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

CSF and Volumetric MRI Biomarkers

Nick C Fox, MD, FRCP
Professor of Neurology, MRC Senior Clinical Fellow
Institute of Neurology,
University College London, UK
On Behalf of the Bapineuzumab Study Investigators

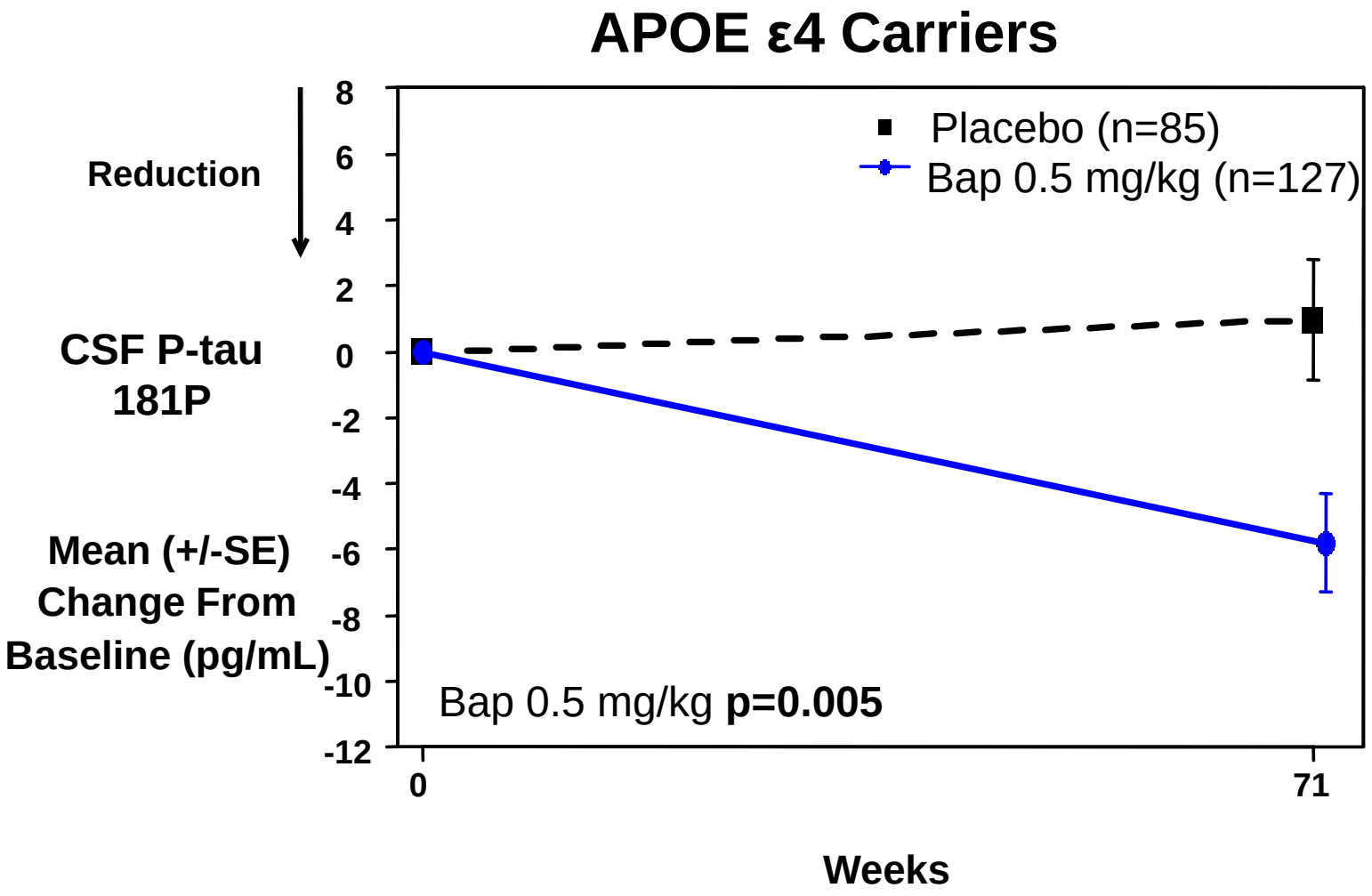
Disclosures

- 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.
- 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. 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. 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.
- 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.

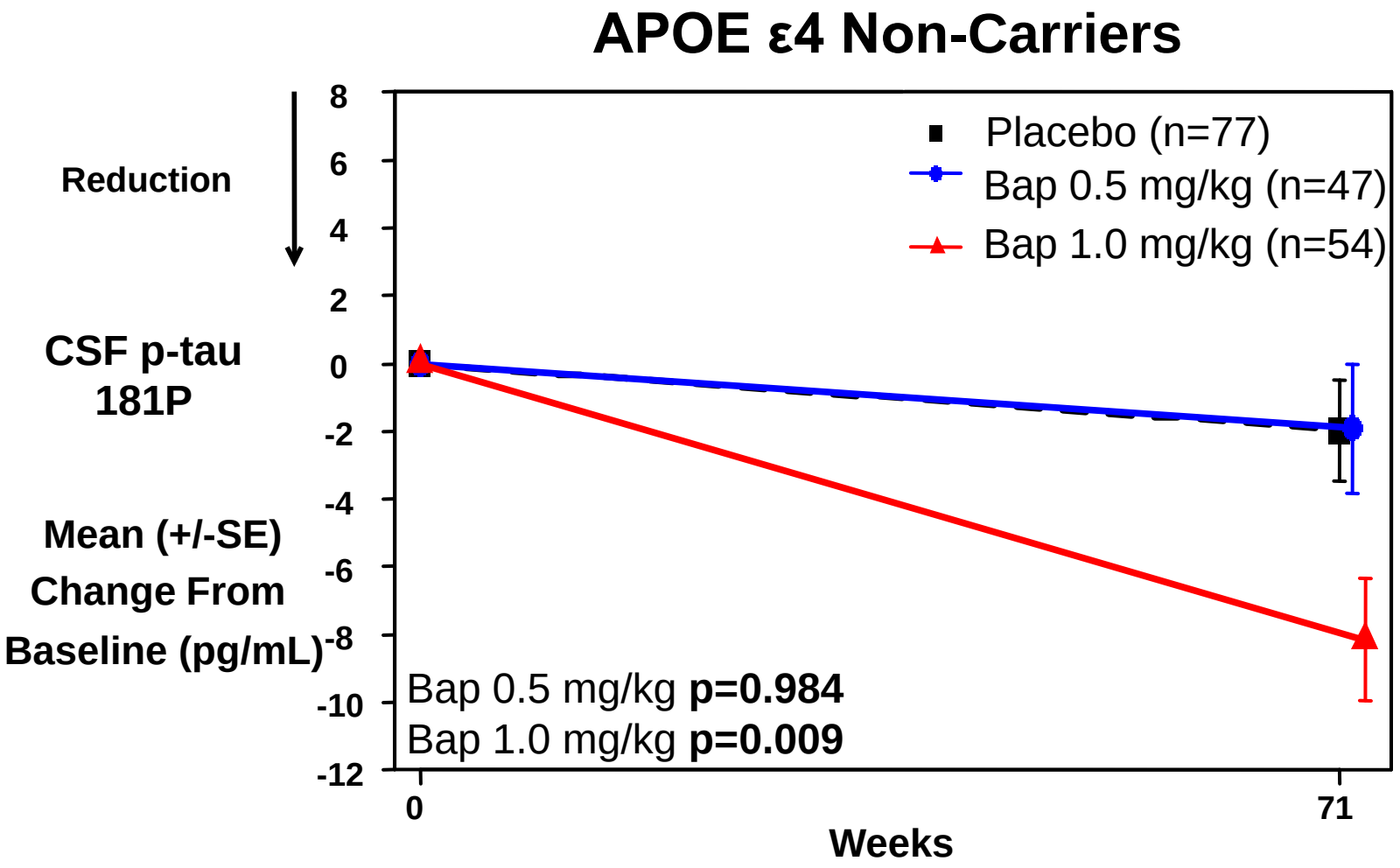
Study funding:
Janssen Alzheimer Immunotherapy and Pfizer Inc

Key Biomarker Secondary Endpoints: CSF p-tau, BBSI

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

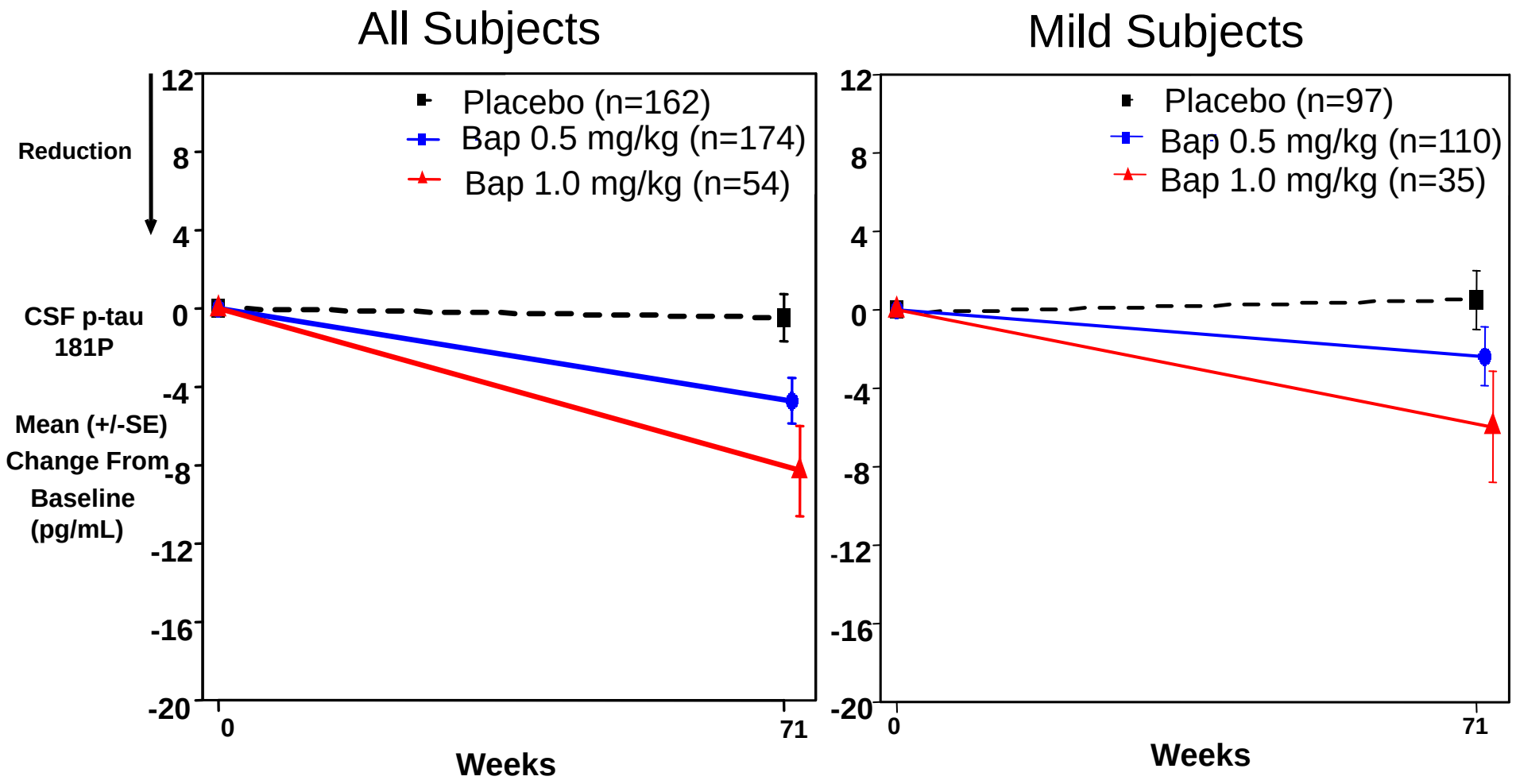


Change in CSF phospho-tau by Treatment Group at Week 71
APOE ε4 Non-Carriers (CSF analysis population)



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

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

Change in CSF Total-tau and Aβ at Week 71

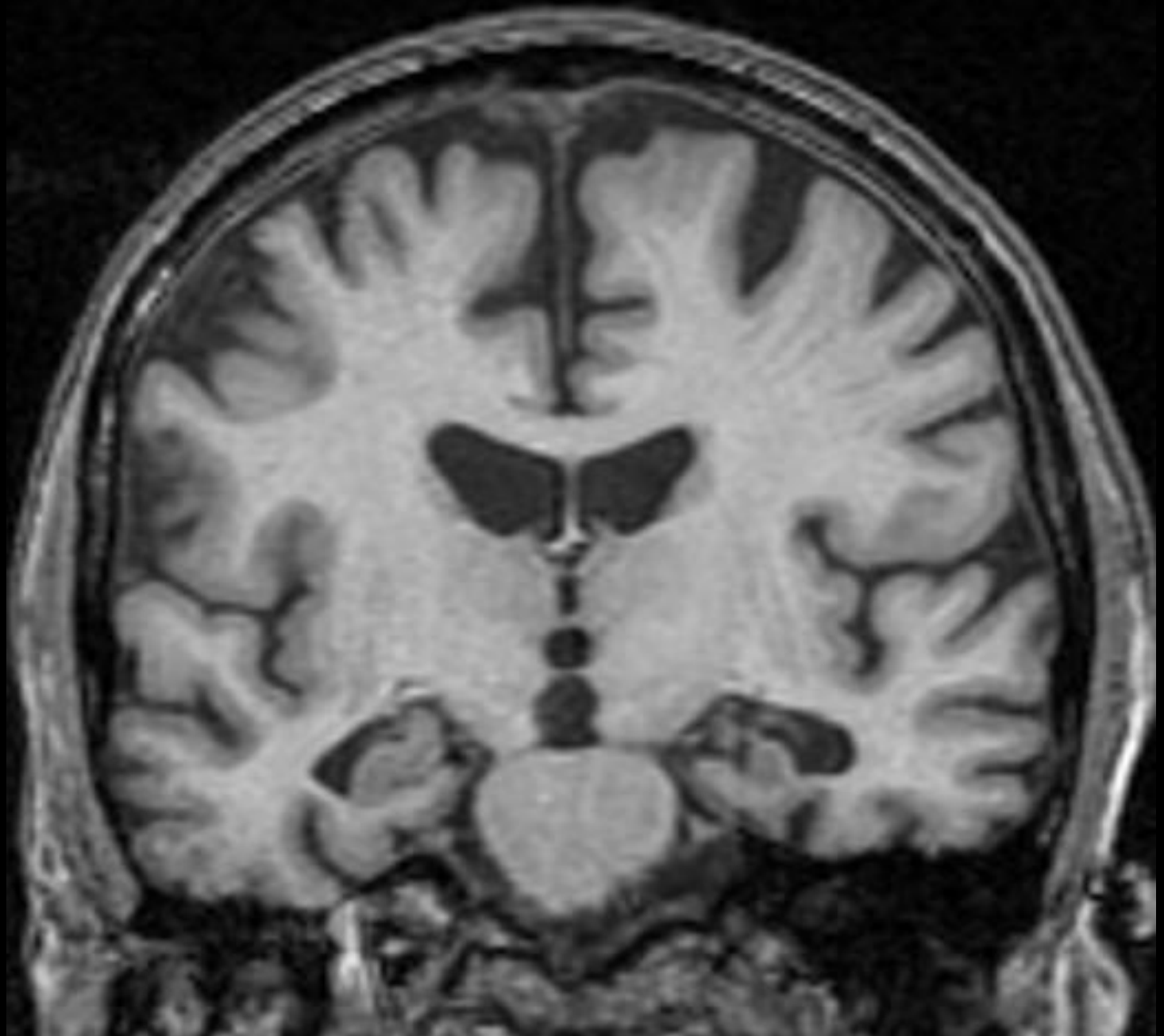
- **Total-tau**
  - Treatment related reductions consistent with changes in p-tau only observed in non-carriers only at 1.0 mg/kg dose ($p<0.05$)
  - No treatment related differences seen in carriers or pooled studies

- **Aβ**
  - No treatment differences observed in levels of $A\beta_{x-40}$ or $A\beta_{x-42}$ in either study

Volumetric MRI

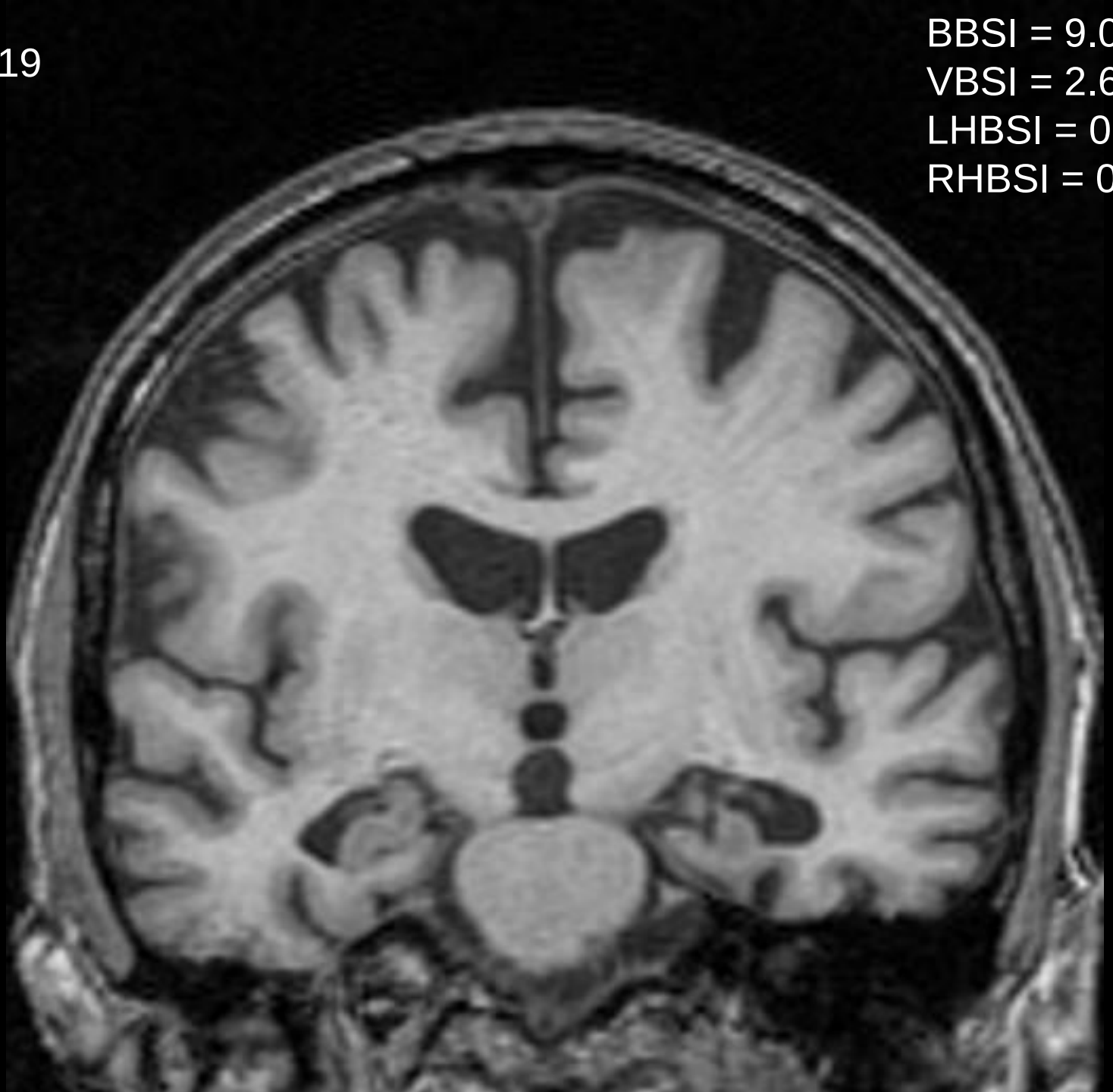
Analyses all based upon registered T1-weighted scans

Baseline



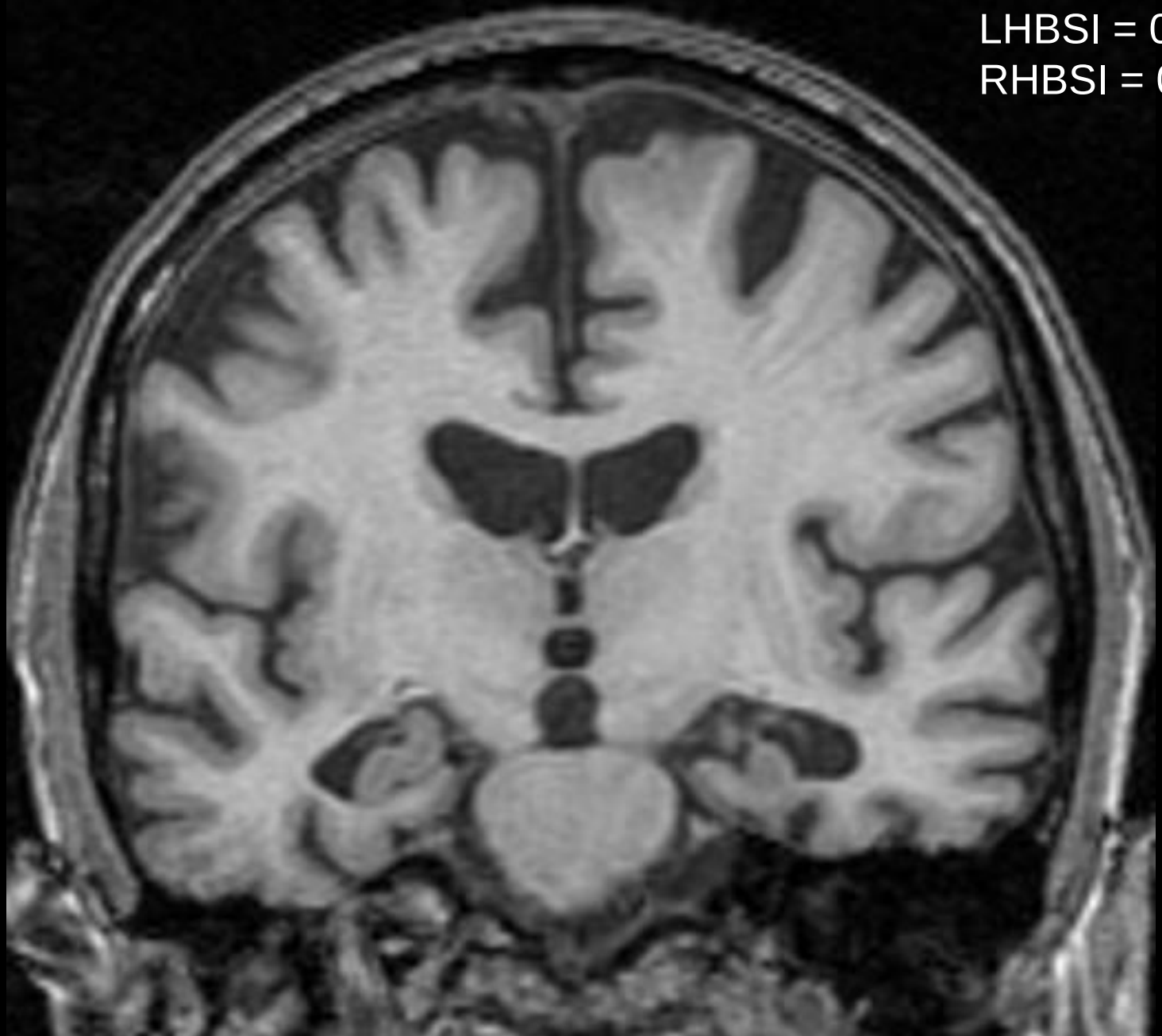
Week 19

BBSI = 9.0ml
VBSI = 2.6ml
LHBSI = 0.021ml
RHBSI = 0.058ml

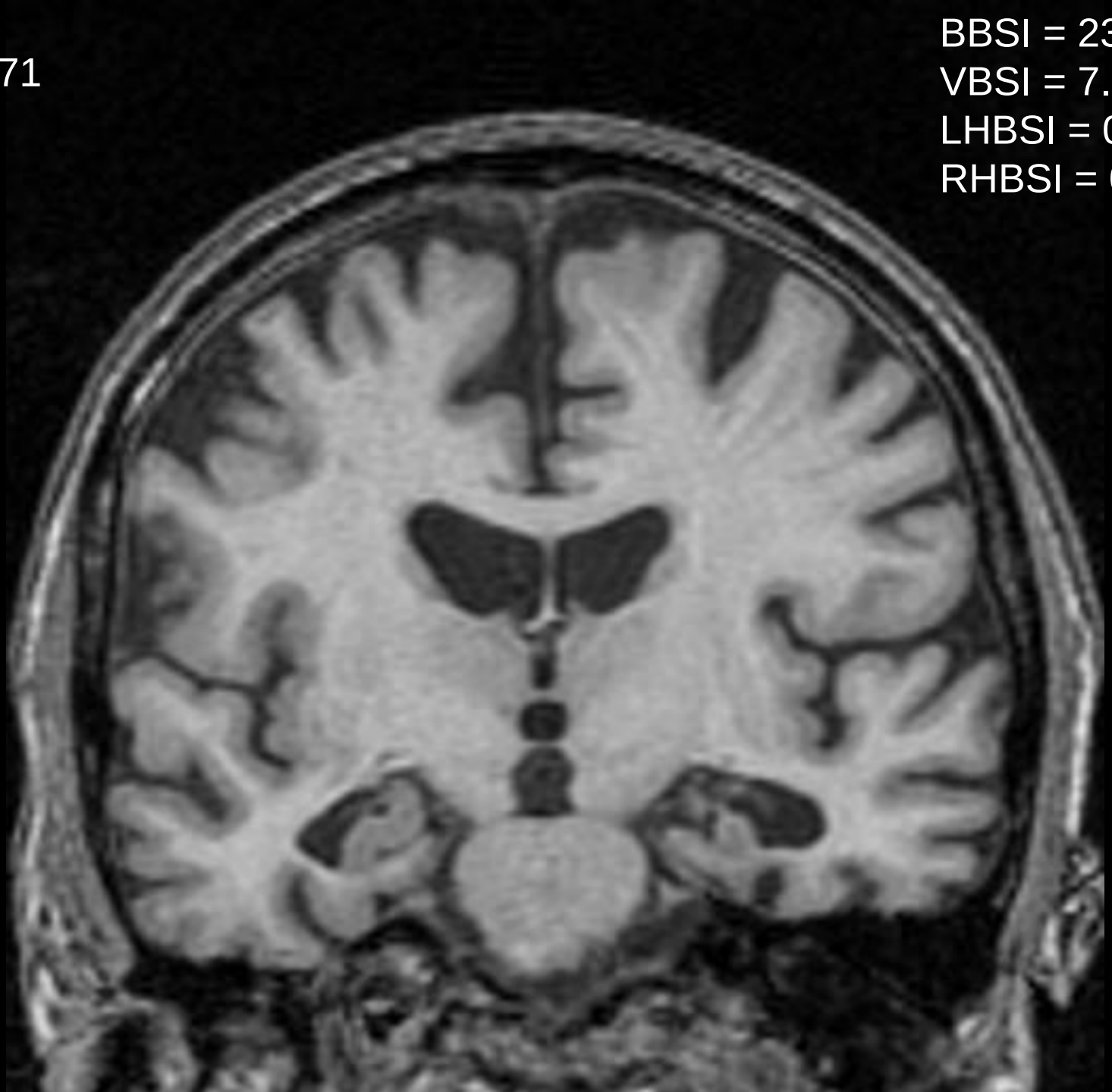


Week 45

BBSI = 15.7ml
VBSI = 4.9ml
LHBSI = 0.048ml
RHBSI = 0.120ml

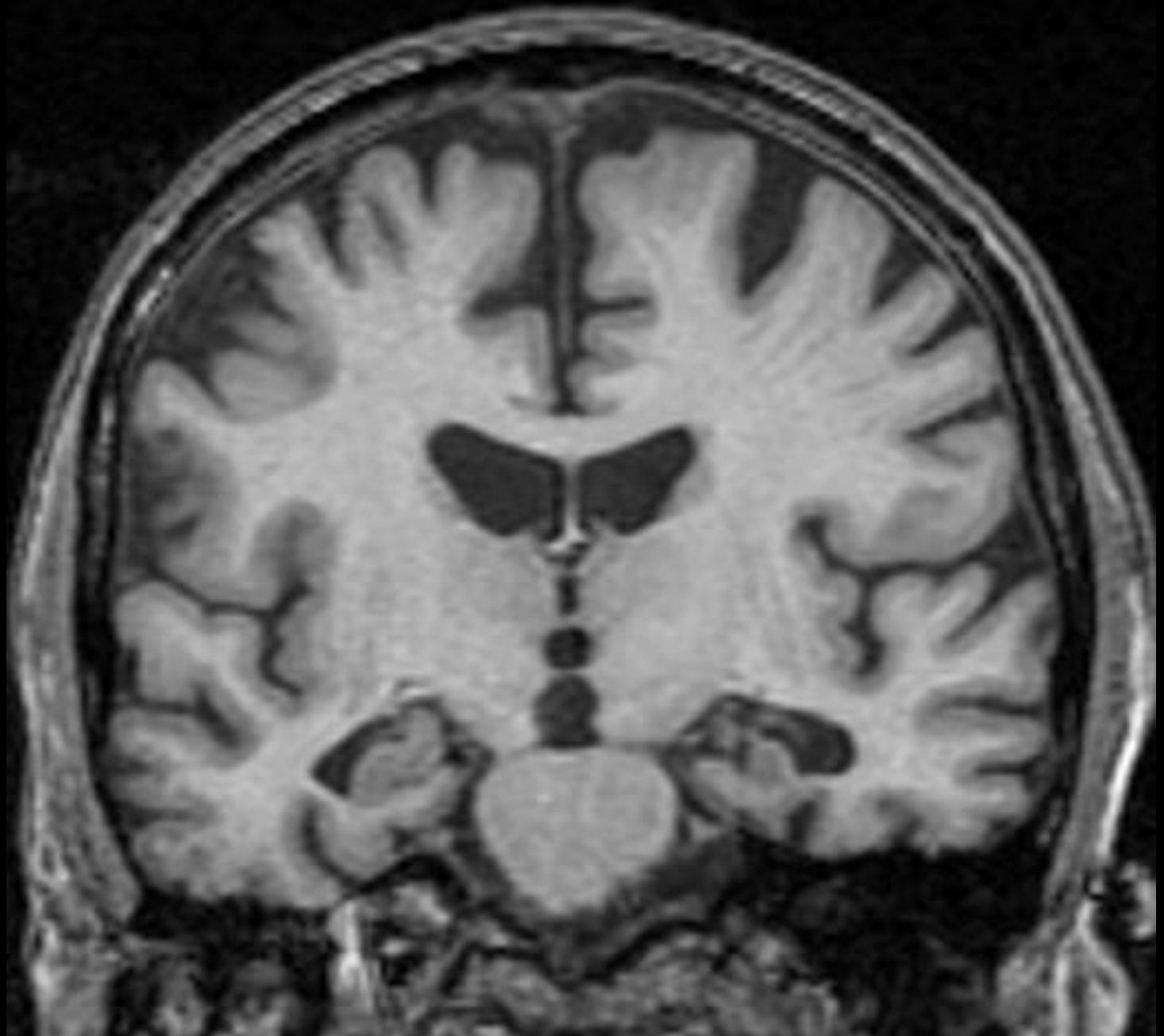


Week 71

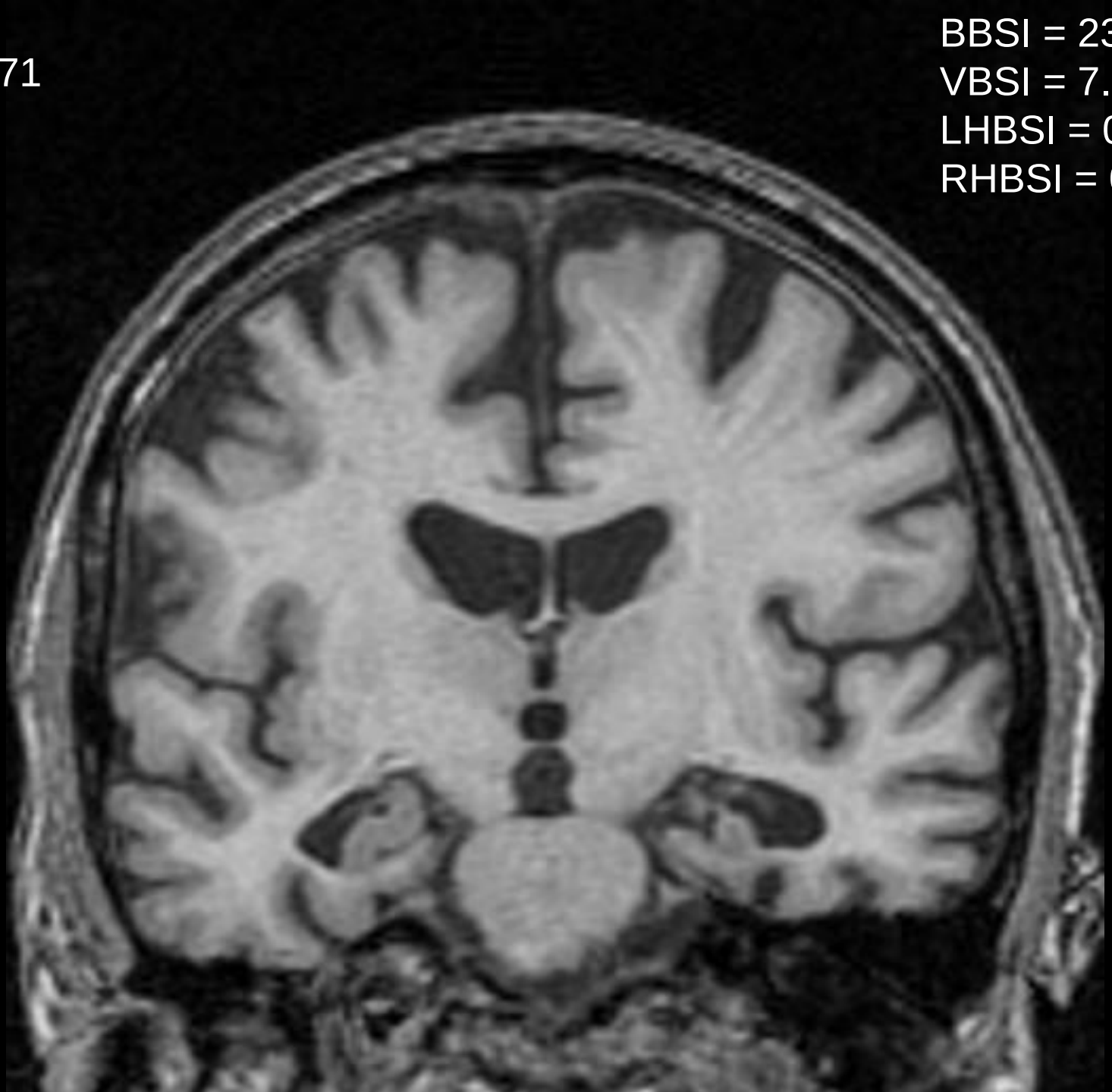


BBSI = 23.9ml
VBSI = 7.3ml
LHBSI = 0.113ml
RHBSI = 0.177ml

Baseline

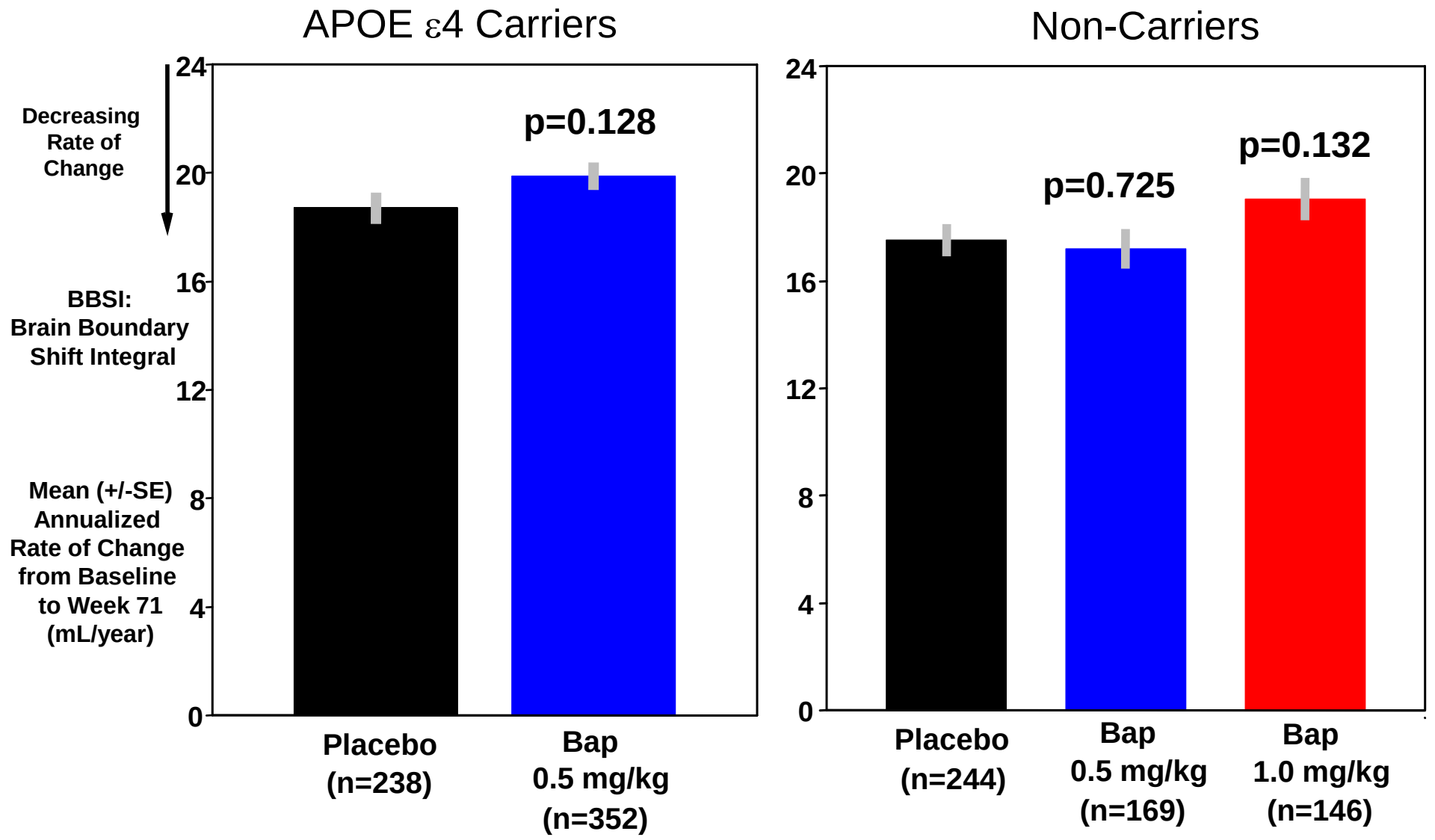


Week 71

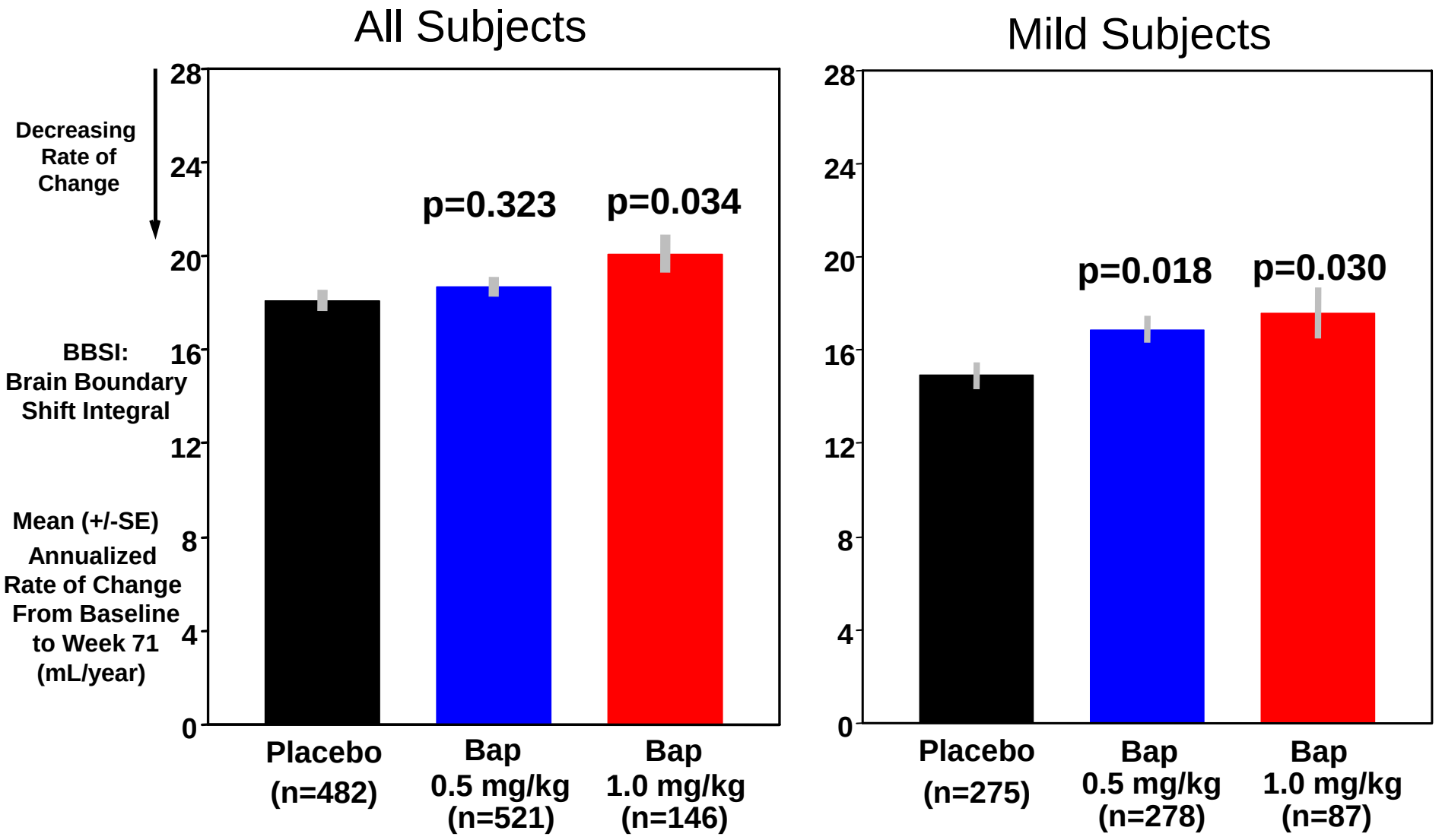


BBSI = 23.9ml
VBSI = 7.3ml
LHBSI = 0.113ml
RHBSI = 0.177ml

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



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

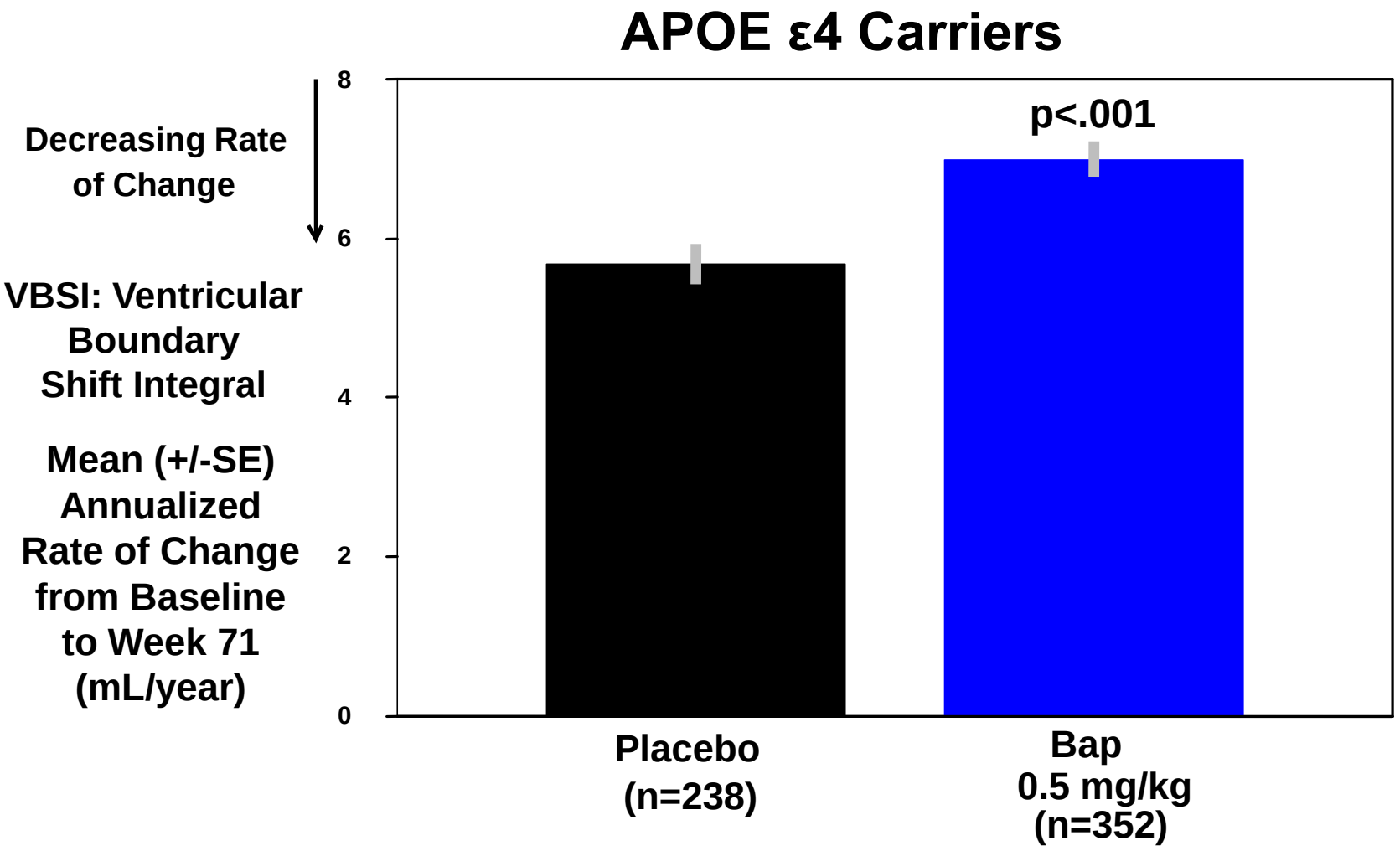


No significant effect in moderate group

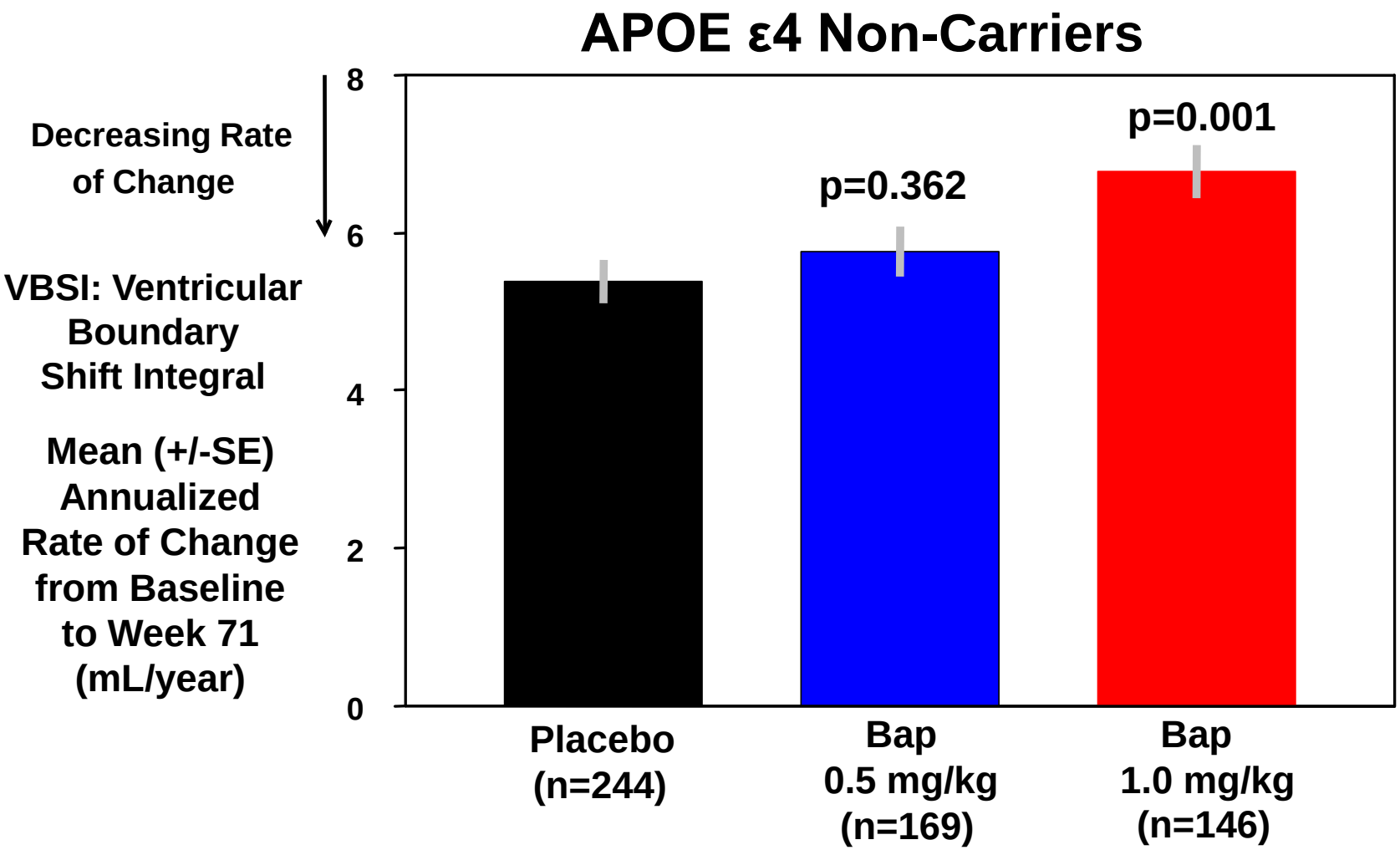
Rate of Change in Hippocampal Volume at Week 71

- **Left Hippocampal Volume**
  - Increased rate of hippocampal volume loss compared to placebo observed only in non-carrier study and only at 1.0 mg/kg dose
    - Rate: 0.111 mL/yr +/- 0.006 vs 0.092 mL/yr +/- 0.005; $p<0.05$
- **Right Hippocampal Volume**
  - No treatment differences observed in either study

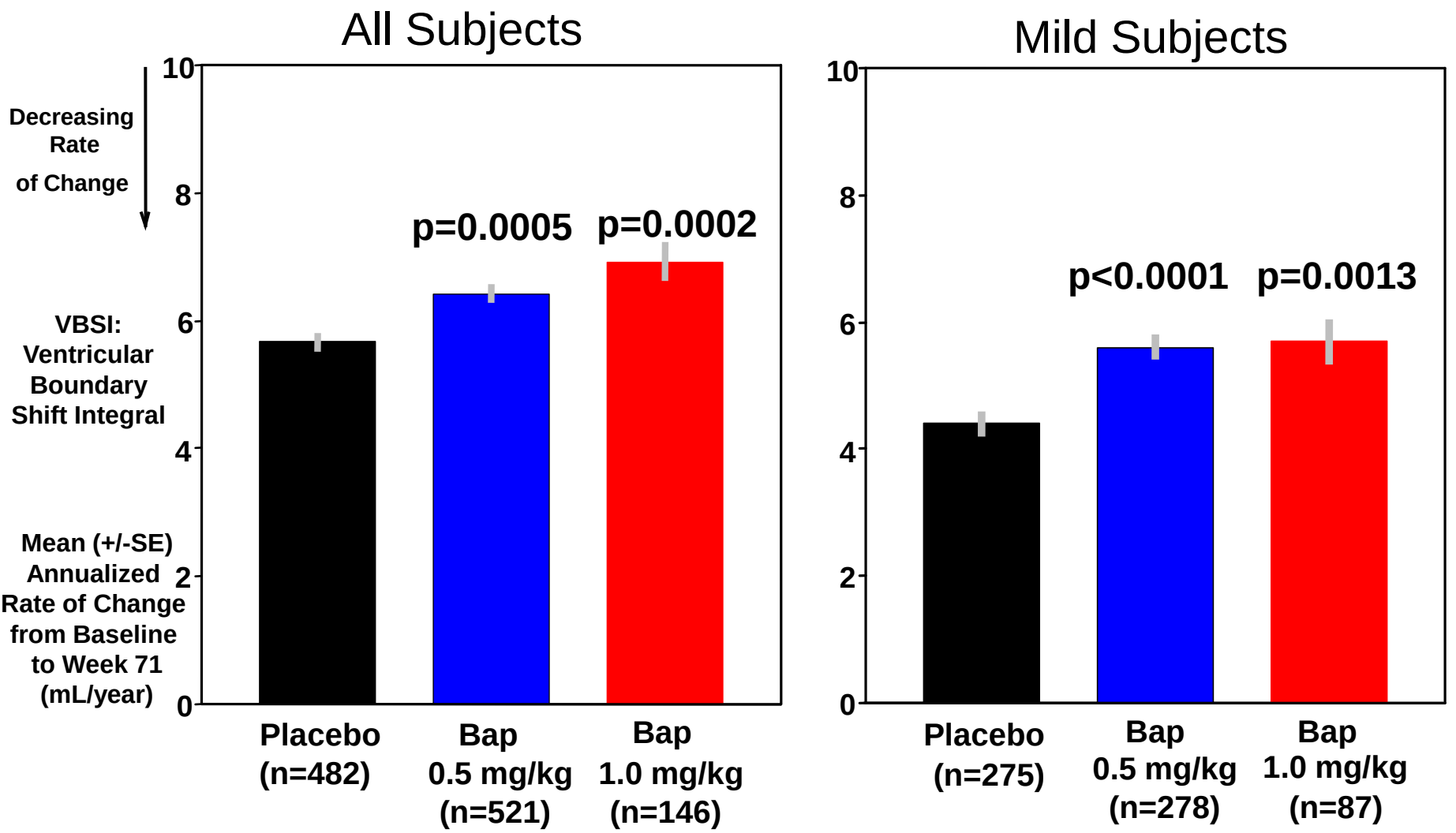
Rate of Change in MRI Ventricular Volume (VBSI) by Treatment Group at Week 71 (vMRI analysis population)



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



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

Biomarker Summary

- Reduced accumulation in amyloid burden on PiB PET relative to placebo observed in carrier and pooled studies
- Reduced CSF p-tau relative to placebo observed in carrier, non-carrier and pooled studies
- Increased rate of brain volume loss relative to placebo observed only in pooled studies
- Increased rate of left hippocampal volume loss relative to placebo observed only in non-carrier study
- Increased rate of ventricular expansion relative to placebo observed in carrier, non-carrier studies and pooled analyses

Interpreting Volumetric MRI

- Increased whole brain volumetric loss
  - Small effect – observed only in pooled studies
- Increased ventricular enlargement and hippocampal loss
  - Concordant with whole brain loss
- Previously reported in AN-1792
- Unknown mechanism
  - Increased neurodegeneration?
  - Amyloid removal?
  - Reduction in amyloid-associated inflammation?
  - Changes in CSF absorption or other fluid shifts?

Dissociation between biomarker activity and primary clinical outcomes

- No significant evidence of clinical effects in mild or moderate AD dementia based on pre-specified MMSE cut points
- Differences in amyloid burden on PET amyloid imaging indicative of target engagement
- Reduction in CSF p-tau consistent with effects on downstream neurodegeneration
- Ventricular volume increase and brain volume loss in treatment group suggests biological effects

Questions

- **Wrong target?**
  - Compelling genetic data supporting role of amyloid
  - Unclear which part of the amyloid cascade to target
  - Evidence of anti-amyloid treatment effects on a downstream marker of neurodegeneration (CSF p-tau)

- **Too little?**
  - Higher doses limited by ARIA-E
  - Though significant differences were seen on PiB-PET, was amyloid lowering insufficient to alter clinical course?

- **Too late?**
  - AD stage may be too far advanced to demonstrate clinical benefit
  - Anti-amyloid therapies may be more efficacious at earlier stages

Future Directions

- Analyses to fully elucidate the findings
  - Amyloid-positive patients only (PET and CSF substudies)
  - Secondary clinical endpoints in mild subgroup
  - Time course of volumetric MRI changes
  - Drug concentrations (AUC) relationship with clinical and biomarker outcomes
  - Relationship of ARIA to clinical and biomarker outcomes
- Very disappointing for patients and families
- These data may inform future anti-amyloid therapeutic trials at earlier stages of AD

Acknowledgments

Thanks to:

- Principal Investigators & Clinical Site Study Staff
- Phase 3 Steering Committee
- Data Safety Monitoring Committee
- Janssen Alzheimer Immunotherapy and Pfizer Study Teams
- *Most of all, grateful acknowledgement of the contribution of the participating AD patients and their caregivers*