Bapineuzumab Phase 3 trials in mild to moderate Alzheimer's disease dementia in *apolipoprotein E ε4* carriers (Study 302) and non-carriers (Study 301)

Safety and PiB PET Amyloid Imaging

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Disclosures

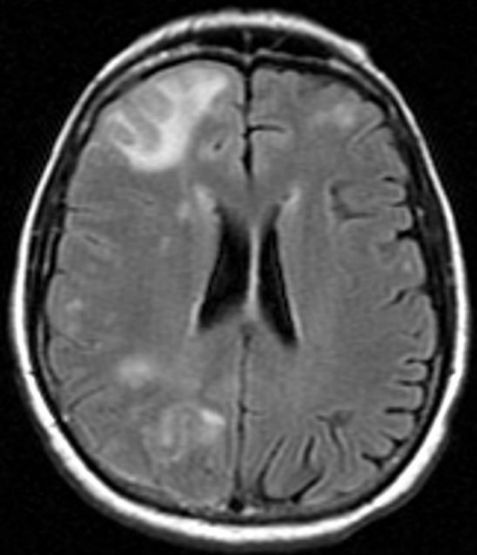
- Dr. Sperling serves on the 301/302 Steering Committee, is a consultant to Janssen AI (unpaid), and was a site investigator in Janssen AI and Pfizer trials for bapineuzumab IV. She is also a consultant for Roche, Merck, Bristol-Myers-Squibb, Eli-Lilly, Satori, Eisai, and Biogen.
- Dr. Salloway is the Chair of 301/302 Steering Committee, is a bapineuzumab IV P3 study investigator, serves on the scientific advisory boards of Janssen AI and Pfizer, and receives honoraria from Janssen AI and Pfizer.
- Dr. Raskind serves on and is a paid member of the 301/302 Steering Committee, and is a bapineuzumab IV P3 study investigator for Janssen AI and Eli Lilly.
- Dr. Ferris serves on the 301/302 Steering Committee,and is a consultant to Pfizer, Eisai, Bristol Myers-Squibb, Eli Lilly, Merck and Baxter.
- Dr. Honig serves on and is a paid member of the Study 301/302 Steering Committee, and is a bapineuzumab IV P3 study investigator.
- Dr. Porsteinsson serves on the Study 301/302 Steering Committee, is a bapineuzumab IV P3 study investigator, and receives honoraria from Janssen AI.
- Dr. Sabbagh serves on the Study 301/302 Steering Committee, is a bapineuzumab IV P3 study investigator, and previously served on speaker's bureau for Pfizer.
- Prof. Fox served on the scientific advisory boards of Alzheimer's Research Form, GE Healthcare, Janssen AI, and Wyeth. He is a paid consultant for Eli Lilly, Abbott Laboratories, Eisai, Elan, Wyeth, Janssen AI, GE Healthcare, Sanofi-Aventis, and Lundbeck, and received research support from GlaxoSmithKline, Elan, Wyeth, Janssen AI, Lundbeck, Sanofi-Aventis, IXICO and Pfizer Inc for contracted image analysis.
- E Liu, E Yuen, Y Lu, D Wang, B Nejadnik, V Guenzler, J Lull, M Miloslavsky, C Tudor, M Reichert, N Ketter, and B Brashear are employees of Janssen Alzheimer Immunotherapy R&D, LLC.
- R Black was an employee of Pfizer Inc.
- M Grundman is a consultant to Janssen Alzheimer Immunotherapy R&D, LLC.

Study funding:
Janssen Alzheimer Immunotherapy and Pfizer Inc

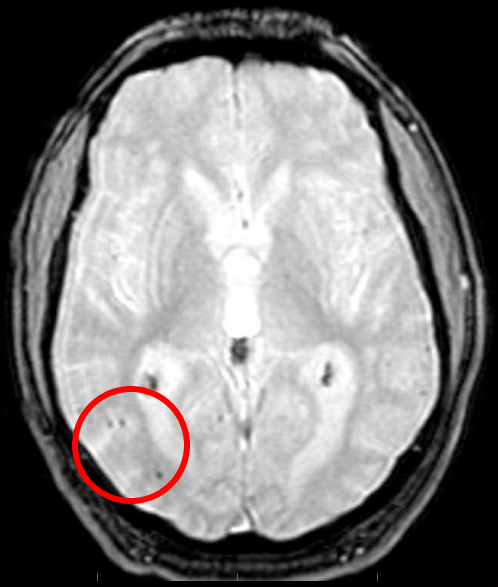
Results: Safety

Amyloid Related Imaging Abnormalities

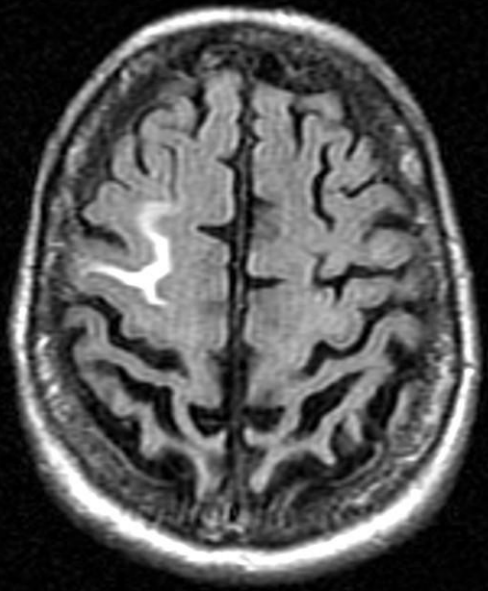
Multi-focal gray and white matter edema (ARIA-E)



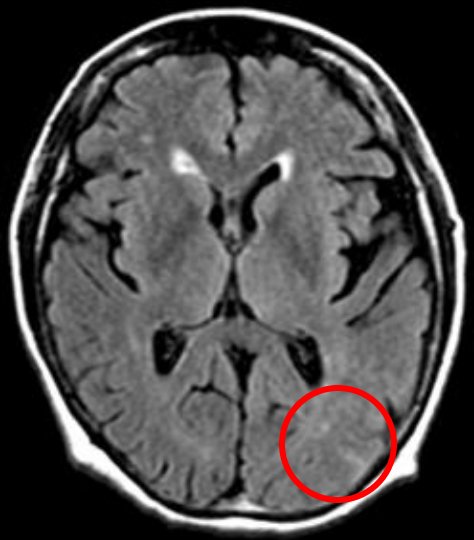
Micro-hemorrhages (ARIA-H)



Sulcal effusion (ARIA-E)



Subtle lepto-meningeal involvement (ARIA-E)



Sperling et al. *Alz & Dementia* 2011

Treatment Emergent Adverse Events of Special Circumstance

APOE ε4 Carriers

AEs of Special Circumstance	Placebo N=448 (%)	Bapineuzumab 0.5 mg/kg N=673 (%)
ARIA-E (vasogenic edema)	**1** (0.2)	**103** (15.3)
Symptomatic ARIA-E*	**0** (0.0)	**16** (2.4)
Intracranial hemorrhage**	**7** (1.6)	**7** (1.0)
Seizure/Convulsion	**1** (0.2)	**7** (1.0)
DVT/PE	**4** (0.9)	**5** (0.7)

Non-Carriers

AEs of Special Circumstance	Placebo N=524 (%)	Bapineuzumab 0.5 mg/kg N=337 (%)	Bapineuzumab 1.0 mg/kg N=329 (%)
ARIA-E (vasogenic edema)	**1** (0.2)	**14** (4.2)	**31** (9.4)
Symptomatic ARIA-E*	**0** (0.0)	**5** (1.5)	**5** (1.5)
Intracranial hemorrhage**	**7** (1.3)	**1** (0.3)	**6** (1.8)
Seizure/Convulsion	**5** (1.0)	**1** (0.3)	**7** (2.1)
DVT/PE	**6** (1.1)	**2** (0.6)	**3** (0.9)

*Symptoms in ARIA-E subjects included: headache, confusional state, cognitive disorder, agitation, dizziness, memory impairment, hemiparesis, abnormal behavior, fatigue, and gait disturbance.
**Excludes hemosiderin deposits, such as microhemorrhage

Treatment Emergent Serious Adverse Events Occurring in ≥1% of Subjects in Any Treatment Group

APOE ε4 Carriers

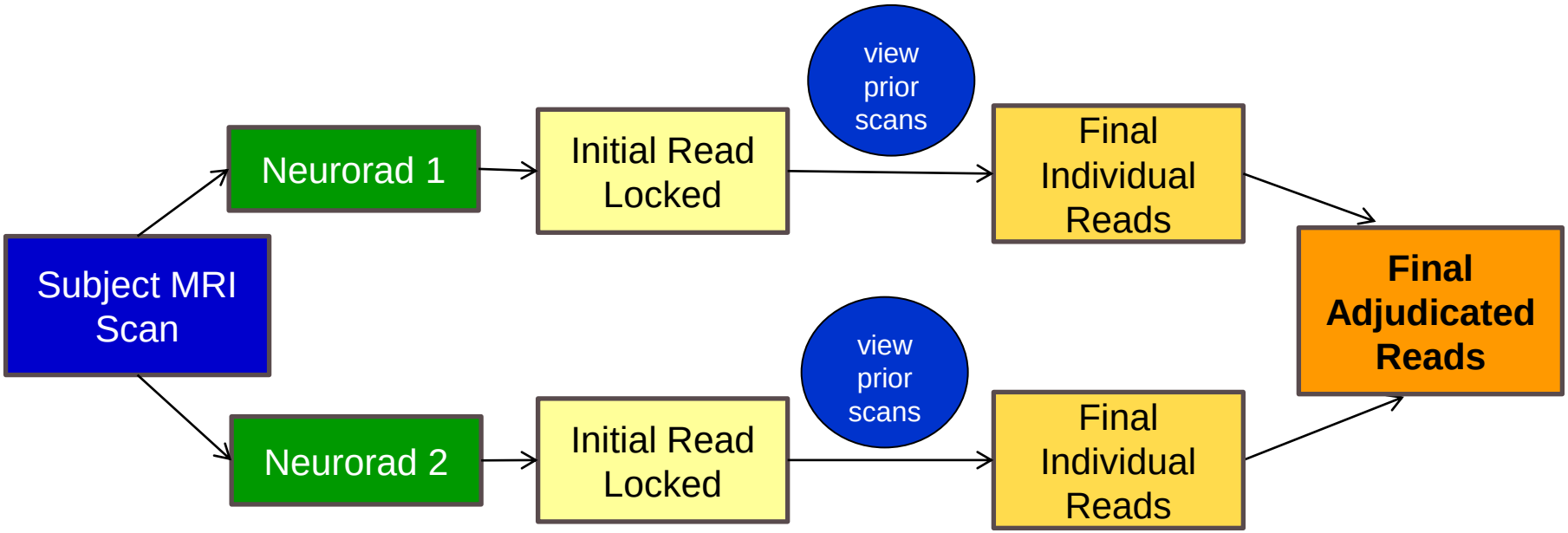
Serious AEs (determined by investigator)	Placebo N=448 (%)	Bapineuzumab 0.5 mg/kg N=673 (%)
ARIA-E (Vasogenic edema)	**0** (0.0)	**14** (2.1)
Syncope	**10** (2.2)	**11** (1.6)
Dehydration	**2** (0.4)	**8** (1.2)

Non-Carriers

Serious AEs (determined by investigator)	Placebo N=524 (%)	Bapineuzumab 0.5 mg/kg N=337 (%)	Bapineuzumab 1.0 mg/kg N=329 (%)
Pneumonia	**8** (1.5)	**3** (0.9)	**8** (2.4)
Convulsion	**4** (0.8)	**1** (0.3)	**6** (1.8)
ARIA-E (Vasogenic edema)	**0** (0.0)	**5** (1.5)	**5** (1.5)
Syncope	**5** (1.0)	**4** (1.2)	**4** (1.2)
Diverticulitis	**1** (0.2)	**0** (0.0)	**4** (1.2)
Hip Fracture	**2** (0.4)	**4** (1.2)	**4** (1.2)
Subdural Hematoma	**6** (1.1)	**0** (0.0)	**2** (0.6)
Urinary Tract Infection	**6** (1.1)	**0** (0.0)	**2** (0.6)
Atrial Fibrillation	**6** (1.1)	**2** (0.6)	**2** (0.6)

Initiation of Final MRI Read Project

- Phase 2 Final Read revealed 40% of ARIA-E cases not detected during the study (Sperling et al, Lancet Neurology, 2012)
- Main Objective:
  - Determine incidence of ARIA uniformly with standardized methods
- Methods:
  - Review of all MRI scans in studies 301 and 302 (>15,000 MRI scans)
  - Neuroradiologist pairs performed sequential, locked readings for the full series of images for each subject after completing the study
  - Final result adjudicated between readers by consensus



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

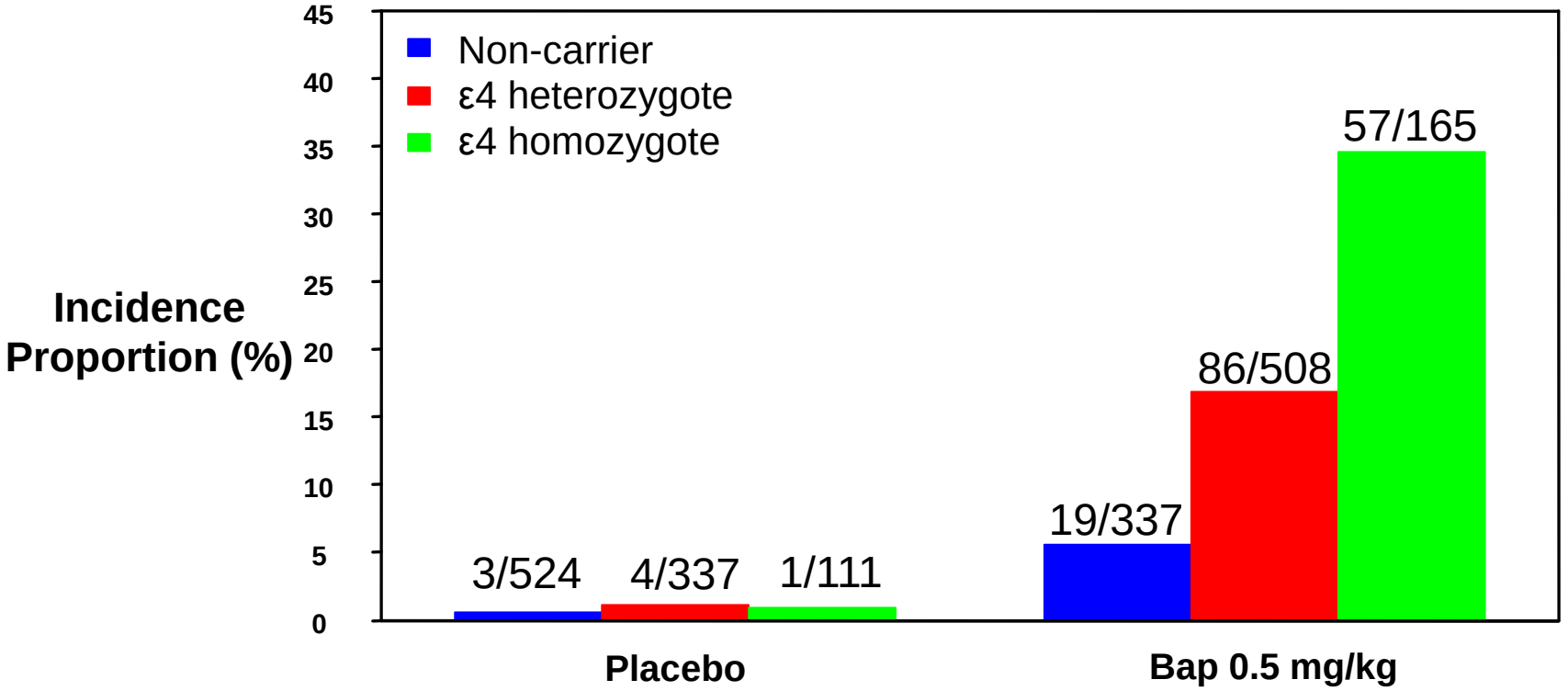
Timing of ARIA-E

- Majority of cases associated with the first three infusions
- A small percentage of cases occurred late (after infusions 4, 5, or 6):
  - 15.4% in carriers; 9.9% in non-carriers
- Proportion of cases associated with first infusion:
  - 27.2% in carriers; 49.5% in non-carriers
- Proportion of cases in non-carriers associated with first infusion increased with bapineuzumab dose level:
  - 0.5 mg/kg: 26.3%; 1.0 mg/kg: 52.3%; 2.0 mg/kg: 60.7%

Median Duration of ARIA-E (days, range)

	Placebo	Bapineuzumab 0.5 mg/kg	Bapineuzumab 1.0 mg/kg	Bapineuzumab 2.0 mg/kg
Carriers	92 (72, 286)	129 (32, 457)	-	-
Non-carriers	97 (44, 189)	141 (88, 234)	108 (49, 390)	91 (11, 274)

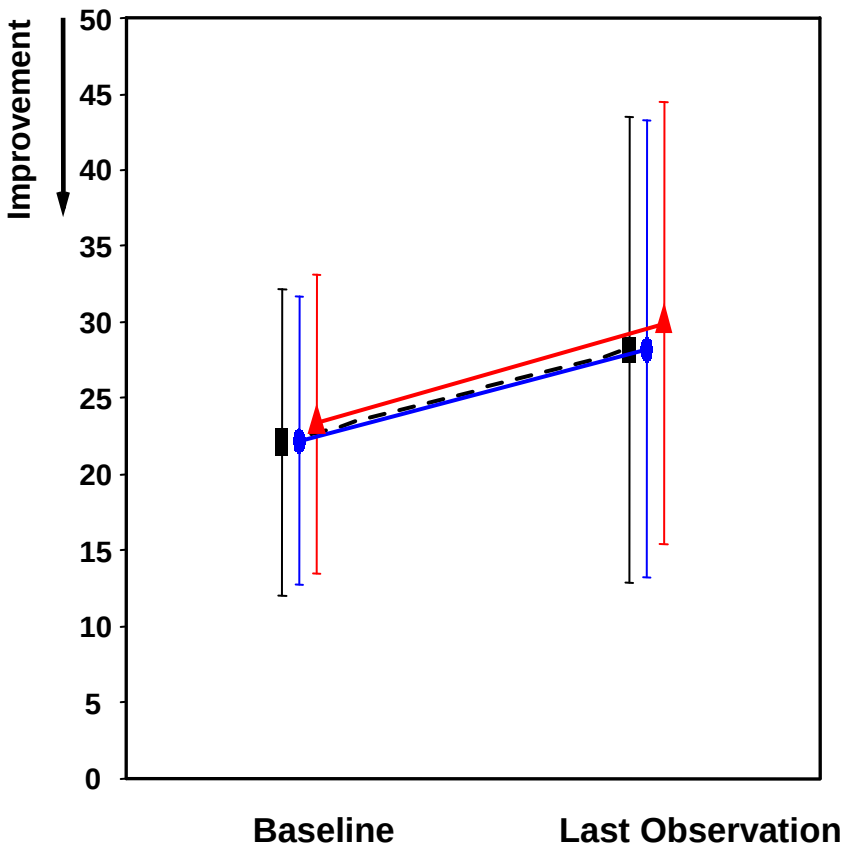
Pooled 302/301: ARIA-E by APOE ε4 Copy Number (Final Read)



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)

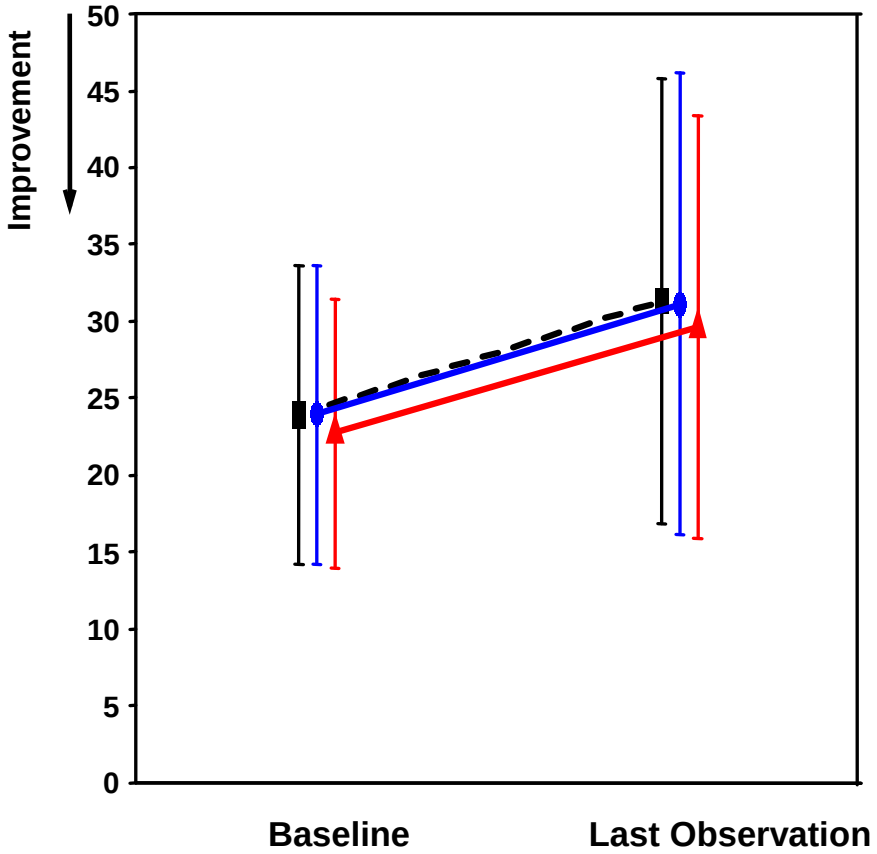
ARIA-E Effect on Cognition: First to Last Measure

Influence of ARIA-E on ADAS-Cog 11
Study 301 – Non-carriers



Placebo non-ARIA-E (n=521)
Bap non-ARIA-E (n=716)
Bap ARIA-E (n=91)

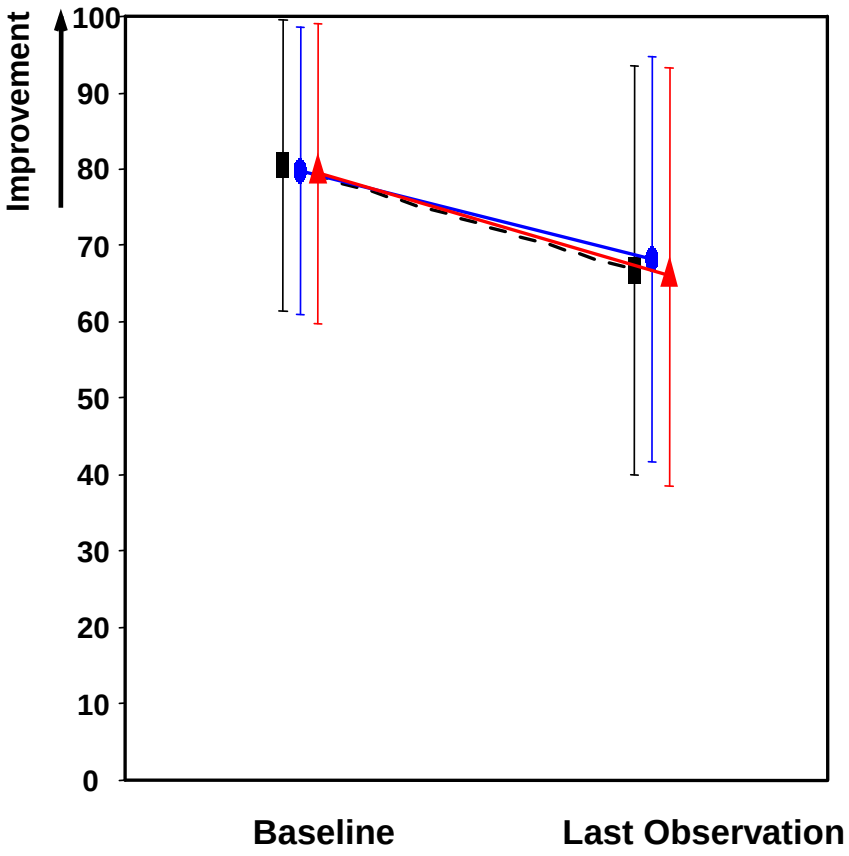
Influence of ARIA-E on ADAS-Cog 11
Study 302 – Carriers



Placebo non-ARIA-E (n=443)
Bap non-ARIA-E (n=530)
Bap ARIA-E (n=143)

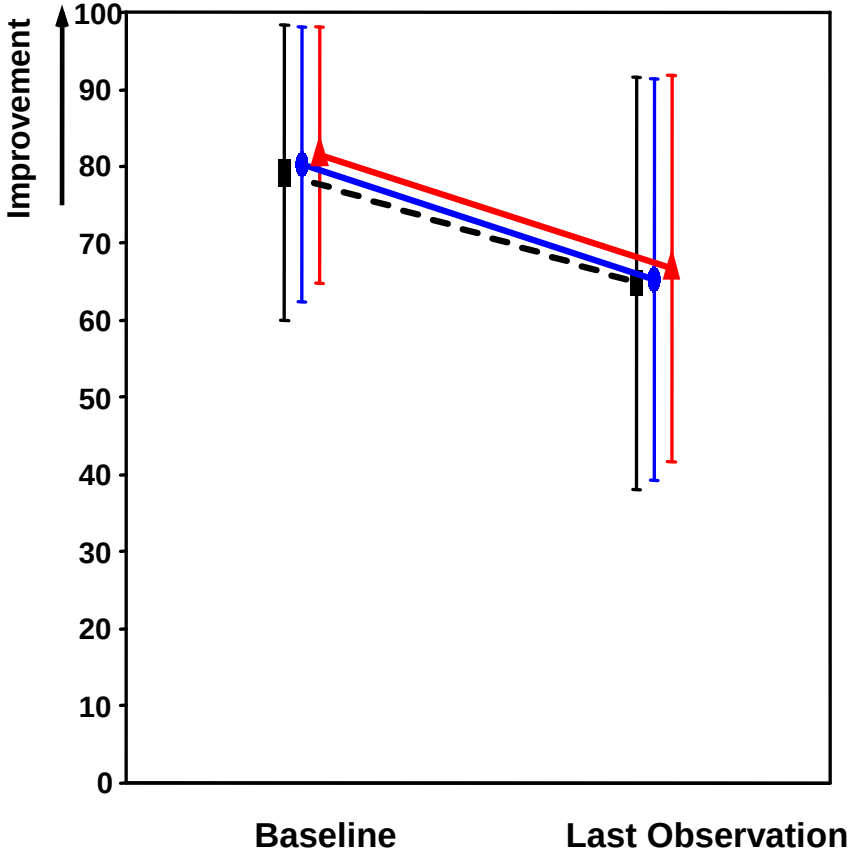
ARIA-E Effect on Function: First vs Last Measure

Influence of ARIA-E on DAD
Study 301 – Non-carriers



Placebo non-ARIA-E (n=521)
Bap non-ARIA-E (n=716)
Bap ARIA-E (n=91)

Influence of ARIA-E on DAD
Study 302 – Carriers



Placebo non-ARIA-E (n=443)
Bap non-ARIA-E (n=530)
Bap ARIA-E (n=143)

Number of Deaths per Study

APOE ε4 Carriers

	Placebo (N=448) n (%)	Bapineuzumab (N=673) n (%)
Total Number of Deaths	**5** (1.1)	**15** (2.2)

Non-Carriers

	Placebo N=524 (%)	Bapineuzumab **0.5 mg/kg** N=337 (%)	Bapineuzumab **1.0 mg/kg** N=329 (%)
Total Number of Deaths	**7** (1.3)	**4** (1.2)	**7** (2.1)

Summary of Treatment Emergent Deaths From All Causes APOE ε4 Carriers

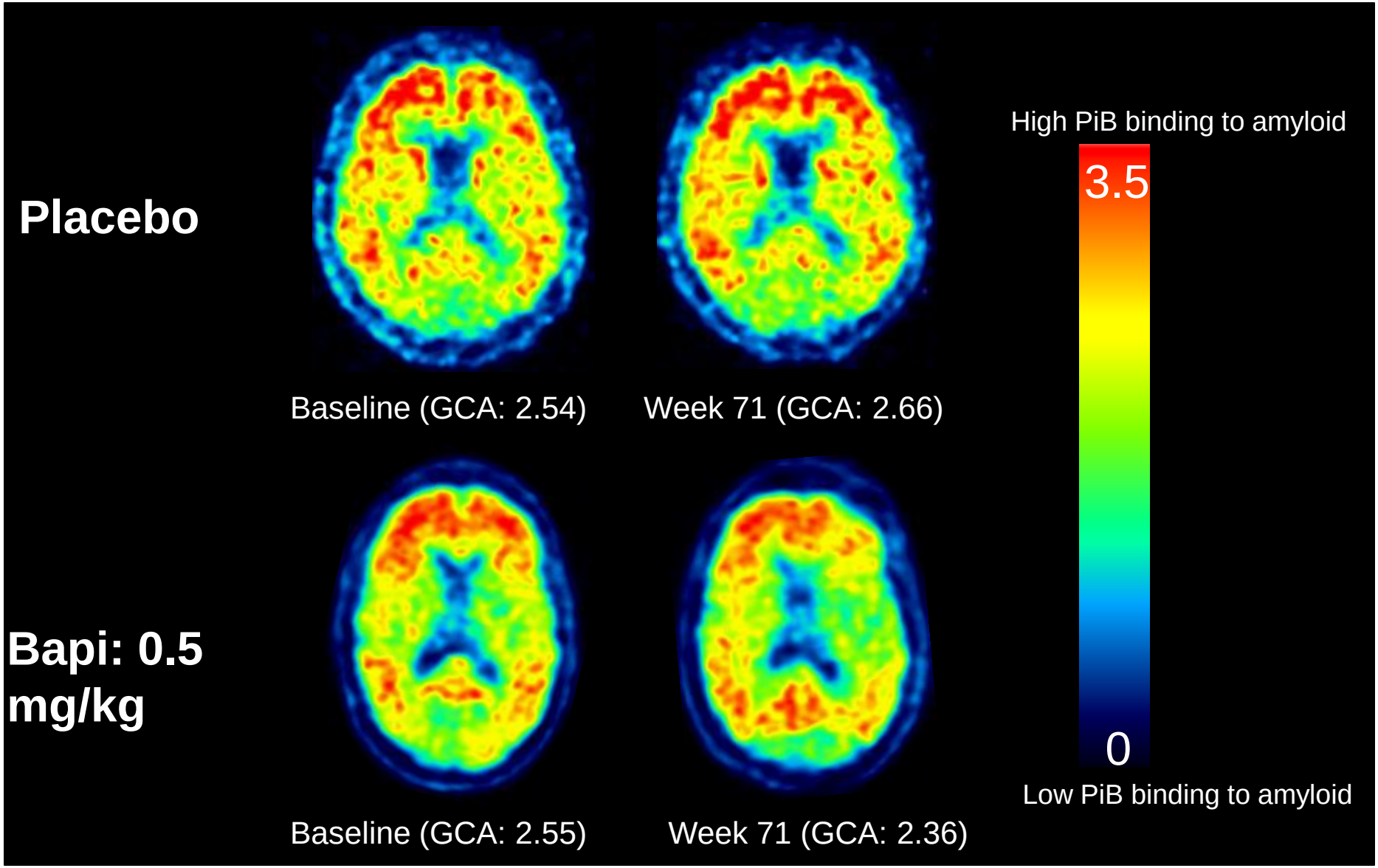
Reason for death	Placebo (N=448) n (%)	Bapineuzumab (N=673) n (%)
Total Number of Deaths	**5** (1.1)	**15** (2.2)
Cancer deaths	**0** (0.0)	**6** (0.9)
Metastases to abdominal cavity	-	1 (0.1)
Oesophageal cancer metastatic	-	1 (0.1)
Ovarian cancer	-	1 (0.1)
Ovarian epithelial cancer	-	1 (0.1)
Pancreatic carcinoma	-	1 (0.1)
Renal cancer metastatic	-	1 (0.1)
Other deaths	**5** (1.1)	**9** (1.3)
AD related deaths	3 (0.7)	3 (0.4)
Asthenia	-	1 (0.1)
Cardiac	1 (0.0)	2 (0.3)
Diabetic ketoacidosis	-	1 (0.1)
Multiple injuries (automobile accident)	-	1 (0.1)
Pneumonia	-	1 (0.1)
Respiratory arrest	1 (0.0)	-

Summary of Treatment Emergent Deaths From All Causes Non-Carriers

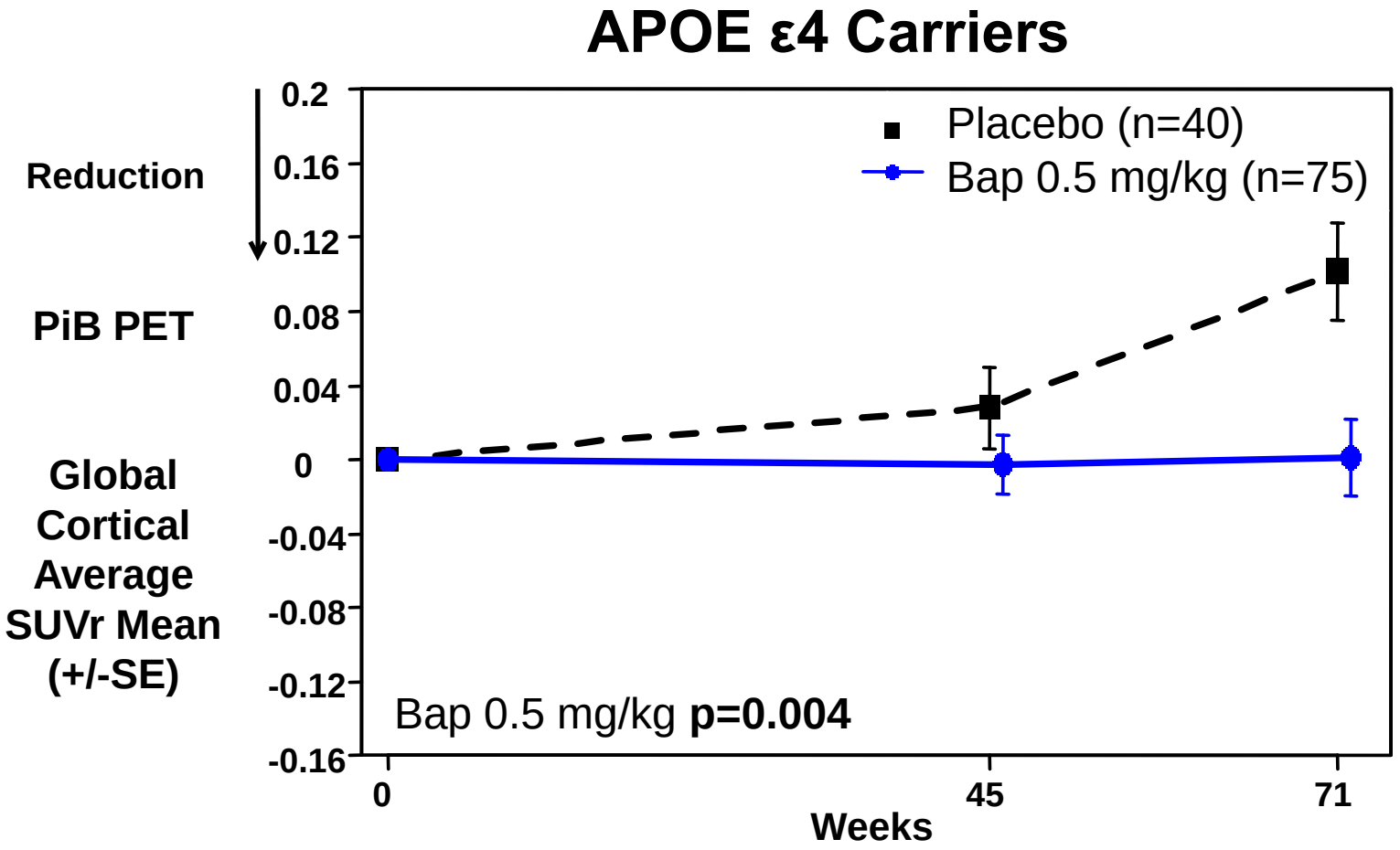
Reason for death	Placebo N=524 (%)	Bapineuzumab 0.5 mg/kg N=337 (%)	Bapineuzumab 1.0 mg/kg N=329 (%)
Total Number of Deaths	**7** (1.3)	**4** (1.2)	**7** (2.1)
Cardiac	-	-	**3** (0.9)
Generalized Disorders	**2** (0.4)	-	
Infections	-	-	**2** (0.6)
Neoplasm	**2** (0.4)	-	**1** (0.3)
Nervous System Disorders	**2** (0.4)	**3** (0.9)	-
Respiratory	-	**1** (0.3)	-
Renal	-	-	**1** (0.3)
Trauma	**1** (0.2)	-	-

Key Biomarker Secondary Endpoint: PiB PET Amyloid Imaging

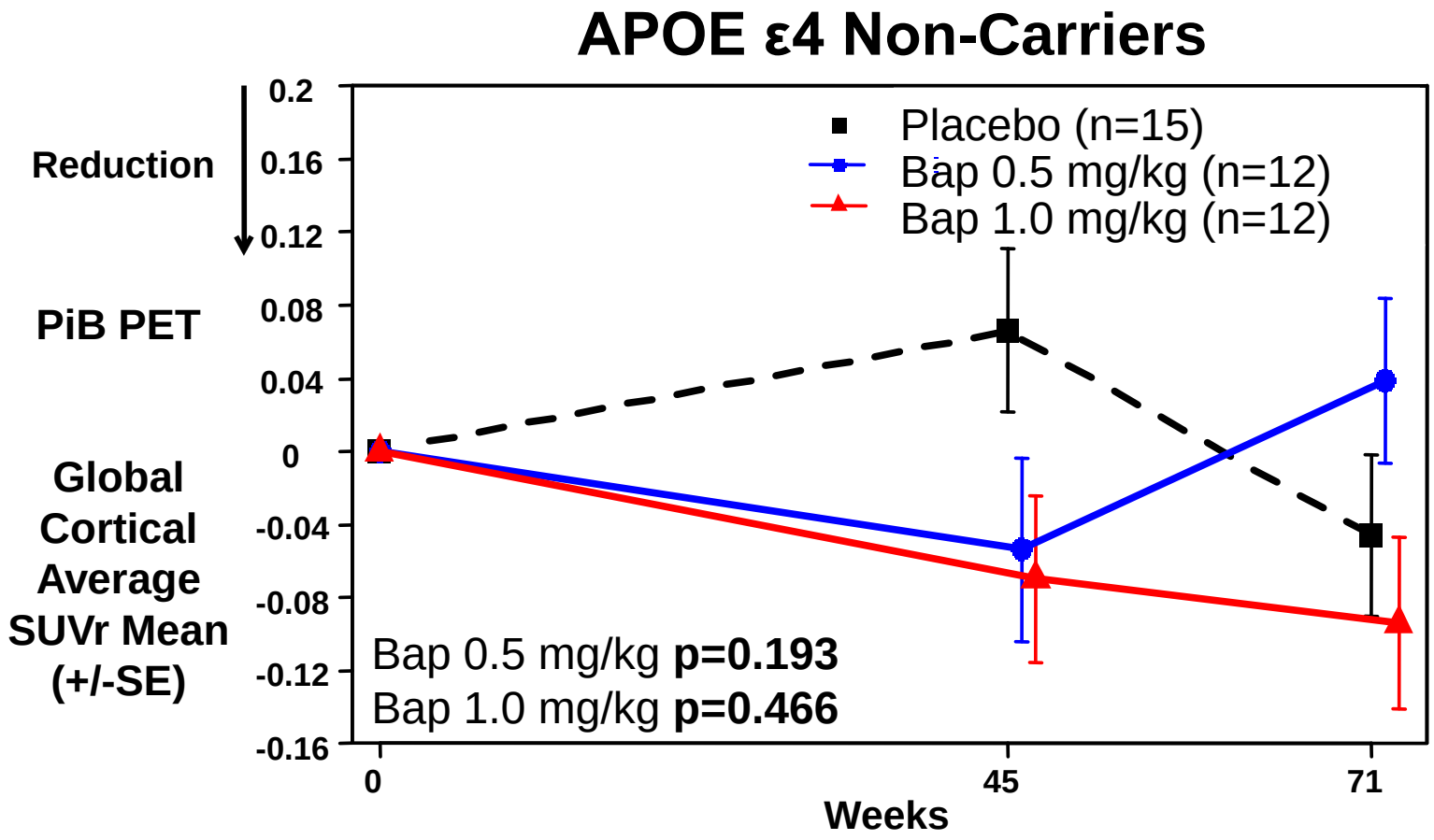
Study 302


Placebo
Baseline (GCA: 2.54)
Week 71 (GCA: 2.66)
Bapi: 0.5 mg/kg
Baseline (GCA: 2.55)
Week 71 (GCA: 2.36)
High PiB binding to amyloid
3.5
0
Low PiB binding to amyloid

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



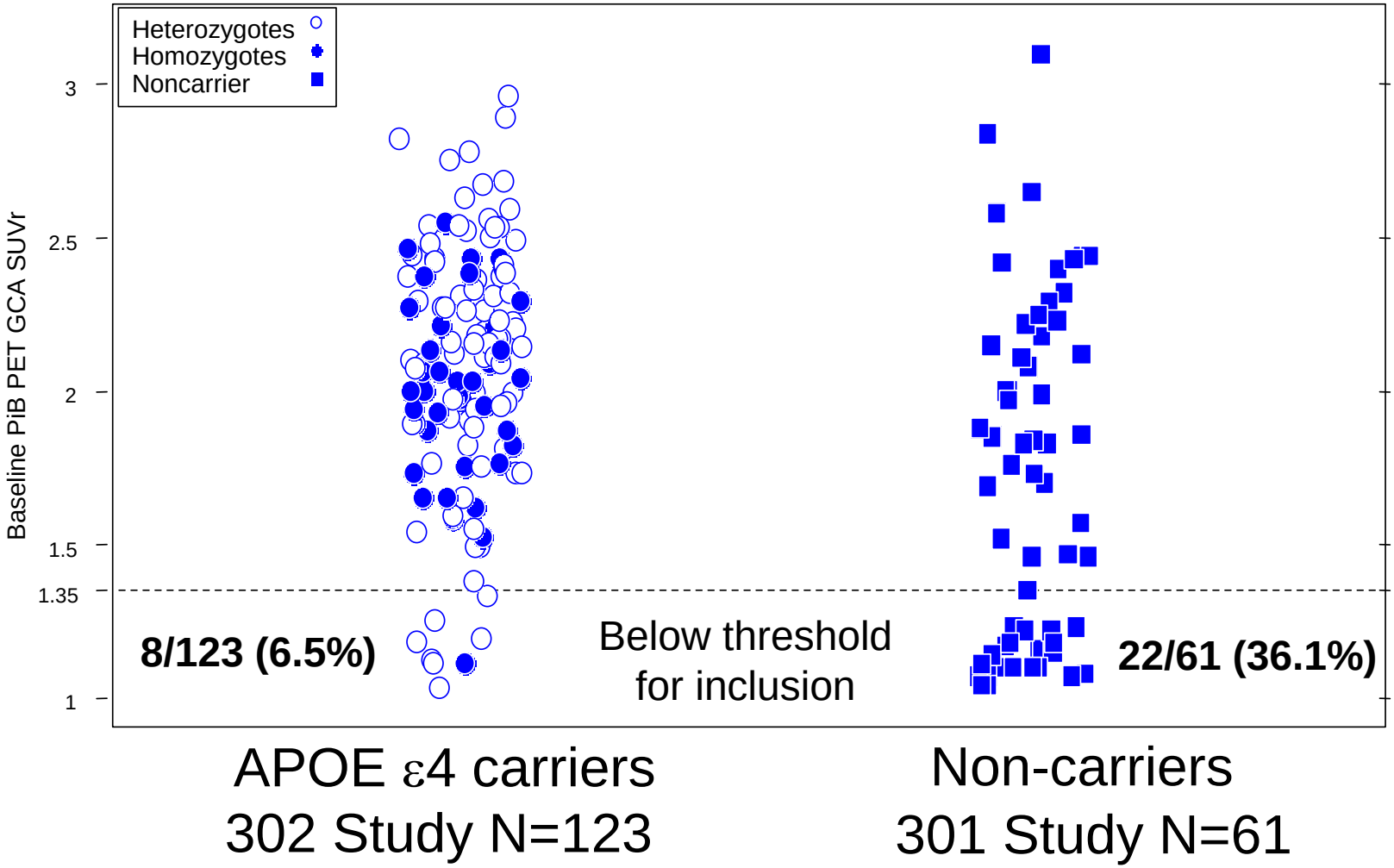
Change in Amyloid Burden as assessed by [^{11}C] PiB-PET at Week 71 APOE ε4 Non-Carriers (PiB PET analysis population)



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

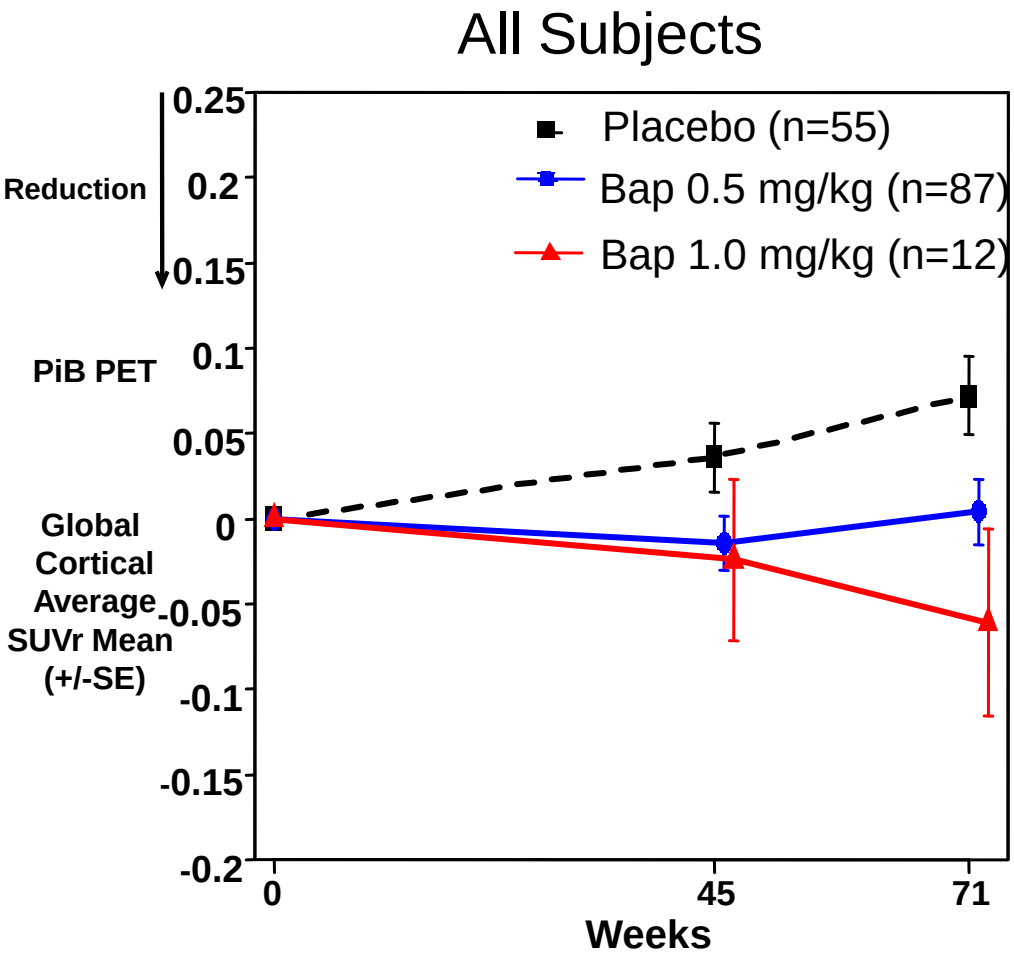
Post hoc exploratory analysis showed a within cohort trend for reduction in PiB PET at 1.0 mg/kg dose (nominal p = 0.057)

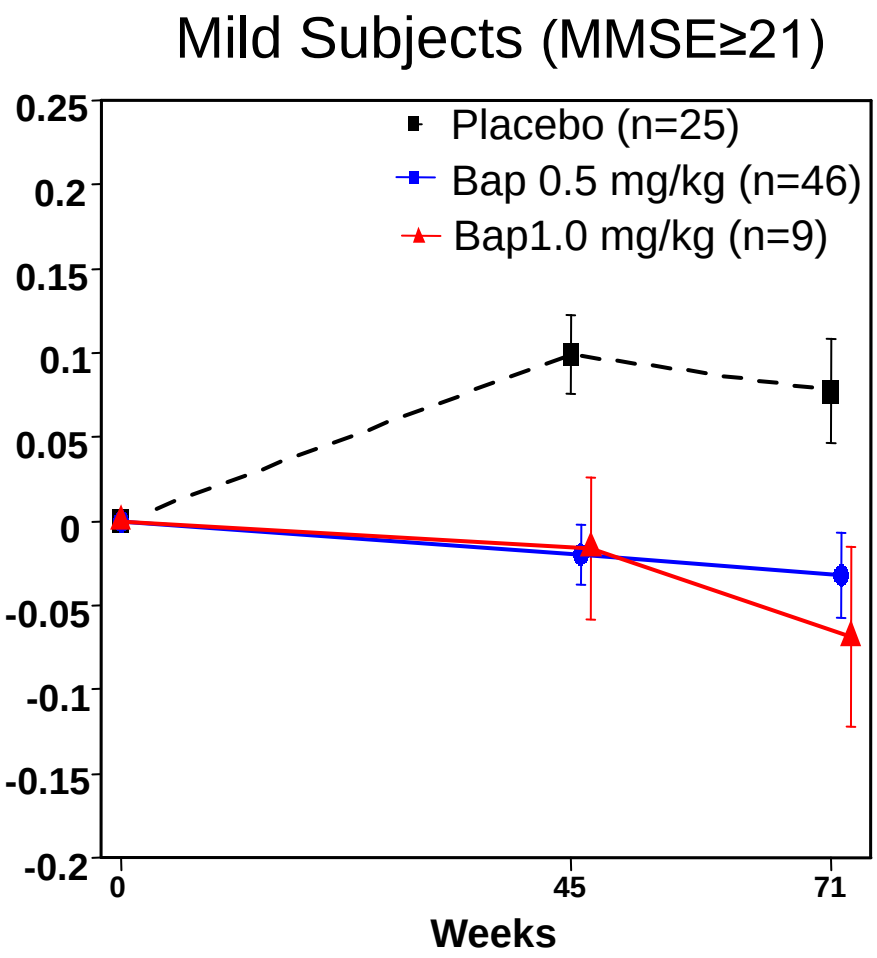
Distribution of PIB PET Global Cortical Average SUVr



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

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

Data Summary – Safety

ARIA-E: .

- ARIA-E associated with bapineuzumab, additional cases identified on final read
- Increased risk in APOE ε4 carriers
- Increased risk with higher dose in non-carriers
- Preliminary analyses did not show evidence of ARIA-E-associated decline in cognition or function

Other Safety:

- Slightly higher rate of seizures in bapineuzumab treated groups

Deaths:

- More deaths in the bapineuzumab–treated carriers, primarily due to cancer
- No imbalance in cancer deaths in non-carriers
- Analyses of all bapineuzumab Phase 3 studies did not show an imbalance of cancer or deaths due to cancer when reviewed by unblinded, independent SMC

Data Summary PiB PET Imaging

- Reduced accumulation in amyloid burden on PiB PET relative to placebo observed in carrier and pooled studies
- High proportion of “amyloid negatives” on PiB among non-carriers
  - Perhaps not surprising given 15-20% of AD patients (across genotypes) do not meet neuropathological criteria for AD at autopsy
  - Evaluate proportion of “amyloid negatives” using CSF
  - Should future anti-amyloid trials, especially in non-carriers, implement amyloid cut-off?