Highlights of Biomarker and Clinical Outcomes in Recent AD Treatment Trials

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BUTLER HOSPITAL

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Disclosure of Interest

Research Support

1. NIA-ADNI
2. NIA-DIAN
3. Alz Assoc-DIAN Clinical Trials
4. Fain Family Foundation, Champlin Foundation, White Family Foundation
5. Avid Radiopharmeceuticals

Speakers Bureau

Athena

Clinical Trials

Elan, Janssen AI, Baxter, BMS, Pfizer, Medivation, Genentech, GE, Avid, Roche, Merck, Biogen

Consultant

Janssen AI, Baxter, Pfizer, Athena, BMS, Merck, Lilly, Medivation

I own no stocks or equity in any pharmaceutical company

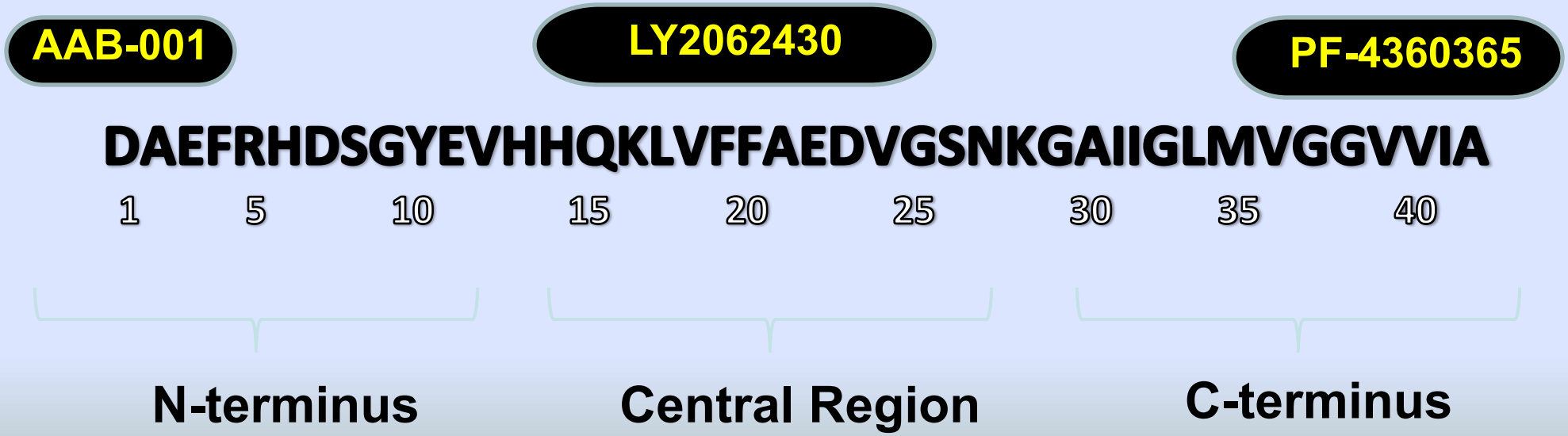
Butler Hospital Memory and Aging Program

Current AD passive immunotherapy trials employ sequence-specific anti-Aβ antibodies

Bapineuzumab (AAB-001)
(Elan, Wyeth)
- Humanized mouse monoclonal
- Binds first 5 a.a. of N-terminus
- Clears plaques and vascular Aβ

LY2062430
(Lilly)
- Humanized mouse Monoclonal
- Binds to amino acids 14-28
- Binds soluble Aβ not deposits

PF-4360365
(Pfizer)
- Binds to C-terminus
- Deglycosylated to decrease Fc effects
- Clears plaques, less microglial action



Bapineuzumab Trial Design

- Multi-center randomized double-blind, placebo-controlled, 18-month clinical trials in mild-moderate AD dementia (MMSE 16-26)
- APOE ε4 carriers: Bapineuzumab 0.5 mg/kg or placebo (ratio 3:2)
- Non-carriers: Bapineuzumab 0.5 mg/kg, 1.0 mg/kg or placebo (ratio 3:3:4)
  - 2 mg/kg dose terminated early in Phase 3 due to amyloid-related imaging abnormalities (ARIA)
- **Primary Clinical Endpoints:**
  - Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog 11)
  - Disability Assessment for Dementia (DAD)
- **Key Biomarker Secondary Endpoints:**
  - Brain amyloid burden on PiB PET
  - CSF phospho-tau
  - MRI brain volume
- **Schedule of Events:**
  - 6 infusions every 13 weeks
  - MRI monitoring for ARIA ~6 weeks after each infusion

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp

Analysis Populations

Study 302
APOE ε4
Carriers
Total Randomized
N = 1121

Population	Placebo N (%)	Bapineuzumab 0.5 mg/kg N (%)
Randomized (Safety population)	**448** (100.0)	**673** (100.0)
mITT	**432** (96.4)	**658** (97.8)
PiB PET	**40** (8.9)	**75** (11.1)
CSF	**85** (19.0)	**127** (18.9)
vMRI	**238** (53.1)	**352** (52.3)

Study 301
Non-Carriers
Total Randomized
N = 1331

Population	Placebo N=524 (%)	Bapineuzumab 0.5 mg/kg N=337 (%)	Bapineuzumab 1.0 mg/kg N=329 (%)
Randomized (Safety population)	**524** (100.0)	**337** (100.0)	**329** (100.0)
mITT	**493** (94.1)	**314** (93.2)	**307** (93.3)
PiB PET	**15** (2.9)	**12** (3.6)	**12** (3.6)
CSF	**77** (14.7)	**47** (13.9)	**54** (16.4)
vMRI	**244** (46.6)	**169** (50.1)	**146** (44.4)

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Baseline Demographics – mITT Population
Study 302 APOE ε4 Carriers

Total Randomized N = 1121

	Placebo (N=432)	Bapineuzumab (N=658)
Age, y (SD)	**72.3** (8.4)	**72.0** (8.0)
Gender (% female)	**242** (56.0)	**358** (54.4)
Race (% Caucasian)	**420** (97.2)	**624** (94.8)
APOE ε4: **% heterozygote ε4** **% homozygote ε4**	 **325** (75.2) **107** (24.8)	 **495** (75.2) **163** (24.8)
AChEI or memantine use (%)	**400** (92.6)	**606** (92.1)
MMSE total score (SD)	**20.7** (3.2)	**20.8** (3.1)
ADAS-Cog 11 total score (SD)	**23.9** (9.5)	**23.5** (9.4)
DAD total score (SD)	**79.4** (18.9)	**80.9** (17.3)

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Baseline Demographics – mITT Population
Study 301 APOE ε4 Non-Carriers

Total Randomized N = 1331*

	Placebo (N=493)	Bapineuzumab 0.5 mg/kg (N=314)	Bapineuzumab 1.0 mg/kg (N=307)
Age, y (SD)	**71.9** (10.1)	**73.1** (9.3)	**73.5** (9.1)
Gender (% female)	**248** (50.3)	**165** (52.5)	**175** (57.0)
Race (% Caucasian)	**469** (95.1)	**298** (94.9)	**292** (95.1)
AChEI or memantine use, (%)	**442** (89.7)	**281** (89.5)	**278** (90.6)
MMSE total score (SD)	**21.2** (3.2)	**21.2** (3.4)	**21.2** (3.3)
ADAS-Cog 11 total score (SD)	**22.2** (10.1)	**22.4** (9.7)	**22.2** (10.0)
DAD total score (SD)	**80.5** (19.2)	**80.0** (18.1)	**80.4** (18.8)

*Bapineuzumab 2.0 mg/kg group (n=141) discontinued early in the course of study; primary cognitive and functional outcomes will not be presented

Solanezumab Trial Design

- Two, multi-center randomized double-blind, placebo-controlled, 18-month clinical trials in mild-moderate AD dementia (MMSE 16-26), Expedition 1 and 2
- Dose: 400 mg IV every 4 weeks

- **Primary Clinical Endpoints:**
  - Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog 11)
  - ADCS Activities of Daily Living (ADCS ADL)
  - ADAS-Cog 14 became the single primary outcome for Expedition 2 based on Expedition 1 data

- **Biomarker Secondary Endpoints:**
  - Plasma Ab
  - Brain amyloid burden on Florbetapir PET
  - CSF Ab and phospho-tau
  - MRI brain volume

Doody, ANA Annual Meeting 2012

EXP 1 Baseline Demographics

	Placebo N=506	Solanezumab N=506	Total N=1012	P-Value
Age (yrs)	74.5	75.3	74.9	0.15
% Female	287 (57%)	299 (59%)	586 (58%)	0.46
Education (yrs)	12.8	12.6	12.7	0.54
%APOE4+	288 (61%)	266(57%)	554(59%)	0.23
Screening MMSE	21.0	21.1	21.0	0.93
ADASCOG11	21.8	21.8	21.8	0.64
CDR-SB	5.1	5.0	5.0	0.20

Primary Clinical Outcomes

- Primary outcomes for bapineuzumab carrier, non-carrier, pooled, mild and moderate were not significant
- Primary outcomes for solanezumab were negative
- Mild benefit seen in solanezumab mild group, MMSE $\geq$ 20, mostly on ADAS-Cog (Exp 1, pooled, and pooled mild)
- Rate of decline increased by stage in both studies

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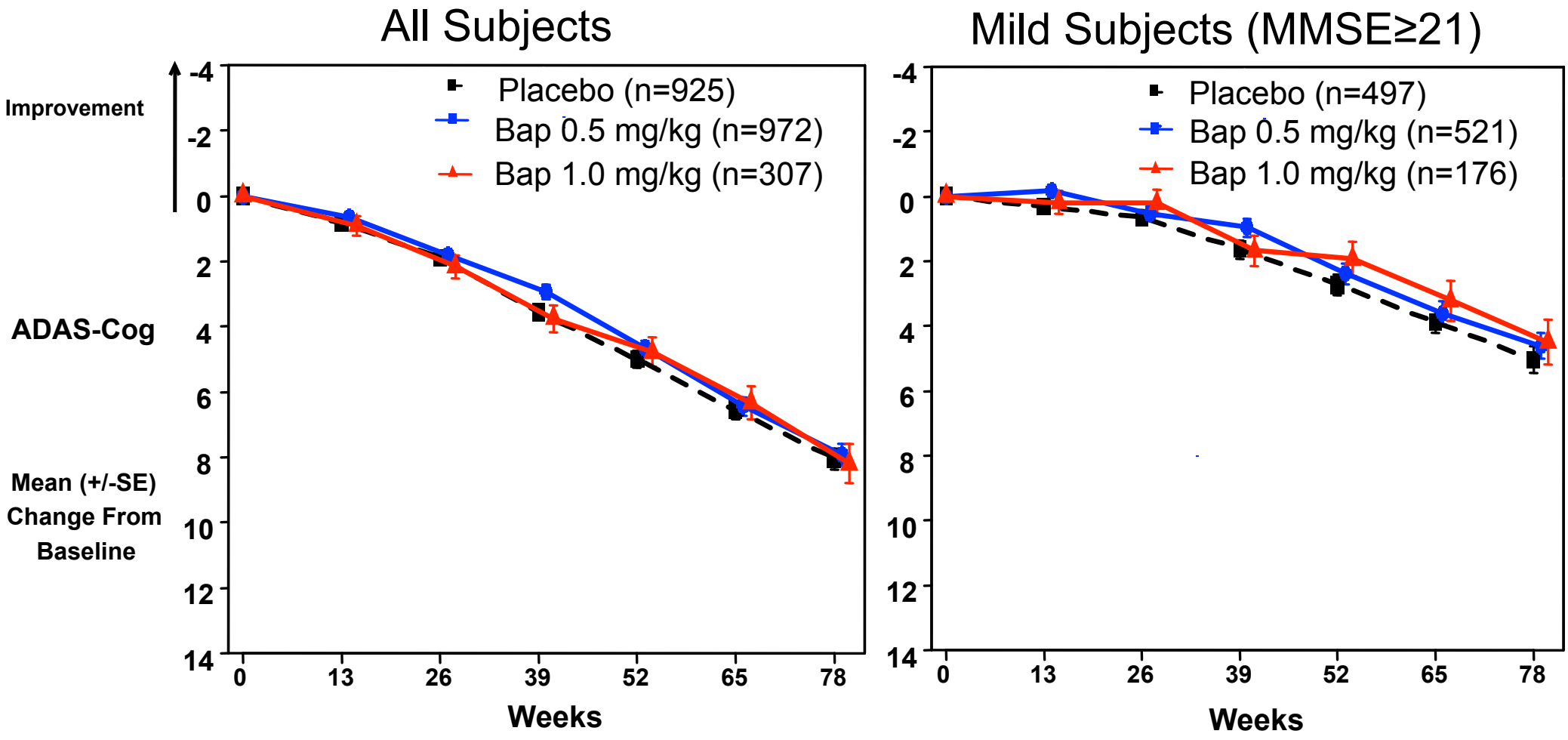
Pooled 302/301: Change in ADAS-Cog 11 by Treatment Group Over 78 Weeks (mITT population)



Placebo vs Bap 0.5 mg/kg **p=0.793**
Placebo vs Bap 1.0 mg/kg **p=0.842**

Placebo vs Bap 0.5 mg/kg **p=0.465**
Placebo vs Bap 1.0 mg/kg **p=0.513**

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Solanezumab Efficacy Results Summary

p values for solanezumab-placebo difference at 80 weeks

	EXP1 overall	EXP1 mild		EXP2 overall	EXP2 mild		Pooled overall	Pooled mild
Cognitive								
$ADAScog_{11}$	**.312**	.008		.060	.097		.042	.001
$ADAScog_{14}$	.155	.006		.075	**.120**		.025	.001
MMSE	.067	.002		.004	.099		.002	.001
Functional								
ADCS-ADL	**.931**	.302		.062	.076		.217	.057
ADCS-iADL	.919	.319		.080	.029		.250	.045

BOLD = primary outcome(s)
RED = statistical significance

Doody, ANA Annual Meeting 2012

Secondary Clinical Endpoints

- **Bapineuzumab**
  - In the overall study population, no differences were seen in NTB, MMSE or CDR-SB in either study 302 or 301
  - Analyses in mild and moderate subgroups are ongoing
- **Solanezumab**
  - MMSE-trend or significant for mild group in Expedition 1 and 2 and pooled mild and pooled all
  - No difference seen in CDR-SB for pooled and mild
  - NPI-no difference

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Biomarker Outcomes

Amyloid PET

- 93% of ApoE4 carriers met the amyloid cut-off for both studies
- 36% and 33% of ApoE4 non-carriers in bapineuzumab and solanezumab did not meet the amyloid cut-off
- Bapineuzumab-mild significant difference in amyloid load in carriers, pooled all and pooled mild, with no difference in non-carriers
  - Amyloid lowering less than phase 2 (Rinne 2010)
- Solanezumab-no difference in florbetapir pooled
  - Increase in plasma $A\beta_{42}$

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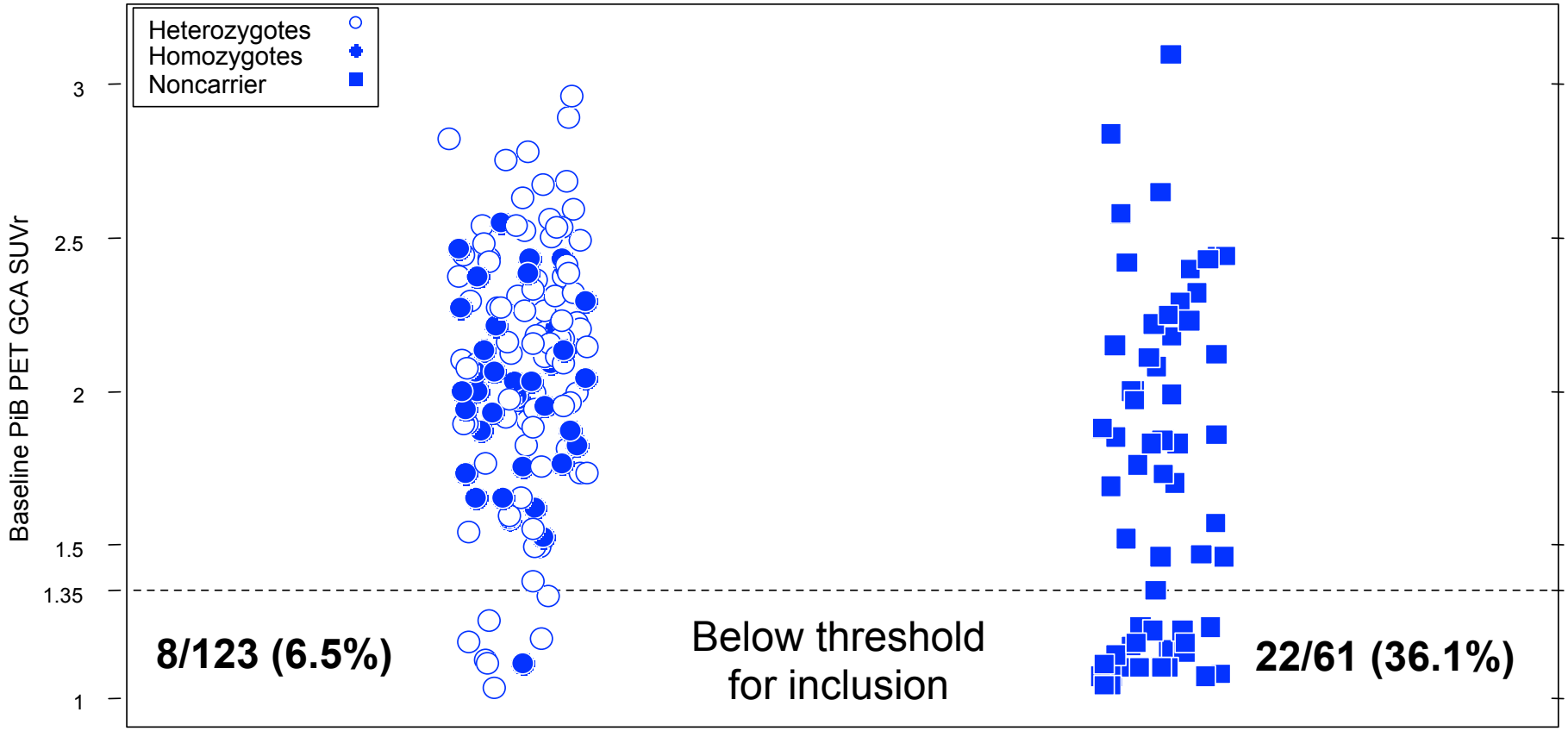
Distribution of PIB PET Global Cortical Average SUVr



	Carrier GCA SUVr	Non-Carrier GCA SUVr	P-value
All PiB PET analysis population	2.07	1.72	p<0.0001
PiB PET analysis population	2.14	2.05	p=0.18

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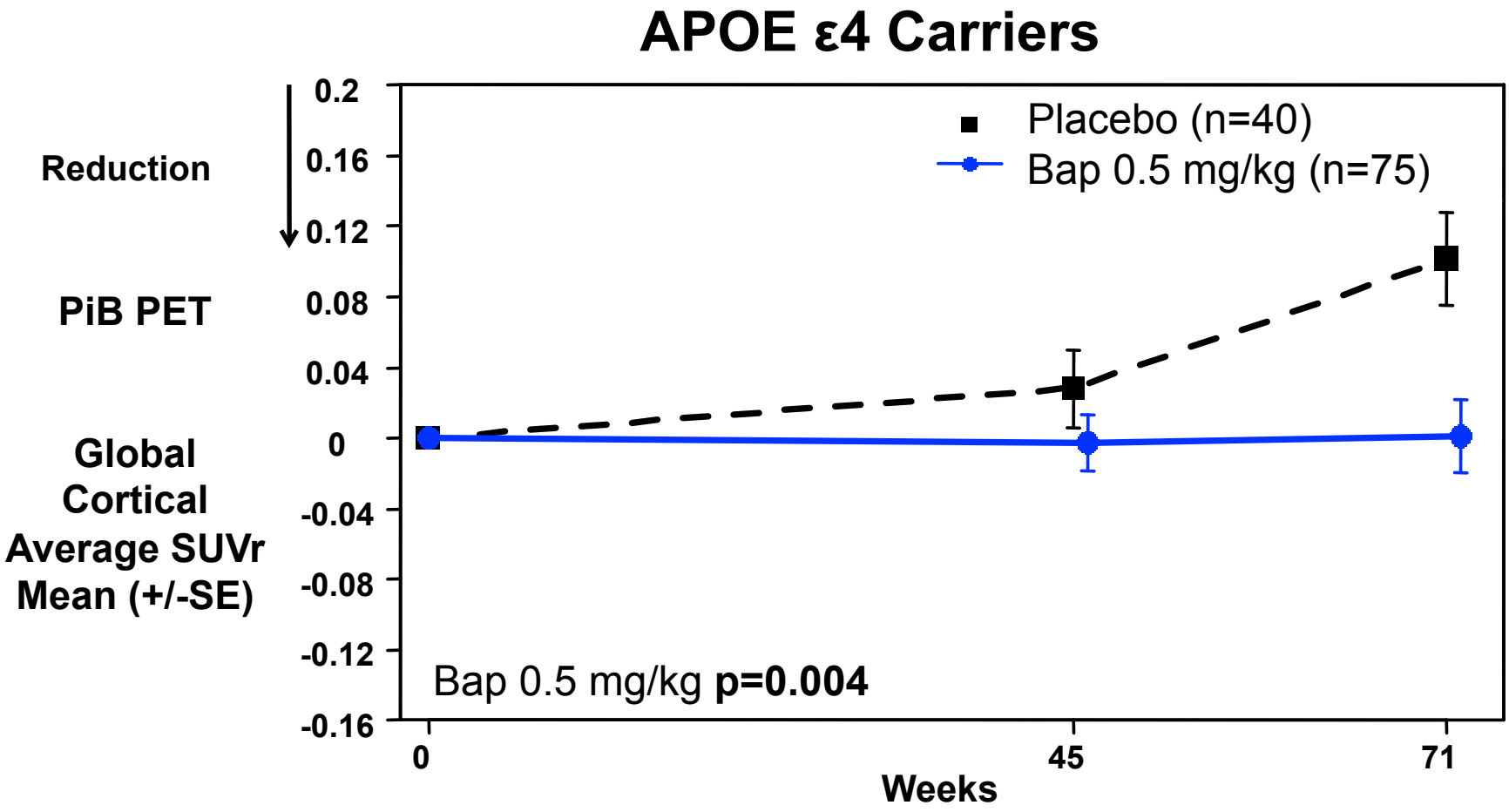
Change in Amyloid Burden as assessed by [^{11}C] PiB-PET at Week 71 APOE ε4 Carriers (PiB PET analysis population)



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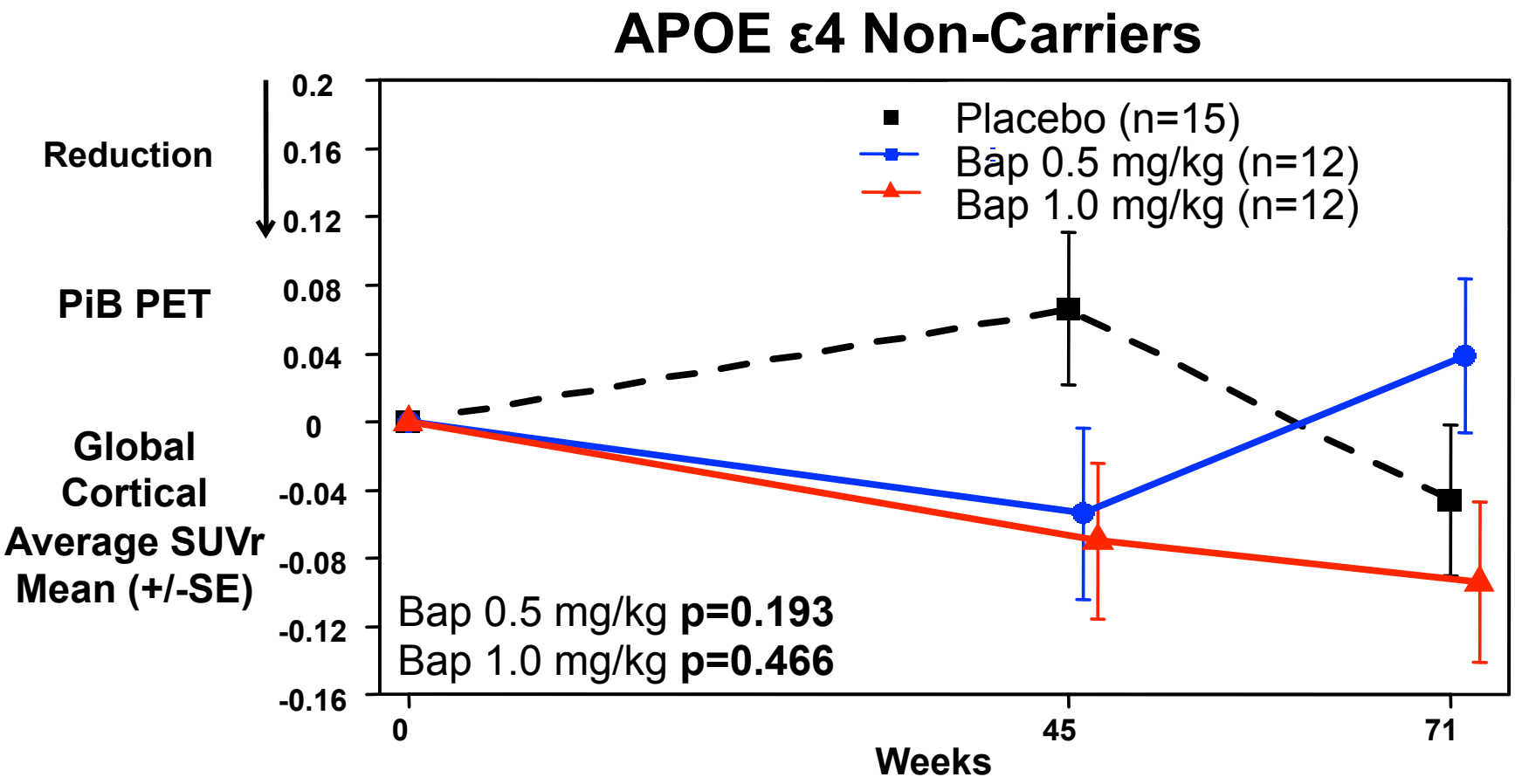
Change in Amyloid Burden as assessed by [^{11}C] PiB-PET at Week 71 APOE ε4 Non-Carriers (PiB PET analysis population)



Pre-specified primary analyses of pooled bapineuzumab doses was not significant, **p=0.724**

Post hoc exploratory analysis showed a within cohort trend for reduction in PiB PET at 1.0 mg/kg dose (nominal p = 0.057)

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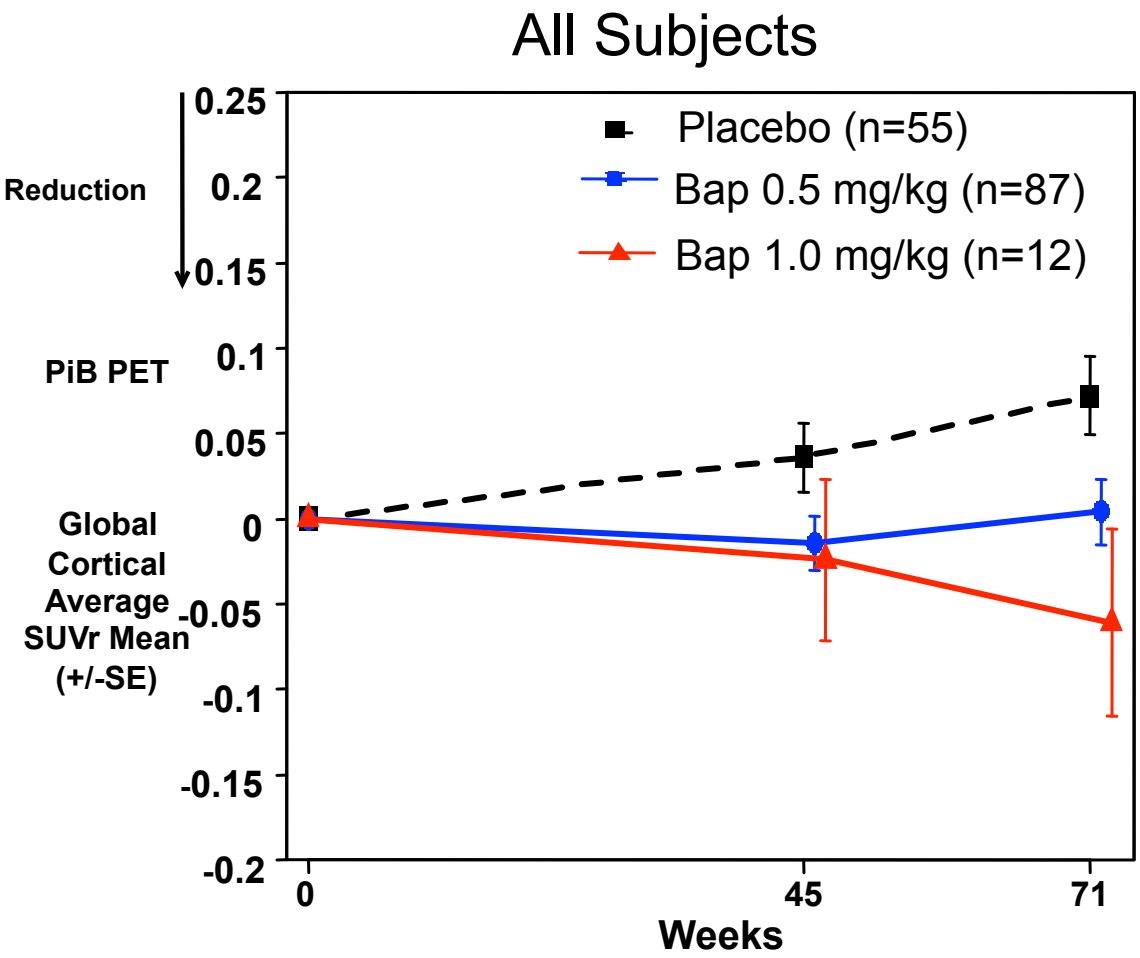
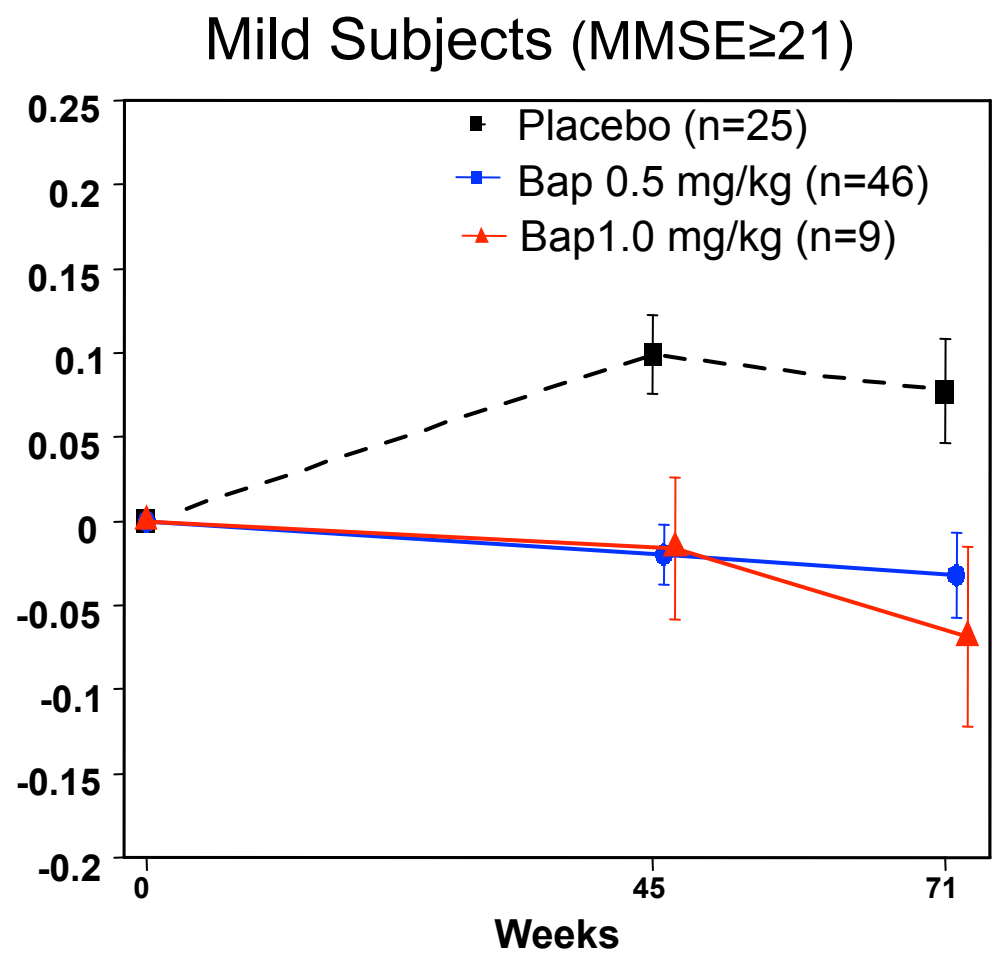
Pooled 302/301: Change in Amyloid Burden as assessed by [^{11}C] PiB-PET at Week 71 (PiB PET analysis population)



Placebo vs Bap 0.5 mg/kg p=**0.027**
Placebo vs Bap 1.0 mg/kg p=**0.028**



Placebo vs Bap 0.5 mg/kg p=**0.009**
Placebo vs Bap 1.0 mg/kg p=**0.020**

No significant effect in moderate group

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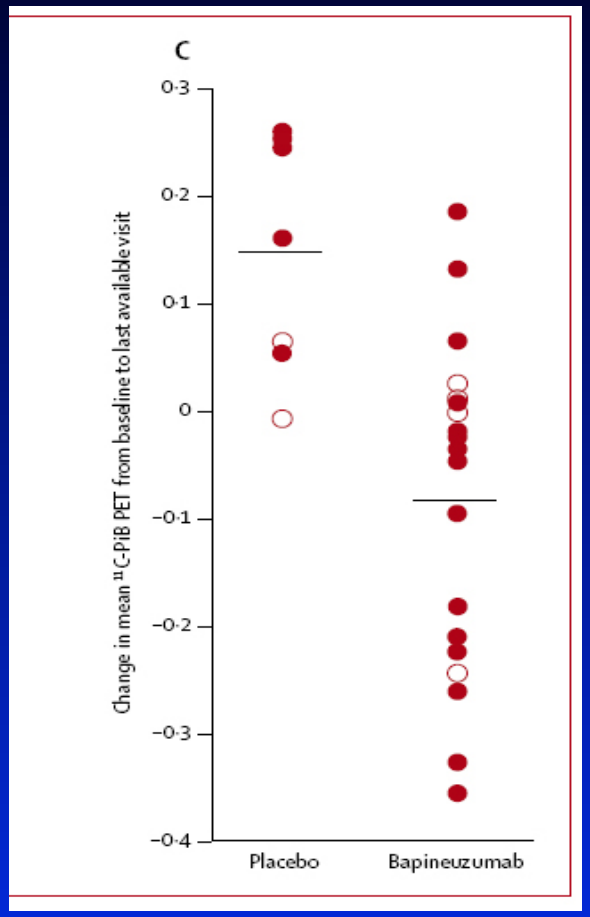
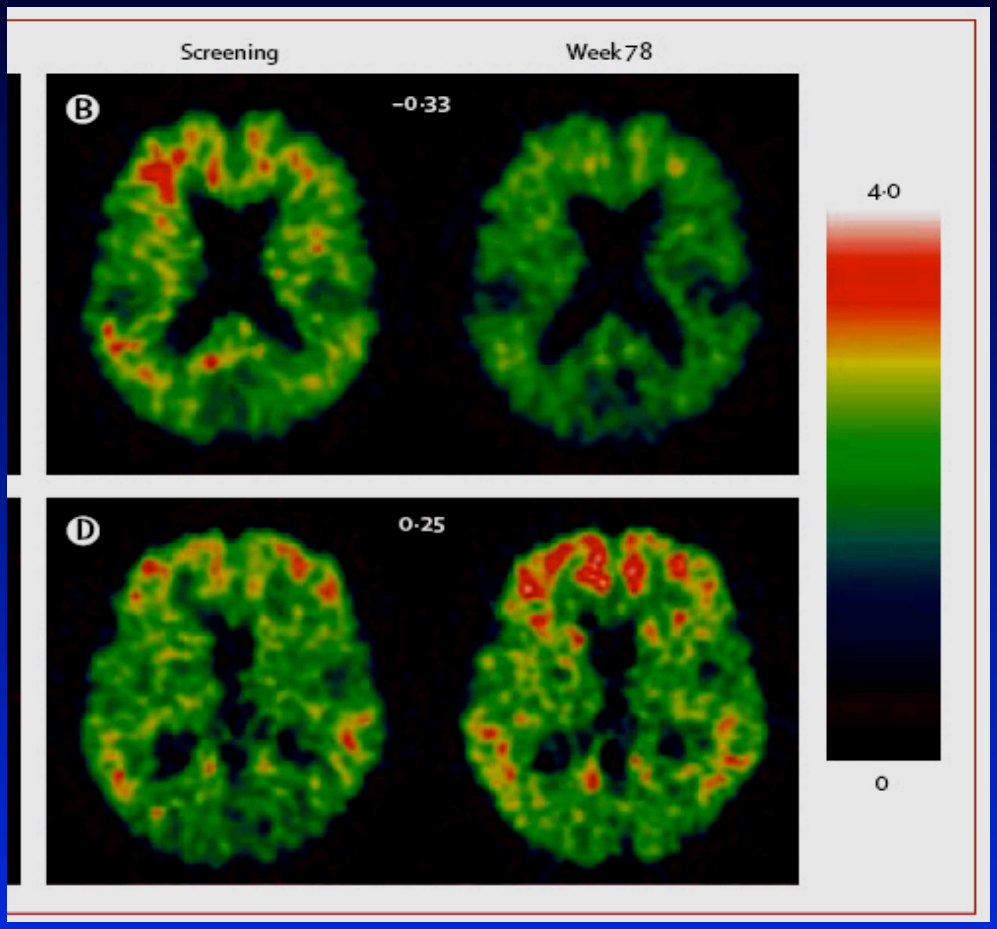
Change in C11 PIB in Bapineuzumab 202





Rinne Lancet Neurology 2010

- Gantenerumab -15.6% 60 mg and -35.7% 200 mg Ostrowitzki, 2011

CSF Phospho-tau, Total tau and $A\beta_{42}$

- Phospho-tau
  - Bapineuzumab-mild significant decrease in phospho-tau in carriers, 1.0 mg non-carriers, pooled all and pooled mild
  - Solanezumab-no difference in phospho-tau
- Total tau
  - Bapineuzumab-no differences seen in carriers or pooled studies, decrease only observed in non-carriers only at 1.0 mg/kg dose
  - Solanezumab-no difference in total tau
- $A\beta_{42}$
  - Bapineuzumab-no difference
  - Solanezumab-increase in total $A\beta_{42,}$ no change in free $A\beta_{42}$

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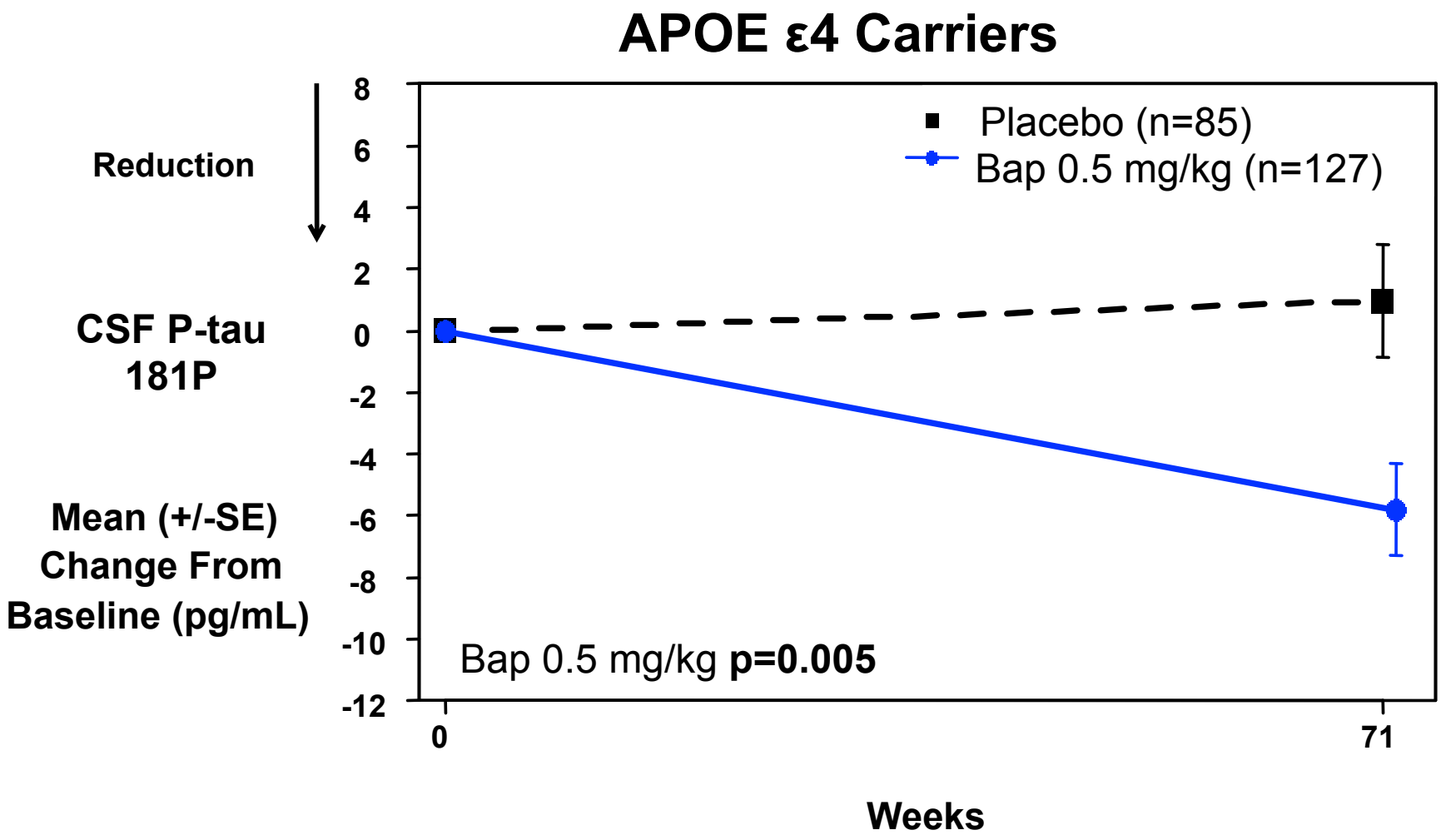
Change in CSF Phospho-tau by Treatment Group at Week 71
APOE ε4 Carriers (CSF analysis population)



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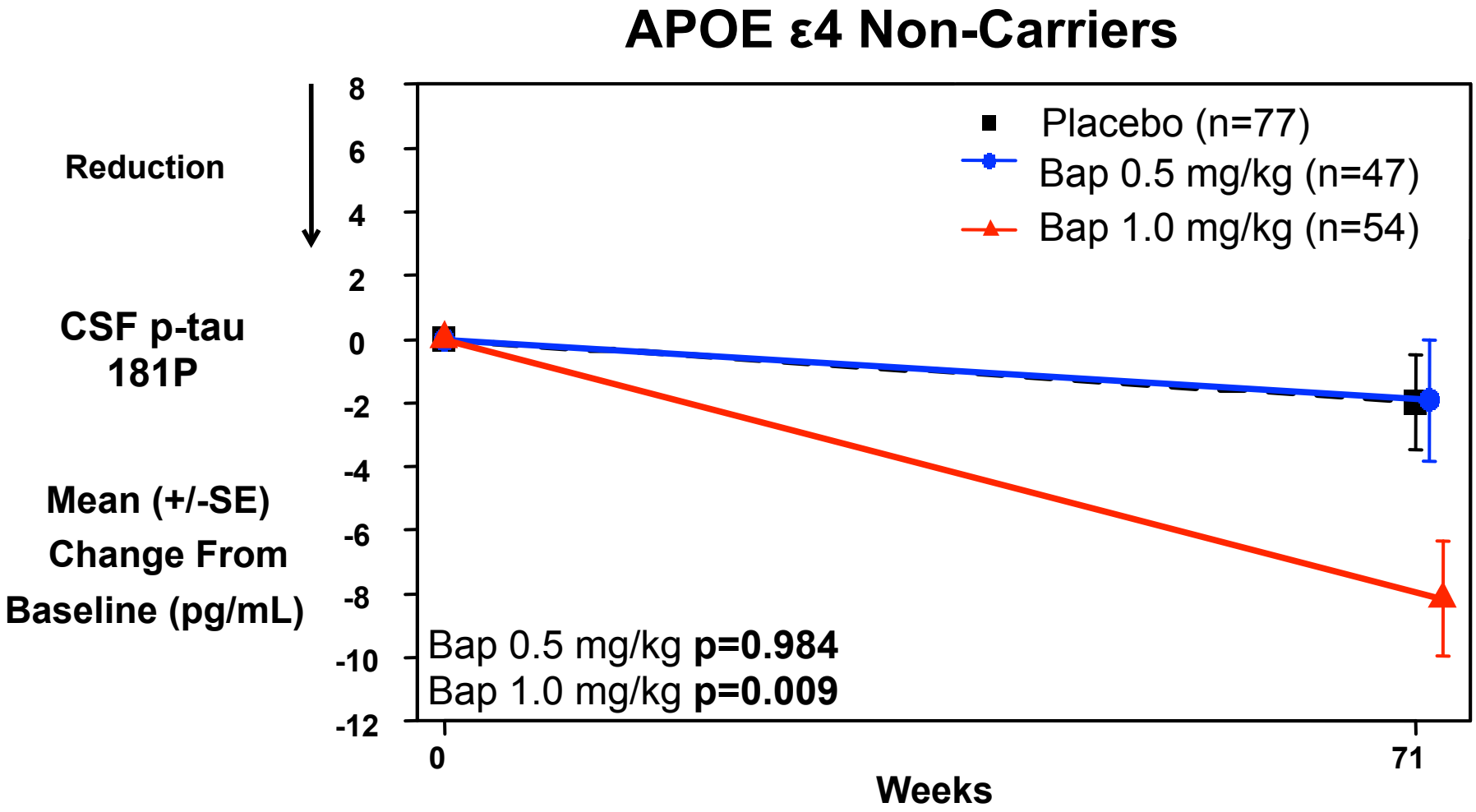
Change in CSF phospho-tau by Treatment Group at Week 71
APOE ε4 Non-Carriers (CSF analysis population)



*Pre-specified primary analyses of pooled bapineuzumab doses was not significant, **p=0.106**

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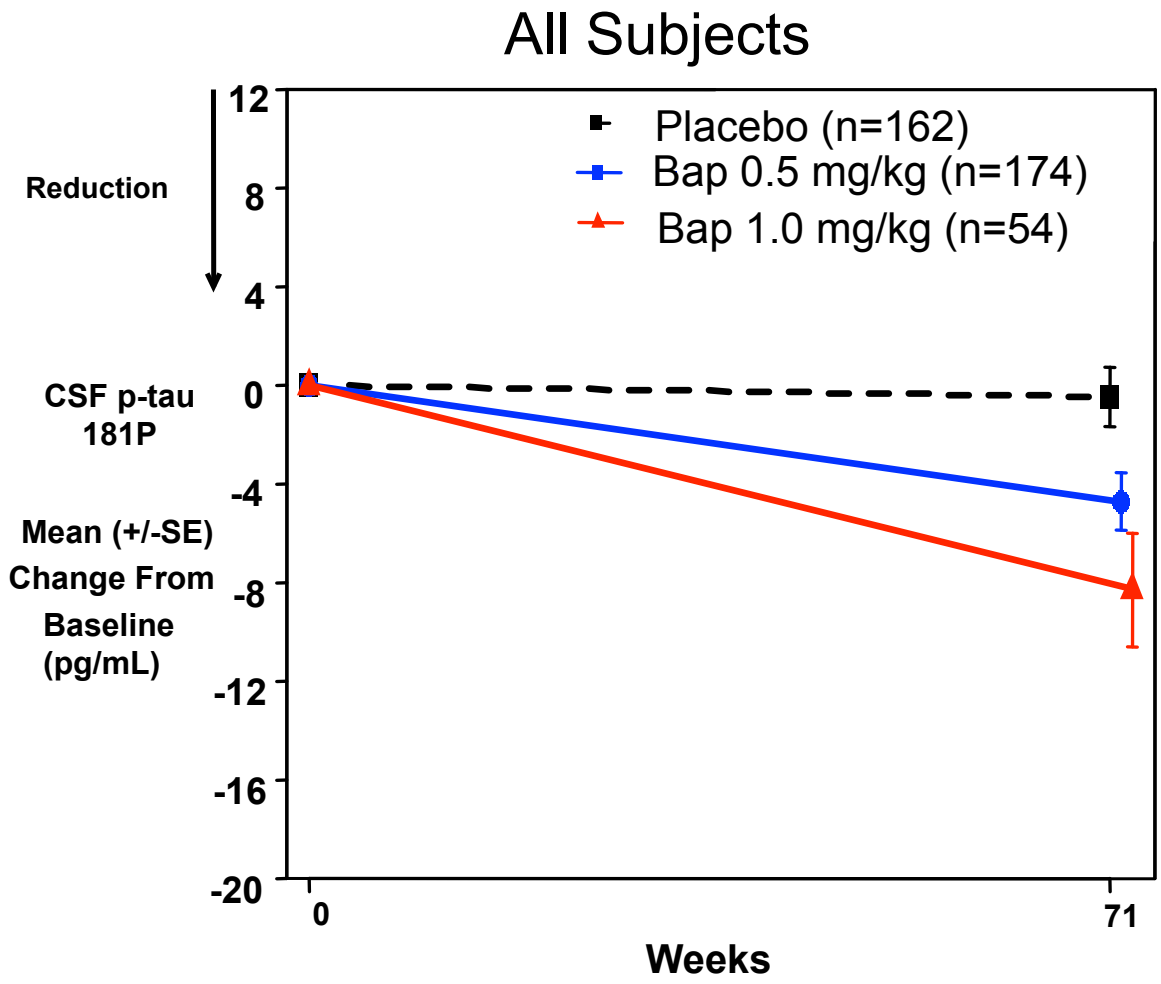
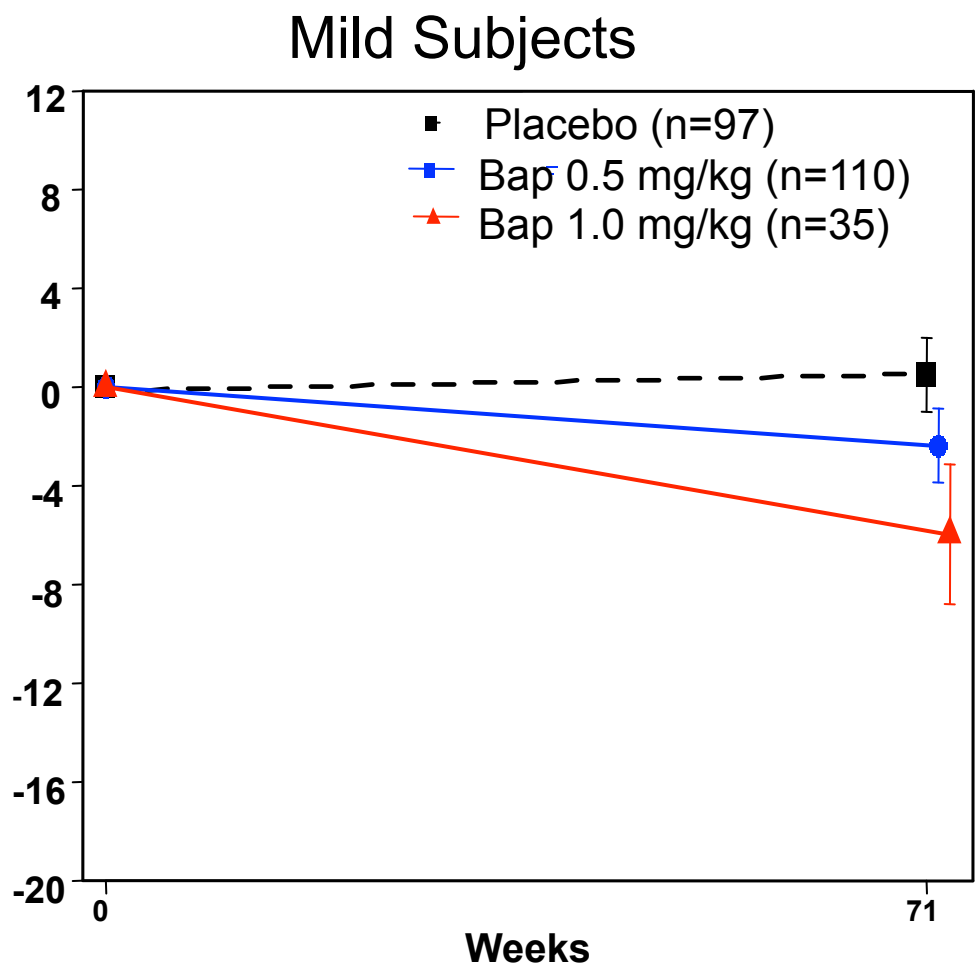
Pooled 302/301: Change in CSF phospho-tau by Treatment Group at Week 71 (CSF analysis population)





Placebo vs Bap 0.5 mg/kg **p=0.014**
Placebo vs Bap 1.0 mg/kg **p=0.002**

Placebo vs Bap 0.5 mg/kg **p=0.185**
Placebo vs Bap 1.0 mg/kg **p=0.041**

Significant effect at both doses in moderate group

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Examples of CSF Outcomes in Other AD Clinical Trials

- CSF
  - AN1792-decreased CSF tau but no change in $A\beta_{42}$ in antibody responders (Gilman, 2005)
  - Scyllo-inositol-decreased $A\beta_{42}$ but no difference in tau or p-tau (Salloway, 2011)
  - Avagasestat phase 2-decrease in CSF $A\beta_{1\text{-}42}$ at highest dose only (Coric, 2012)
  - Solanezumab phase 2-12 weekly doses, dose-dependent increase in plasma and CSF total $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ (bound and unbound) and increase in unbound CSF $A\beta_{1\text{-}42}$ (Farlow, 2012)
  - Bapineuzumab phase 2-decreased p-tau and trend for decreased tau but no difference in $A\beta_{42}$ (Blennow 2012)

Volumetric MRI

- Rate of cortical atrophy
  - Bapineuzumab-no difference in carriers and non- carriers, slight increase in pooled 1.0 mg and pooled mild
  - Solanezumab-no difference
- Increase in ventricular volume
  - Bapineuzumab-increase in ventricular volume in carriers, 1.0 mg non-carriers, pooled all and pooled mild
  - Solanezumab-no difference

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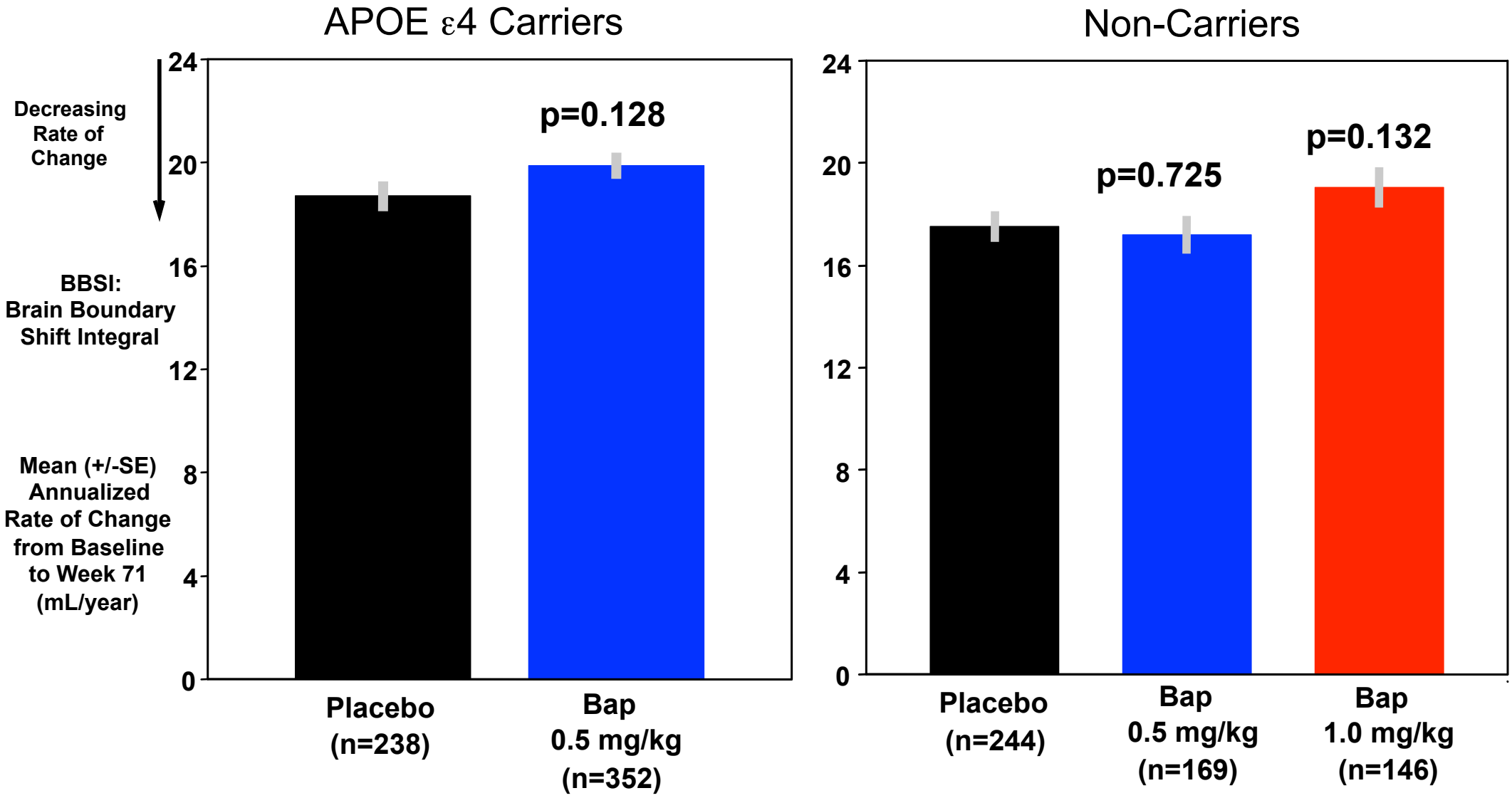
Rate of Change in MRI Brain Volume (BBSI) by Treatment Group at Week 71 (vMRI analysis population)



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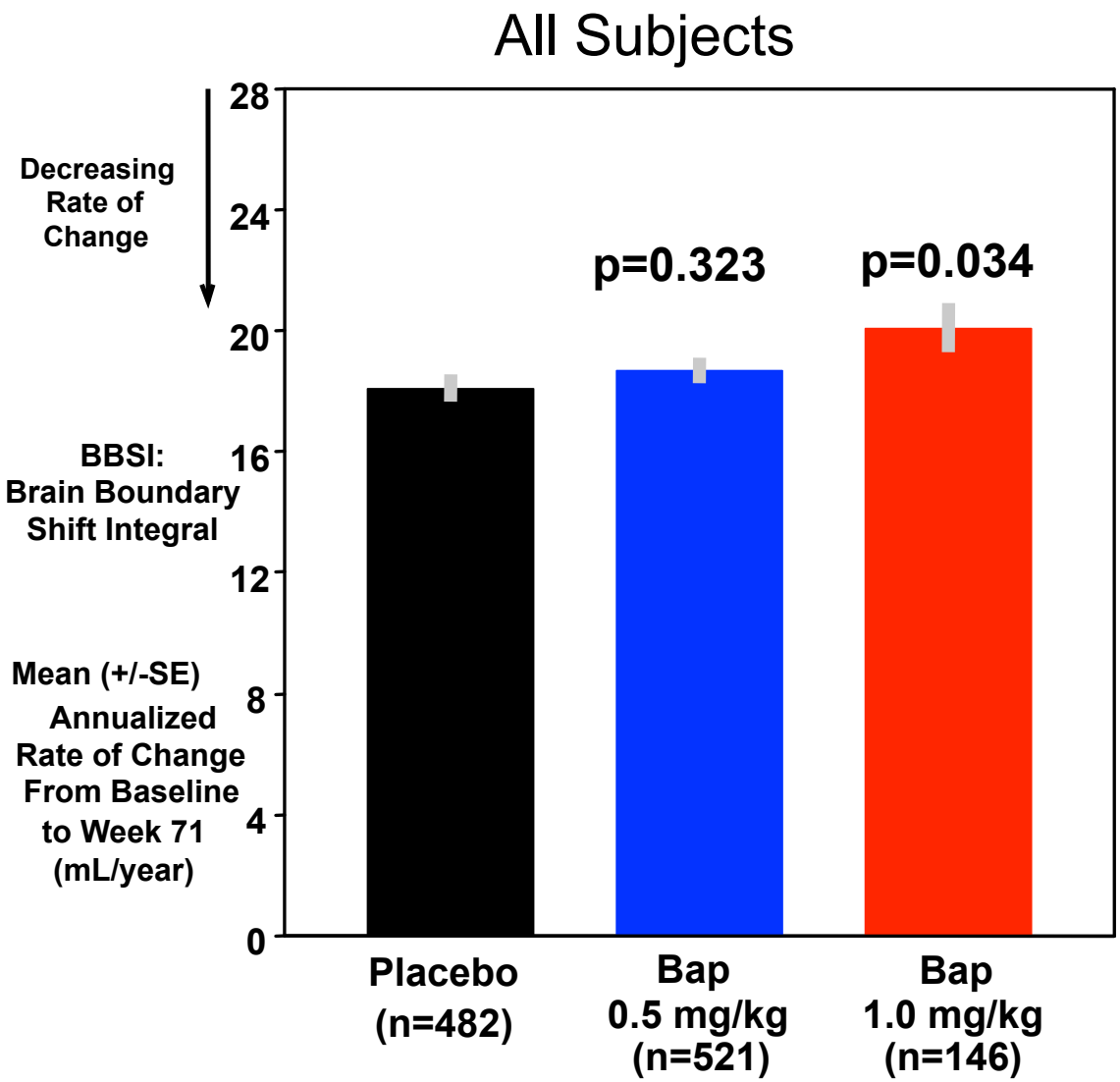
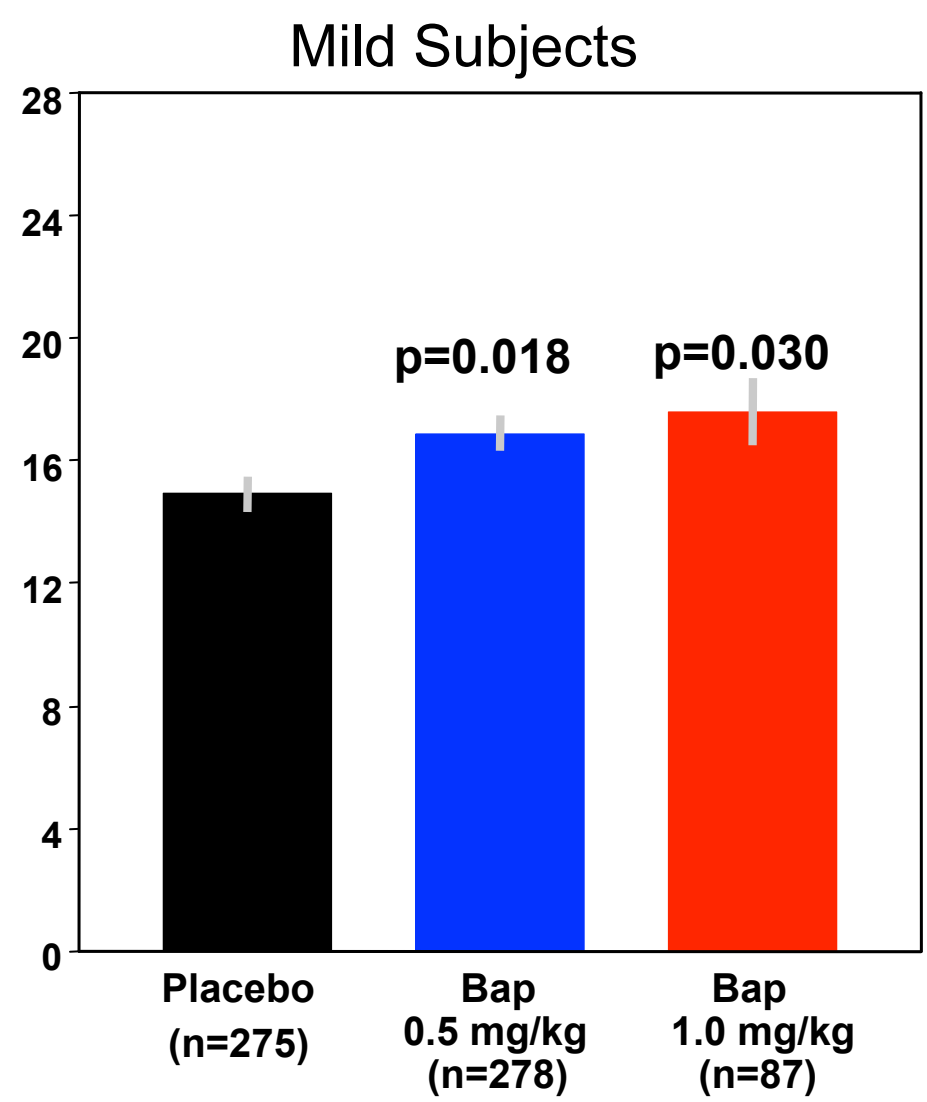
Pooled 302/301: Rate of Change in MRI Brain Volume (BBSI) by Treatment Group at Week 71 (vMRI analysis population)

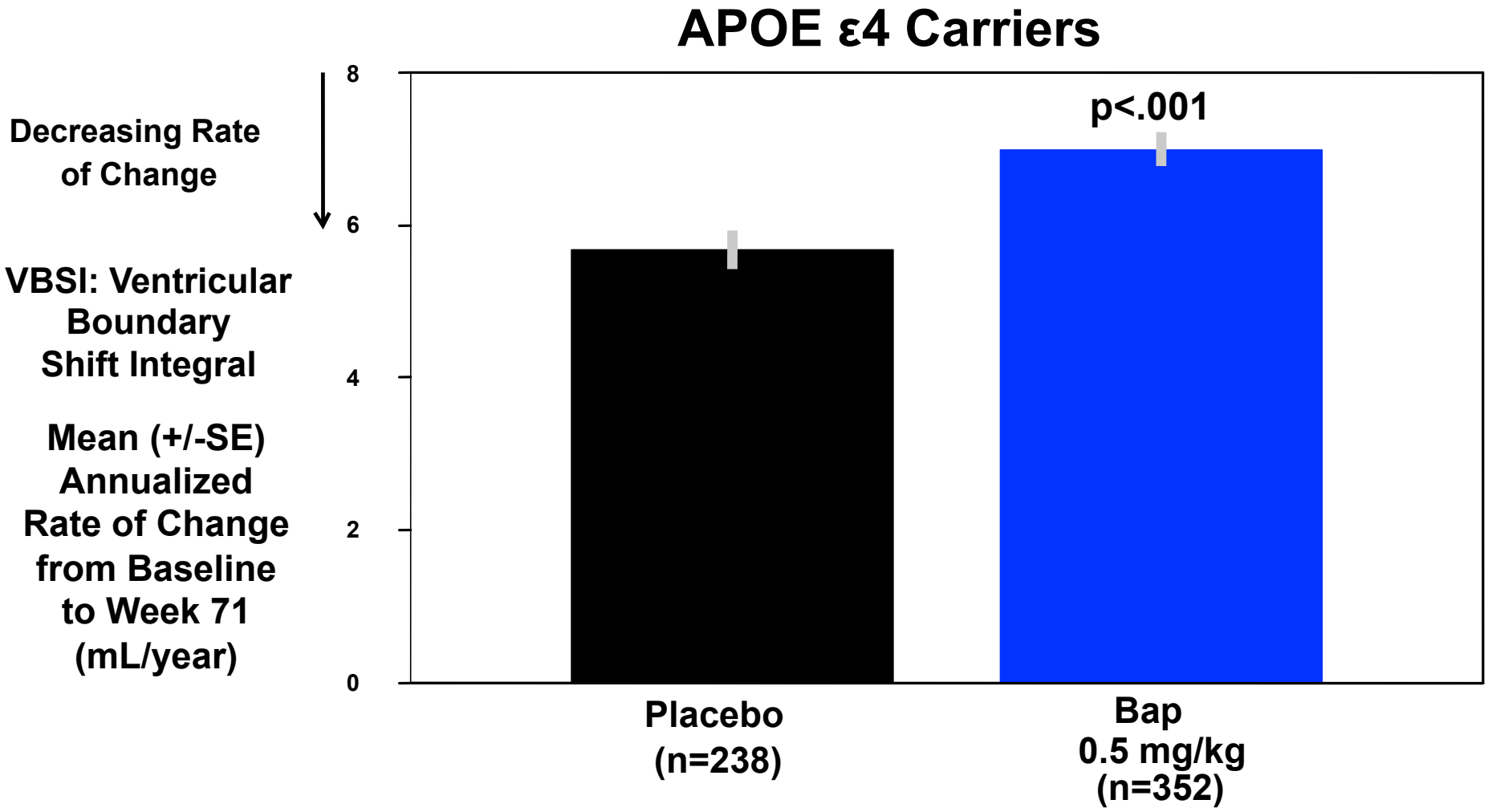




No significant effect in moderate group

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp

Rate of Change in MRI Ventricular Volume (VBSI) by Treatment Group at Week 71 (vMRI analysis population)



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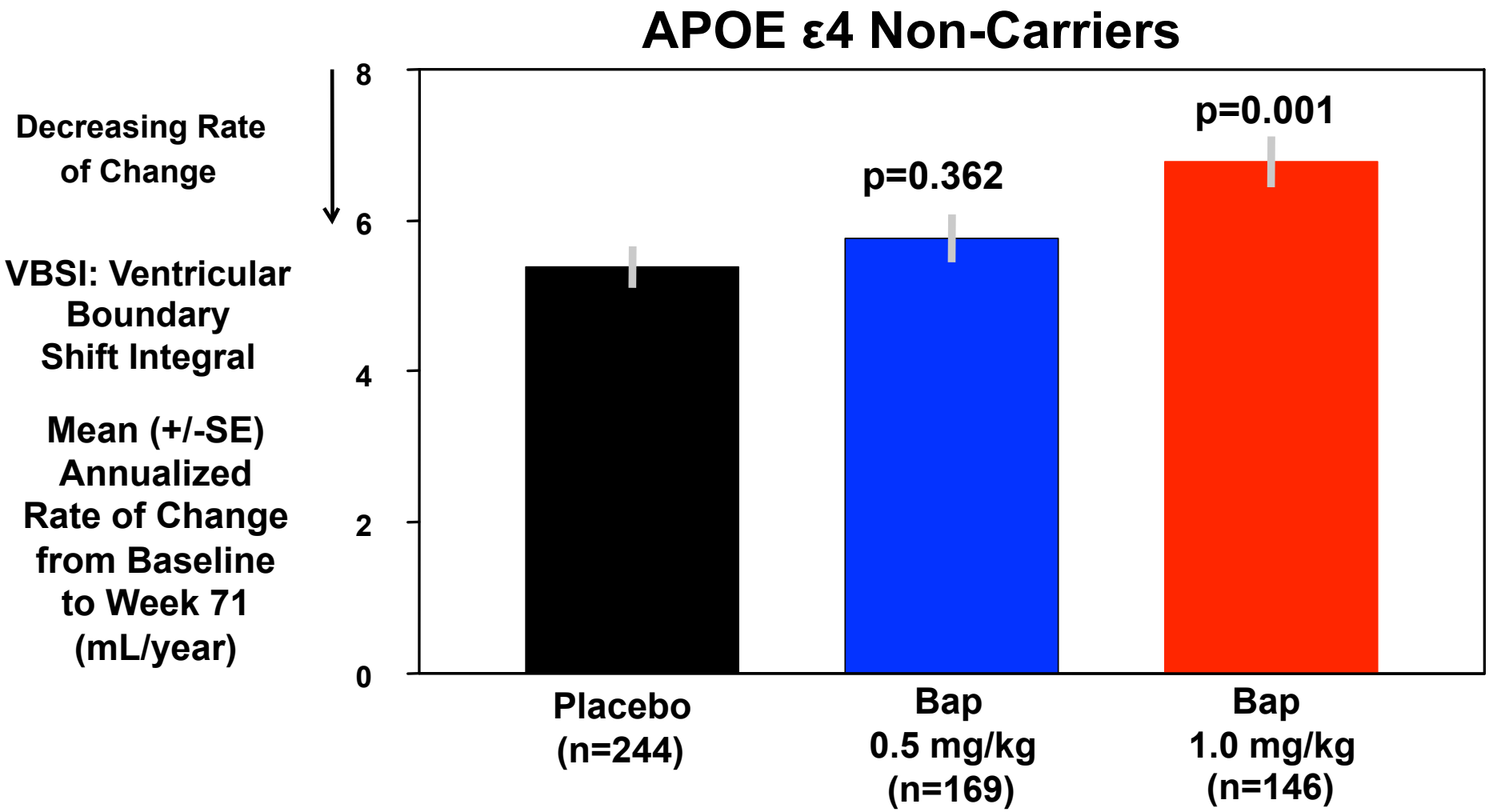
Rate of Change in MRI Ventricular Volume (VBSI) by Treatment Group at Week 71 (vMRI analysis population)



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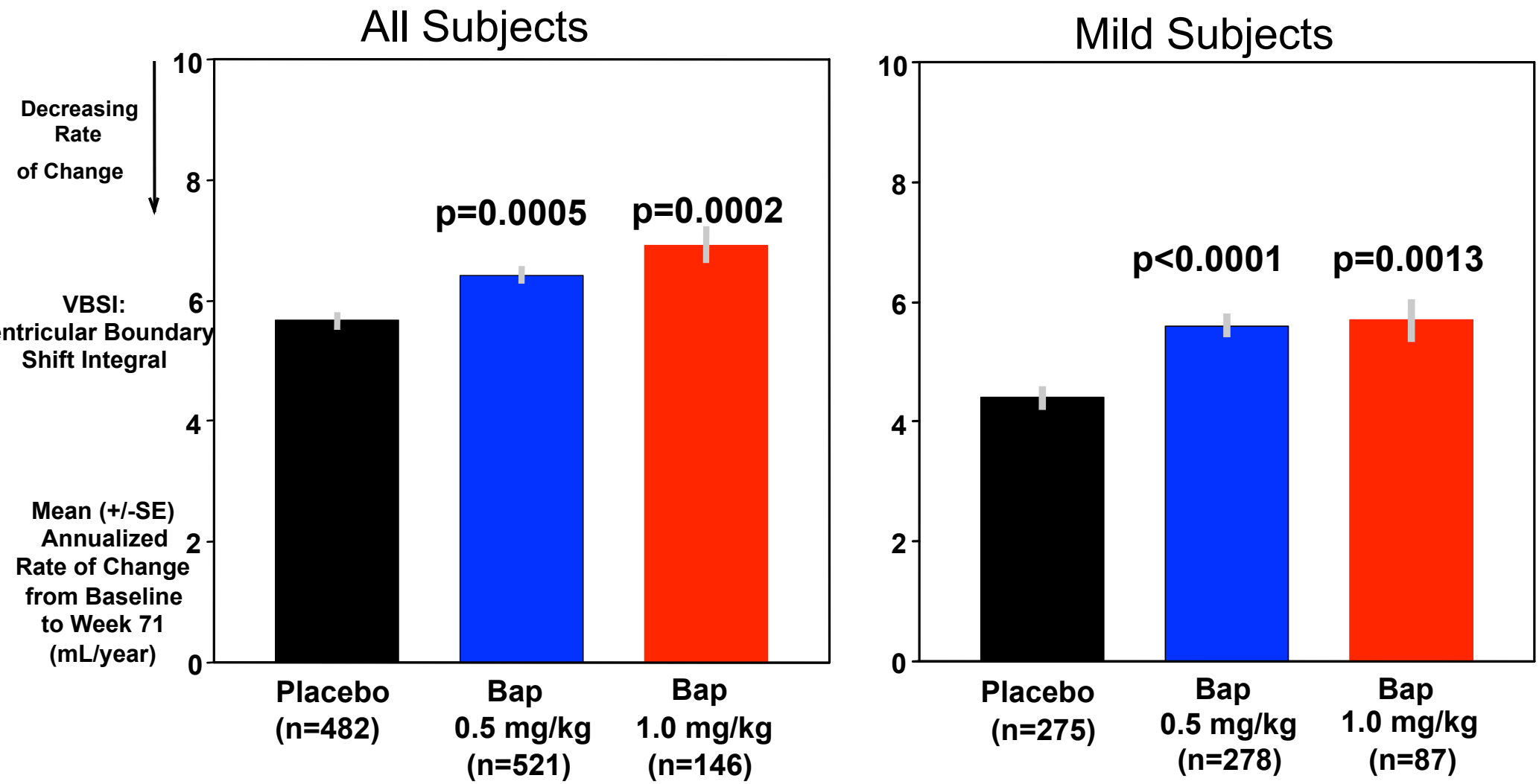
Pooled 302/301: Rate of Change in MRI Ventricular Volume (VBSI) by Treatment Group at Week 71 (vMRI analysis population)



No significant effect in moderate group

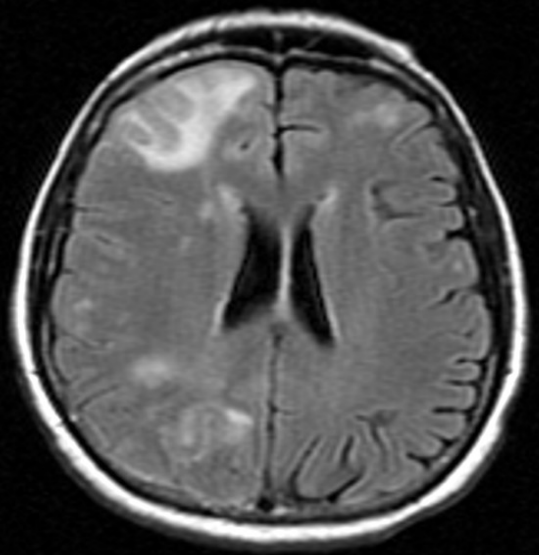
Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp

Examples of vMRI Outcomes in Other AD Clinical Trials

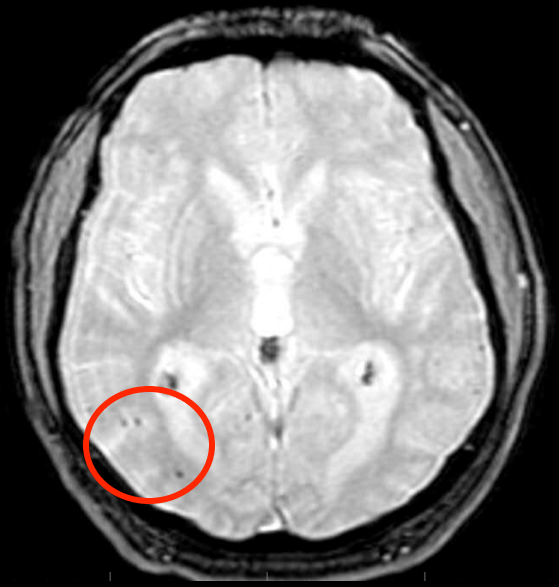
- MRI
  - AN1792-antibody responders had greater loss of brain volume and larger ventricles but no difference in Hc and no correlation with cognitive decline (Fox, 2005)
  - Bapineuzumab phase 2-no difference in brain volume for all Rx groups combined. Less volume loss in ApoE 4 non-carriers and increased ventricular size in ApoE4 carriers (Salloway, 2009)
  - Scyllo-inositol-No difference in cortical volume but increase in ventricular volume in the 250 mg group (Salloway, 2011)
  - Semagasestat phase 3-n=229, 4.3% decrease in hc volume and 1% decrease in WBV with treatment (Siemers, AAIC 2011)

Amyloid Related Imaging Abnormalities

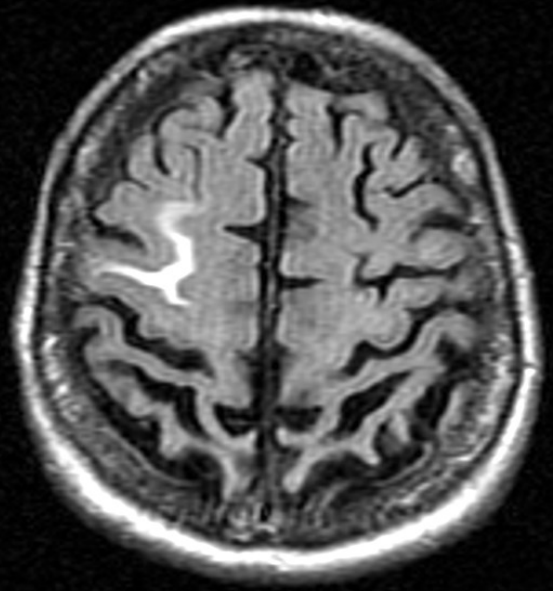
Multi-focal gray and white matter edema (ARIA-E)



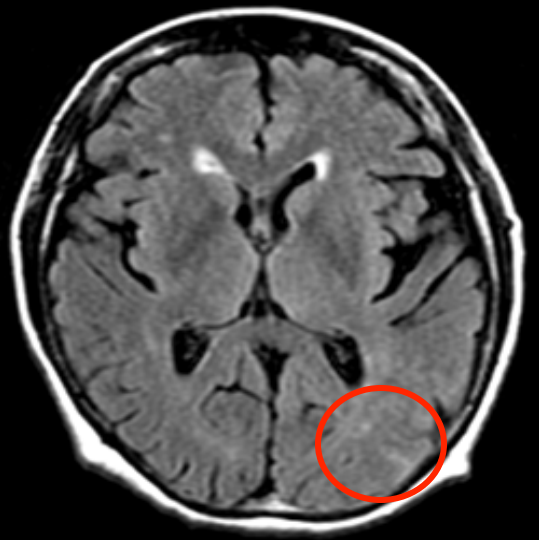
Micro-hemorrhages (ARIA-H)



Sulcal effusion (ARIA-E)



Subtle lepto-meningeal involvement (ARIA-E)



Sperling et al. *Alz & Dementia* 2011

ARIA-E

- ARIA-E occurred at low rates in the placebo groups (0.5-1.1%)
- **Bapineuzumab**
  - Rate of ARIA-E related to dose and ApoE carrier status
  - New cases detected on Final Read
  - Most cases asymptomatic and transient
  - **Symptomatic ARIA-E higher in 2.0 mg dose**
  - Most cases occurred with first 3 doses
  - ARIA E associated with an increased rate of incident microhemorrhage
  - Treating through ARIA-E not associated with clinical decline
- **Solanezumab**
  - Low rate of ARIA-E-1% solanezumab vs. 0.5% placebo
  - Onset distributed throughout the 18 months of the trial, all but one case asymptomatic
  - All ARIA-E cases in the placebo group were ApoE4 carriers, while cases in the solanezumab group were carriers and non-carriers

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp, Aisen CTAD 2012

Treatment Emergent ARIA-E on MRI by Safety Read and Final Read

APOE ε4 Carriers

Analysis Group	Placebo N=448 (%)	Bapineuzumab 0.5 mg/kg N=673 (%)
Safety Read	1 (0.2)	103 (15.3)
Final Read	**5** (1.1)	**143** (21.2)

Non-Carriers

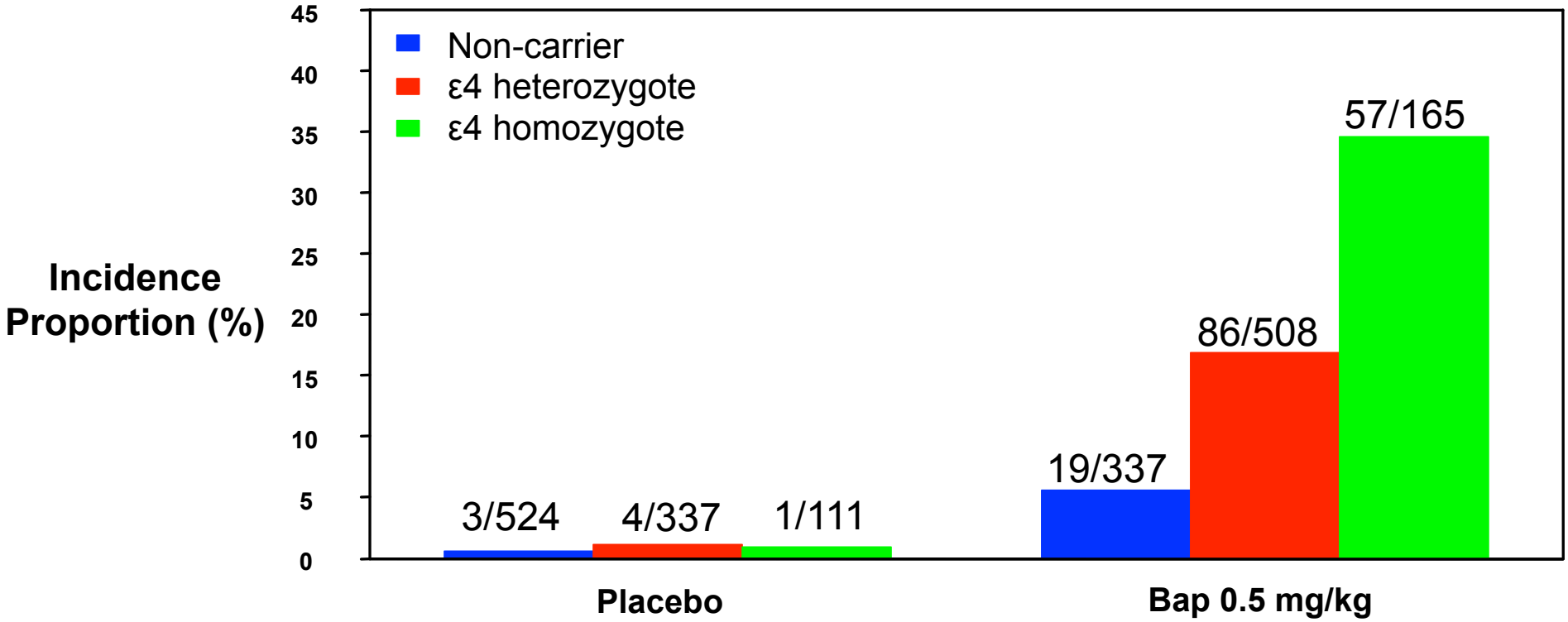
Analysis Group	Placebo N=524 (%)	Bapineuzumab 0.5 mg/kg N=337 (%)	Bapineuzumab 1.0 mg/kg N=329 (%)	Bapineuzumab 2.0 mg/kg N=141 (%)
Safety Read	1 (0.2)	14 (4.2)	31 (9.4)	20 (14.2)
Final Read	**3** (0.6)	**19** (5.6)	**44** (13.4)	**28** (19.9)

Reasons for additional cases of ARIA-E in Final Read:

1. Not detected by local radiologist (central reads implemented during study)
2. Not detected by central neuroradiologist
3. Site PI did not acknowledge ARIA-E finding at safety read

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp

Pooled 302/301: ARIA-E by APOE ε4 Copy Number (Final Read)



ε4 heterozygote: RR=3.0 (95% CI: 1.9 – 4.8; p<0.0001)
ε4 homozygote: RR=6.1 (95% CI: 3.8 – 9.9; p<0.0001)

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp

Questions

- **Is $A\beta_{42}$ the right target for mild-moderate AD?**
  - Compelling genetic data supporting role of amyloid but unclear which part of the amyloid cascade to target
  - Evidence of mild bapineuzumab anti-amyloid treatment effects on a downstream marker of neurodegeneration (CSF p-tau) without clear clinical benefit
  - What is the mechanism of action for solanezumab? Is a biomarker effect necessary to see a clinical benefit?
- **Too little?**
  - Higher doses limited by ARIA-E with bapineuzumab, possible room to increase dose of solanezumab
  - Amyloid lowering on PIB PET probably insufficient to alter clinical course
  - What is the clinical impact of mild cognitive improvement only in mild AD pt?
- **Too late?**
  - AD stage may be too far advanced for these drugs to demonstrate a major clinical benefit
  - Will anti-amyloid therapies may be more efficacious at earlier stages and what effect size might we see?
  - Combination therapies may be required for maximizing clinical benefit

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp

Issues Regarding Biomarker Outcomes

Amyloid PET

- Include amyloid cut-offs in future AD trials, especially in non-carriers
  - Ensures sample more likely to have AD
  - Avoids exposing individuals to the risks treatments with little chance of benefit
- Determine the diagnosis and rate of progression in amyloid-negative subjects
  - Measure outcomes for amyloid + subjects (CSF and amyloid PET)
  - Compare PIB and CSF for subjects who participated in both studies
- Reasons for decreased amyloid lowering in phase 3
  - Lower doses, separate cohorts for carriers and non-carriers
- Rate of change in biomarkers may vary by disease stage

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp

Issues Regarding Biomarker Outcomes

vMRI

- Risks in choosing vMRI as outcome measure
  - Uncertainty regarding direction of change
  - Effect on sample size calculation
- Possible mechanisms for increased rate of cortical atrophy and ventricular enlargement
  - Increased neurodegeneration
  - Amyloid removal
  - Reduction in amyloid-associated inflammation
  - Changes in CSF absorption or other fluid shifts

Salloway, Sperling, Fox, CTAD 2012, . J Nutrition, Health and Aging 2012;16:797 www.ctad.fr/12-press/press.asp