features a green chevron pointing upwards and to the right, positioned above the letter 'e'. The word "elan" is written in a dark blue, lowercase, cursive script font.

*elan*

The logo for Wyeth consists of the word "Wyeth" written in a bold, red, serif font.

**Wyeth**