EXPEDITION3: A Phase 3 Trial of Solanezumab in Mild Dementia due to Alzheimer's Disease

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On behalf of the EXPEDITION3 Study Team

Disclosure Statement

- I will discuss investigational use only.
- Dr. Honig has received support as a consultant/steering committee member from Forum, Fujirebio, Lundbeck, and Eli Lilly.
- Dr. Honig has received research funding as an investigator for AstraZeneca, Bristol-Myer Squibb, Forum, Genentech, Janssen, Eli Lilly, Lundbeck, Pfizer, Roche, TauRx, vTv.
- EXPEDITION3 is funded by Eli Lilly and Company.

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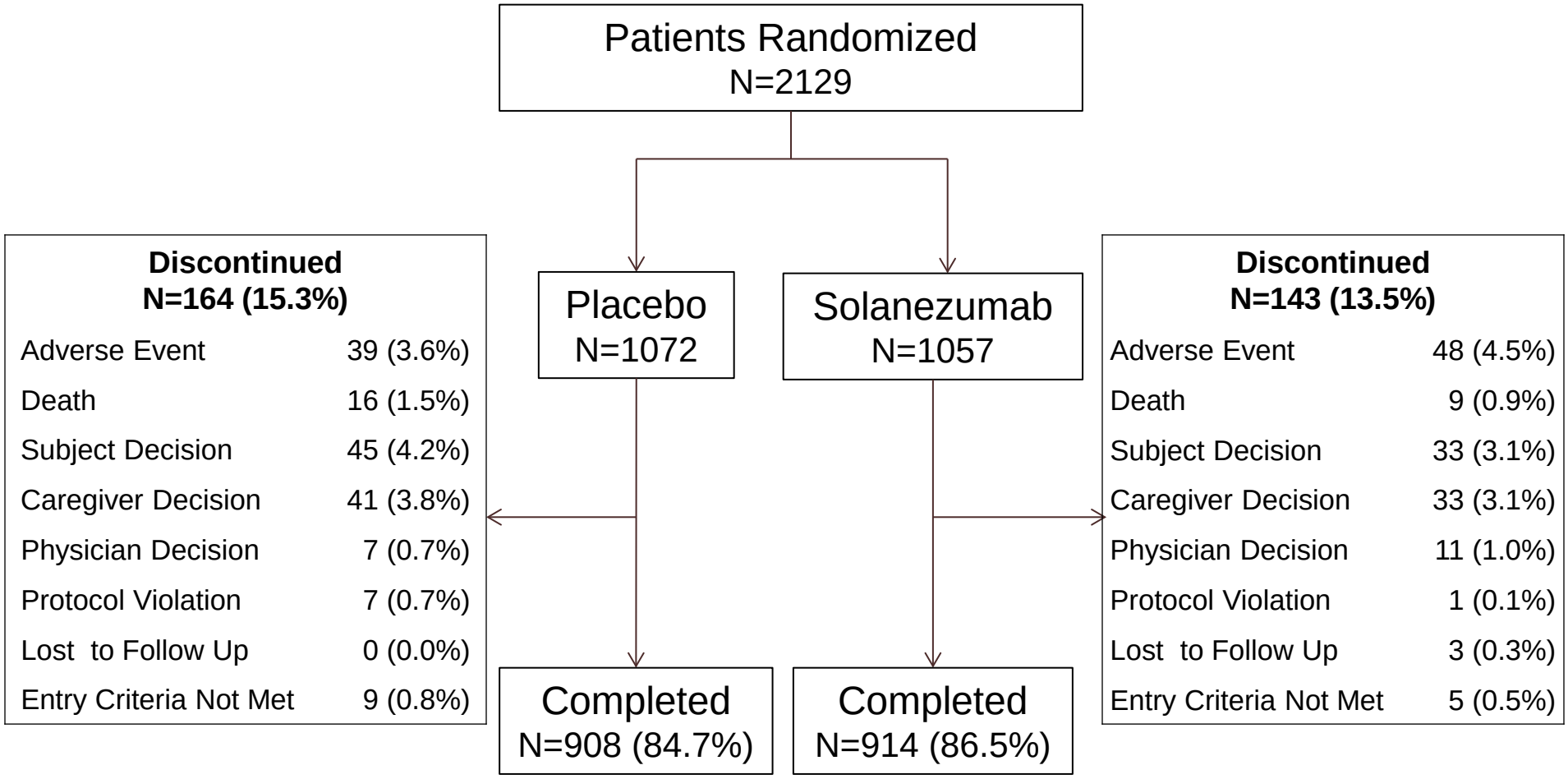
Patient Disposition



Abbreviations: AD=Alzheimer's disease; ECG=electrocardiogram; N=number.

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Study Design for EXPEDITION3

- Study LZAX (NCT01900665): double-blind, Phase 3, randomized to solanezumab (400 mg per dose) or placebo every 4 weeks for 80 weeks; optional open-label extension
- Age 55 to 90 years
- Probable AD by NINCDS/ADRDA criteria[1]
- Amyloid positive by F18 florbetapir PET or CSF $A\beta_{1-42}$
- MMSE score 20-26 inclusive
- On stable standard of care therapy (drug and non-drug)
  - Acetylcholinesterase inhibitors and/or memantine
  - Continued concomitant medication use allowed throughout study
- Conducted in 11 countries at 210 sites

Abbreviations: NINCDS/ADRDA=National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; PET=positron emission tomography; CSF=cerebrospinal fluid; MMSE=Mini Mental State Exam.

1. McKhann et al. Neurology, 1984; 34(7):939-944

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Baseline Demographics

Demographic	Placebo N=1072	Solanezumab N=1057	p-value
Age, years, mean (SD)	73.3 (8.0)	72.7 (7.8)	.073
Female, n (%)	631 (58.9%)	600 (56.8%)	.335
Race, n (%)			.758
White	894 (90.7%)	878 (90.5%)	
Black or African American	19 (1.9%)	14 (1.4%)	
Asian	71 (7.2%)	75 (7.7%)	
APOE ε4 carriers, n (%)*	685 (66.3%)	712 (69.3%)	.144
Education, years, mean (SD)	13.7 (3.8)	13.7 (3.7)	.906
Symptom onset, years, mean (SD)	4.3 (2.6)	4.2 (2.5)	.413
Diagnosis, years, mean (SD)	1.6 (1.7)	1.5 (1.6)	.132
AChEI and/or memantine use, n (%)	856 (79.9%)	822 (77.8%)	.244

*Based on number of patients with available APOE status (placebo N=1033; solanezumab N=1027).

Abbreviations: AD=Alzheimer's disease; n=number; SD=standard deviation; APOE=apolipoprotein E.

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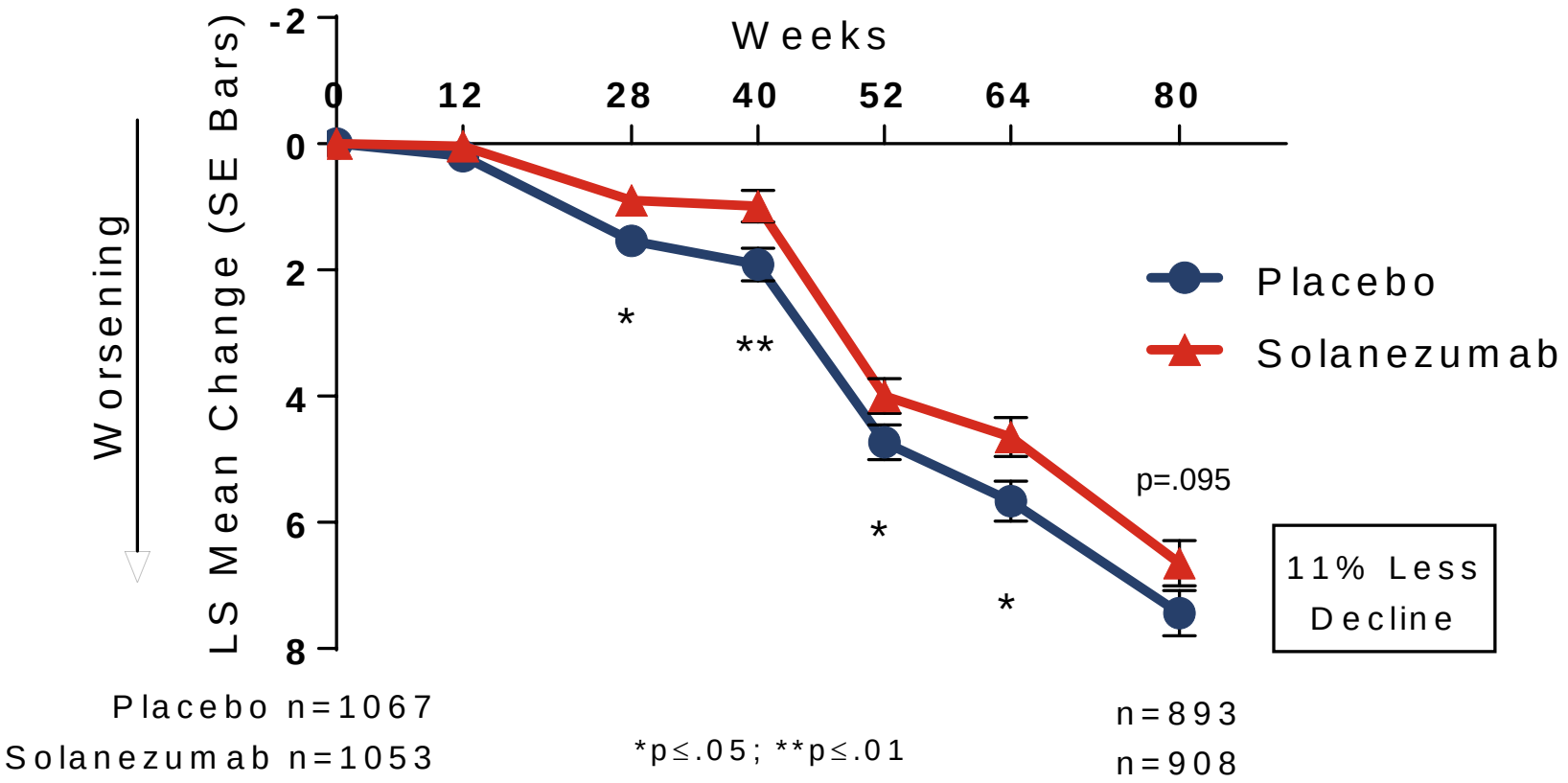
Change in Cognition - ADAS-Cog$_{14}$ (Primary)



Abbreviations: AD=Alzheimer's disease; ADAS-Cog$_{14}$=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=standard error.

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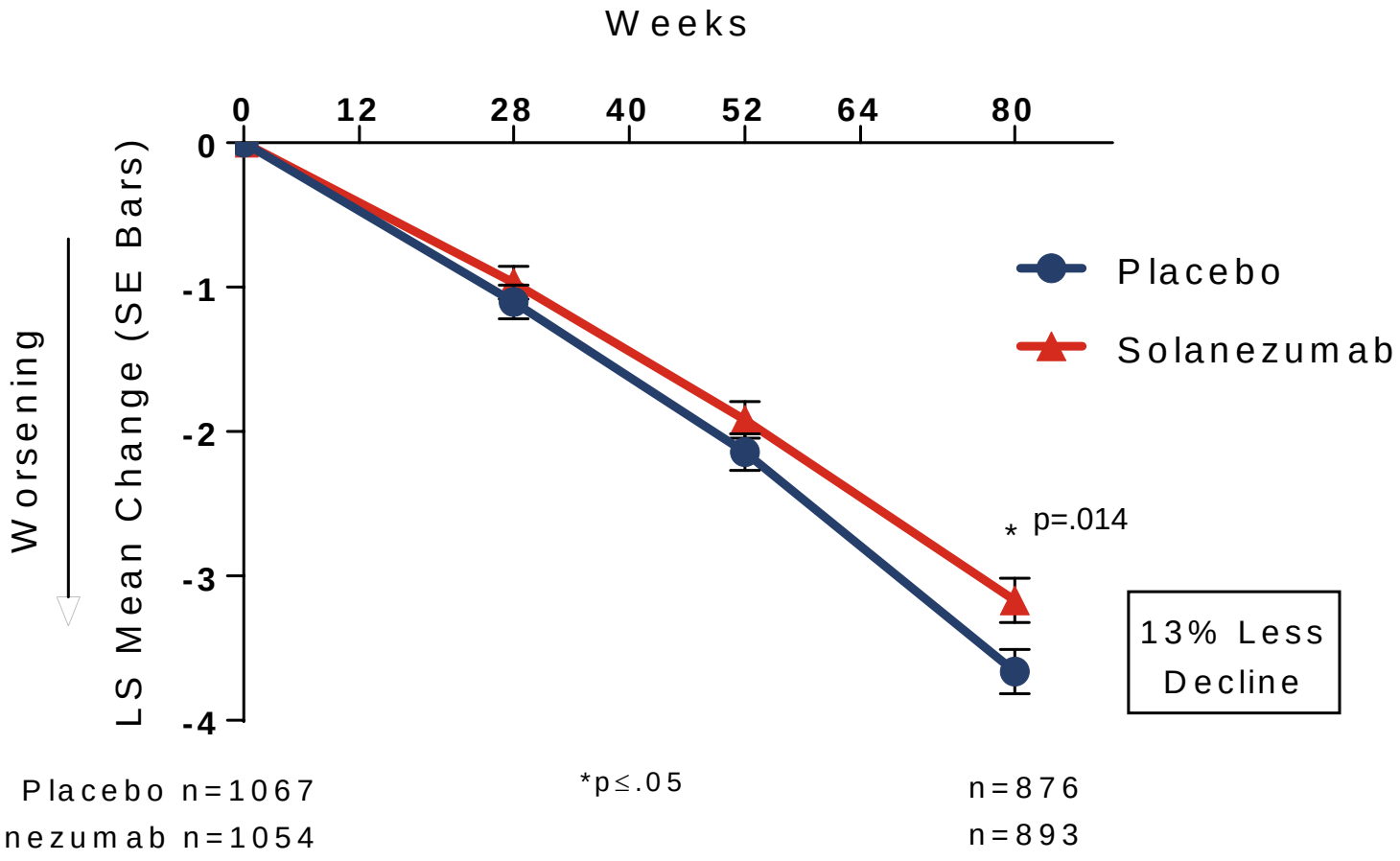
Change in Cognition - MMSE



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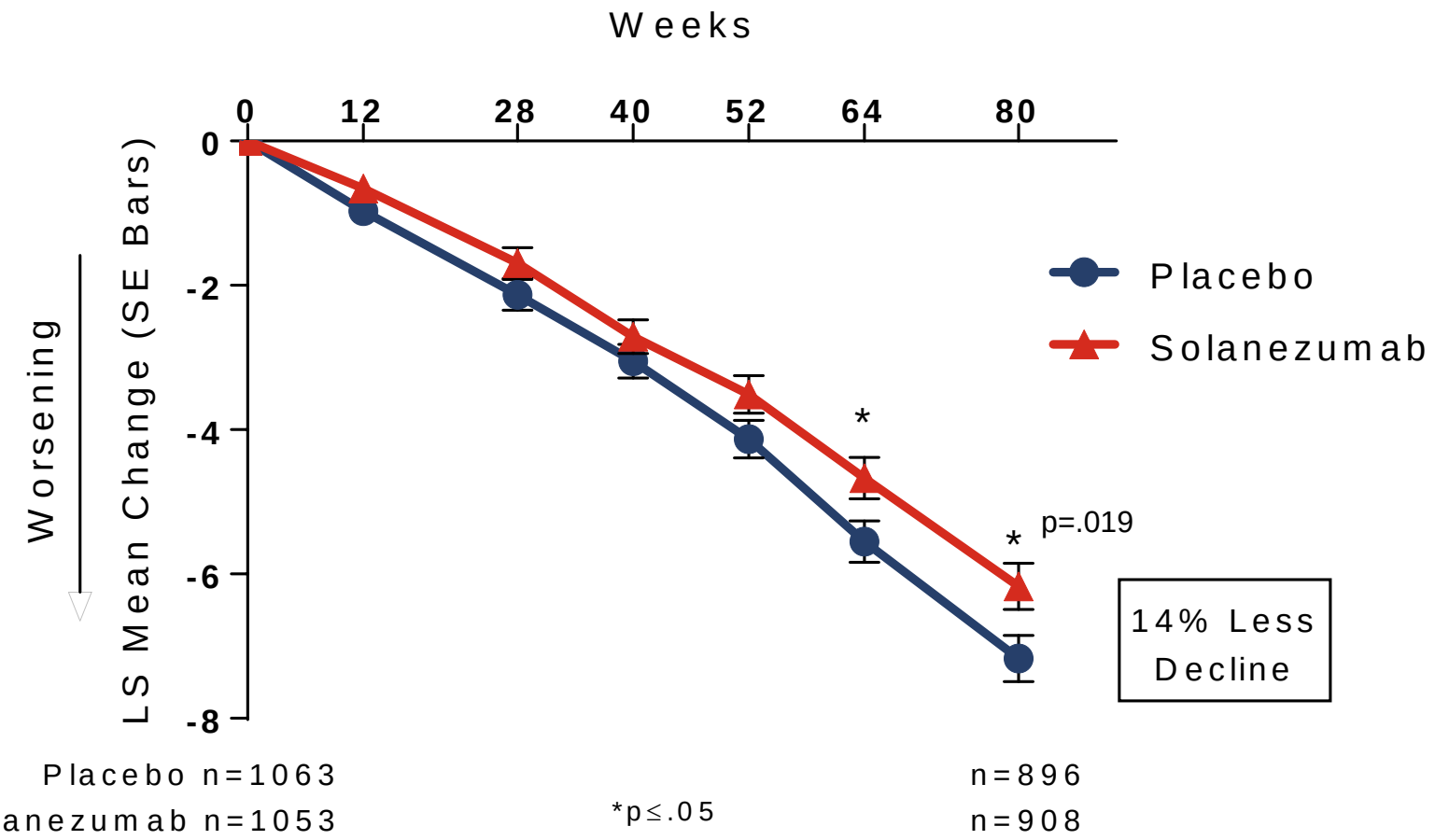
Change in Complex ADLs - ADCS-iADL



Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; SE=standard error.

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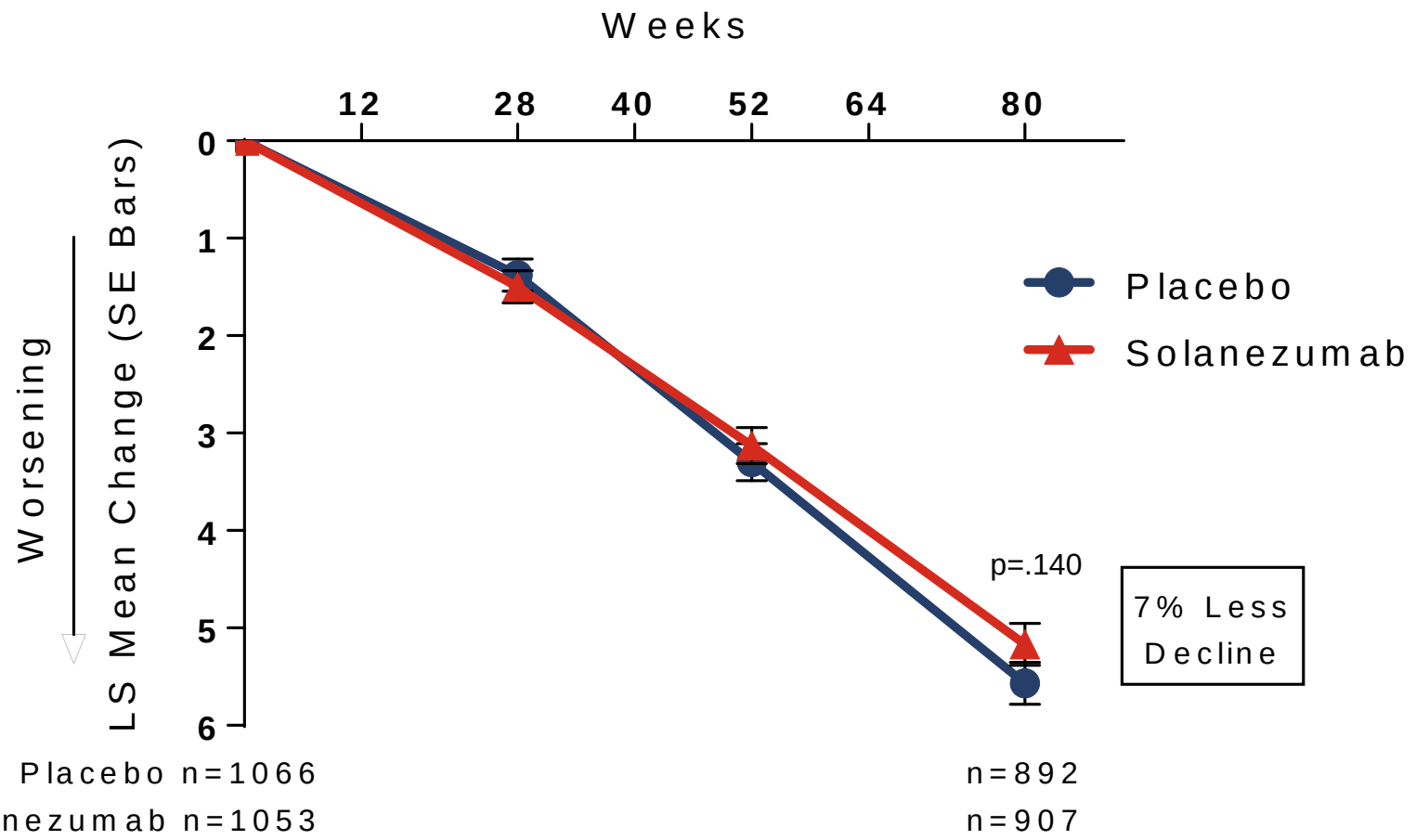
Change in Complex ADLs - FAQ



Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; FAQ=Functional Activities Questionnaire; LS=least squares; n=number; SE=standard error.

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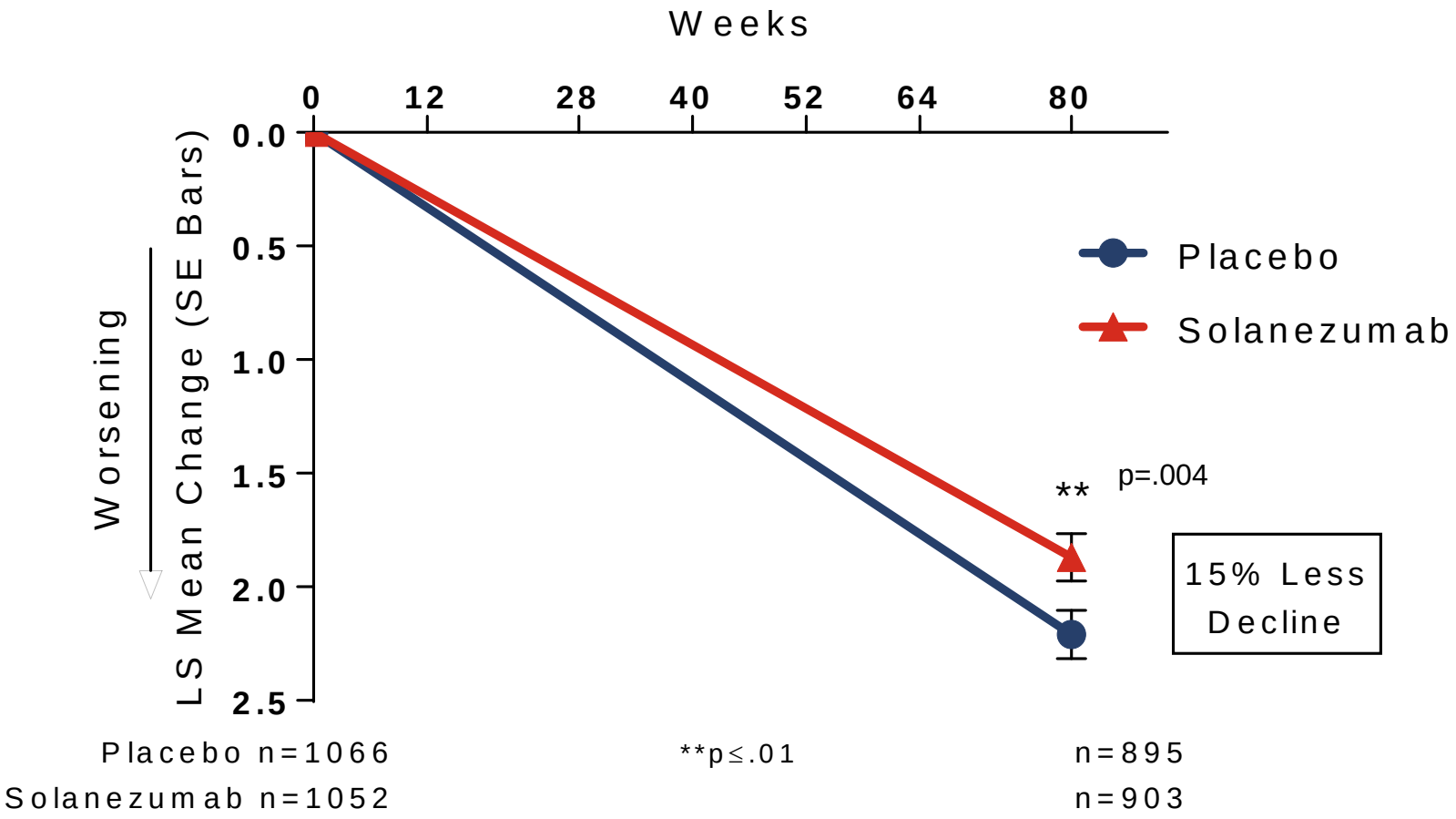
Change in Composite Scale - CDR-SB



Abbreviations: AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating Sum of Boxes; LS=least squares; n=number; SE=standard error.

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Change in Cognition and ADLs at 80 Weeks

	LS Mean Change (SE) at 80 Weeks		Less Decline	p-value
	Placebo	Solanezumab		
ADAS-Cog$_{14}$	7.44 (0.36)	6.65 (0.36)	11%	.095
MMSE	-3.66 (0.16)	-3.17 (0.15)	13%	.014
ADCS-iADL	-7.17 (0.32)	-6.17 (0.32)	14%	.019
ADCS-ADL	-8.77 (0.39)	-7.42 (0.39)	15%	.009
FAQ	5.57 (0.21)	5.17 (0.21)	7%	.140
CDR-SB	2.21 (0.11)	1.87 (0.10)	15%	.004

Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADAS-Cog$_{14}$=AD Assessment Scale-Cognitive 14-item Subscale; ADCS-ADL=AD Cooperative Study-Activities of Daily Living; CDR-SB=Clinical Dementia Rating Sum of Boxes; FAQ=Function Activities Questionnaire; iADRS=Integrated AD Rating Scale; LS=least squares; n=number of patients with evaluable 80-Week scale data; N/A=not applicable; MMSE=Mini–Mental State Examination; SE=standard error.

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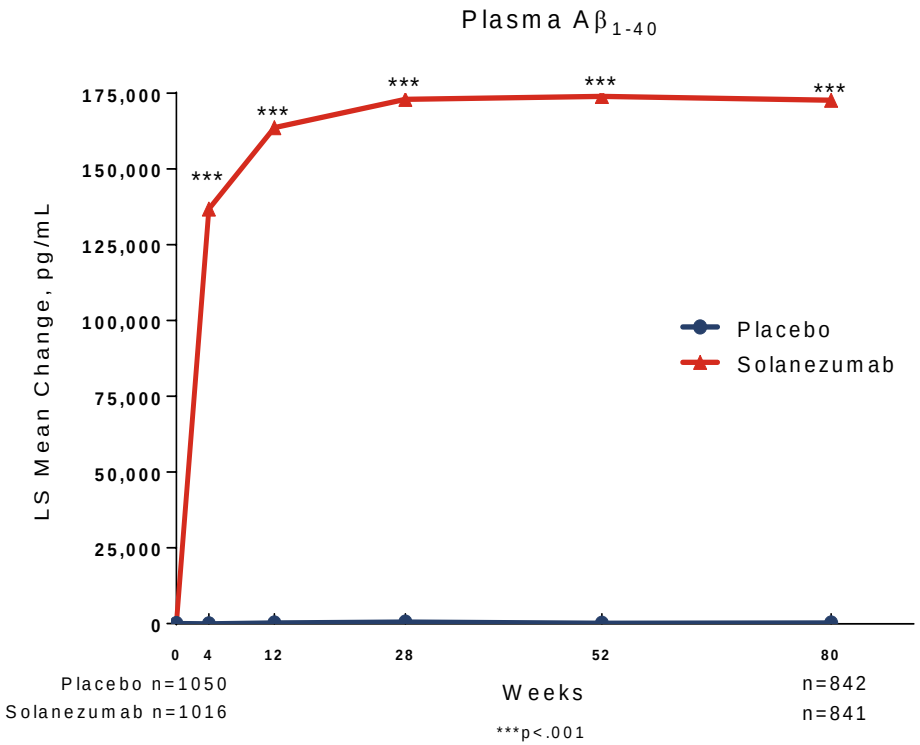
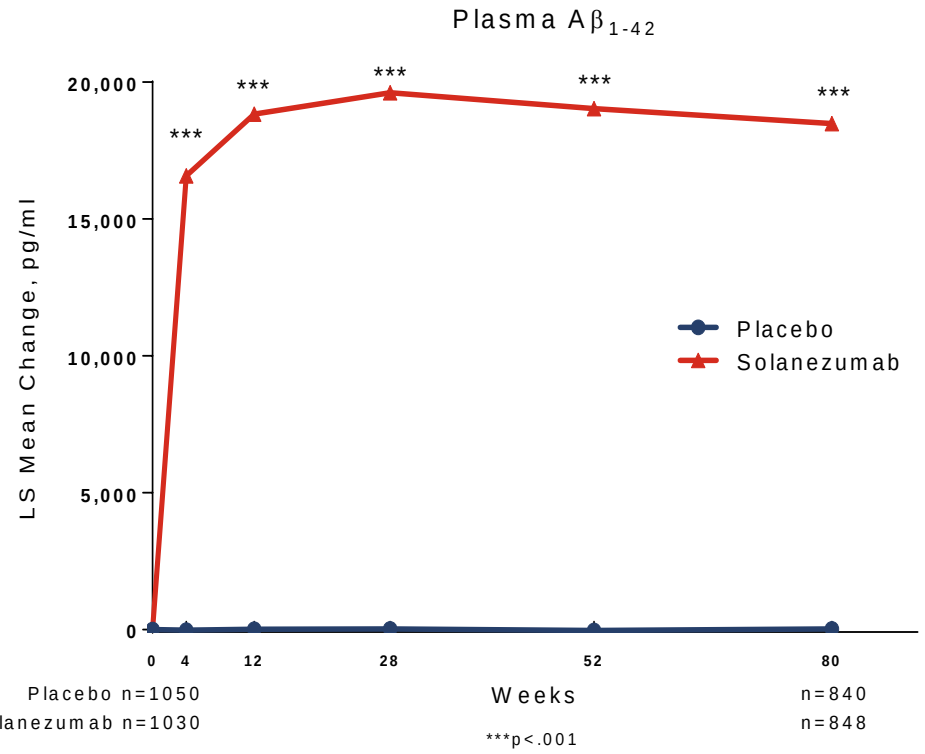
Plasma Changes in $A\beta_{1-40}$ and $A\beta_{1-42}$





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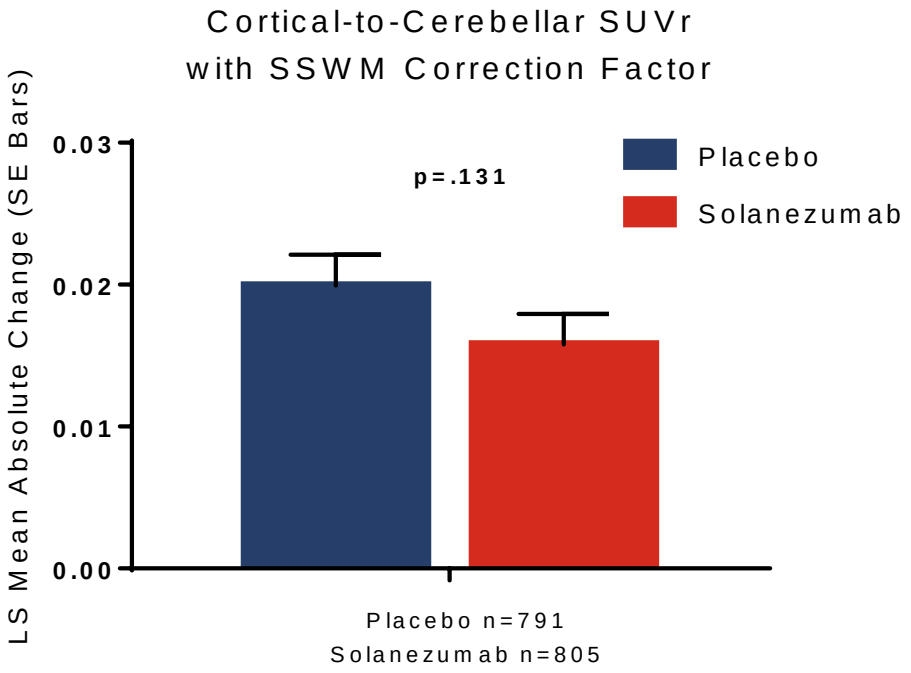
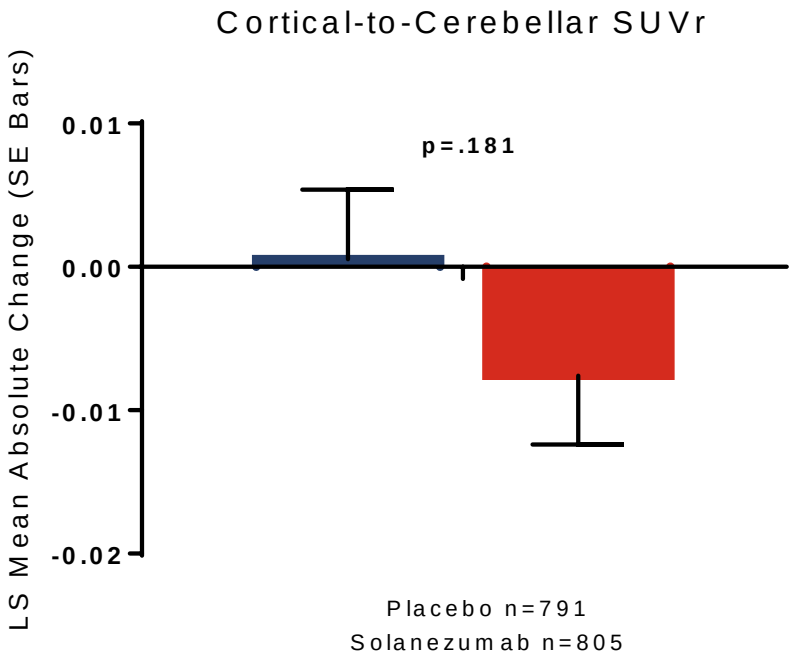
Florbetapir PET Change in Amyloid Deposition





The cortical SUV is a composite summary that consists of the following 6 regions: medial orbital frontal, anterior cingulate, parietal, temporal, posterior cingulate, and precuneus

Abbreviations: AD=Alzheimer's disease; PET=positron emission tomography; LS=least squares; n=number; SUVr=Standard Uptake Value ratio; SE=standard error; SSWM=subject-specific white matter.

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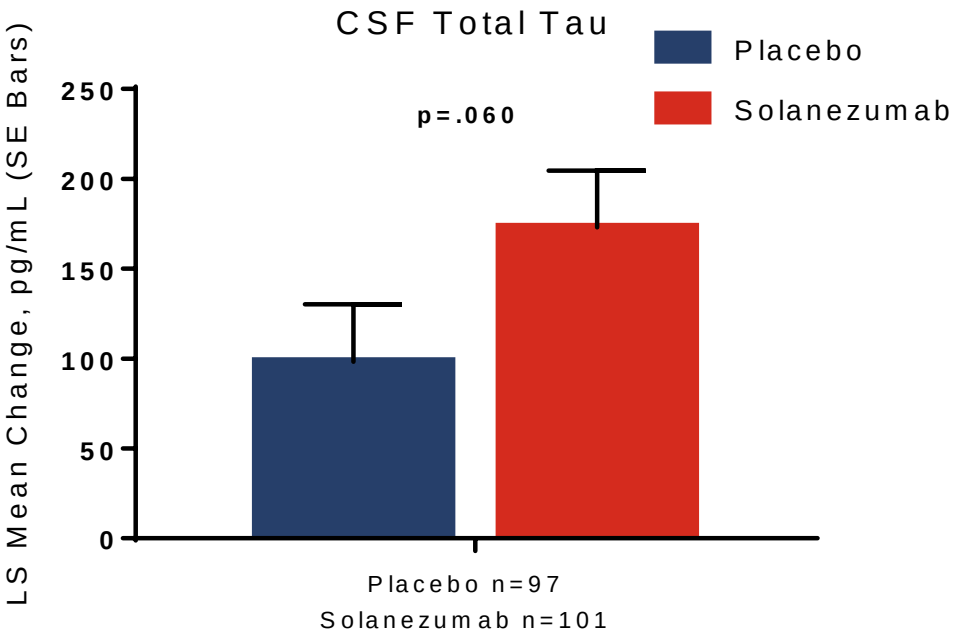
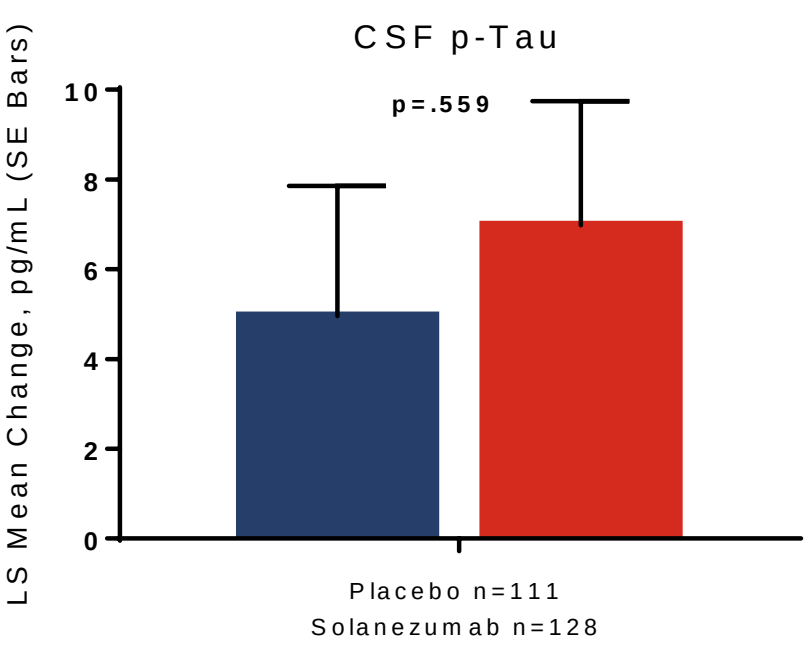
CSF Changes in Total Tau and p-Tau





Abbreviations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; LS=least squares; n=number, p-tau=phosphorylated tau; SE=standard error.

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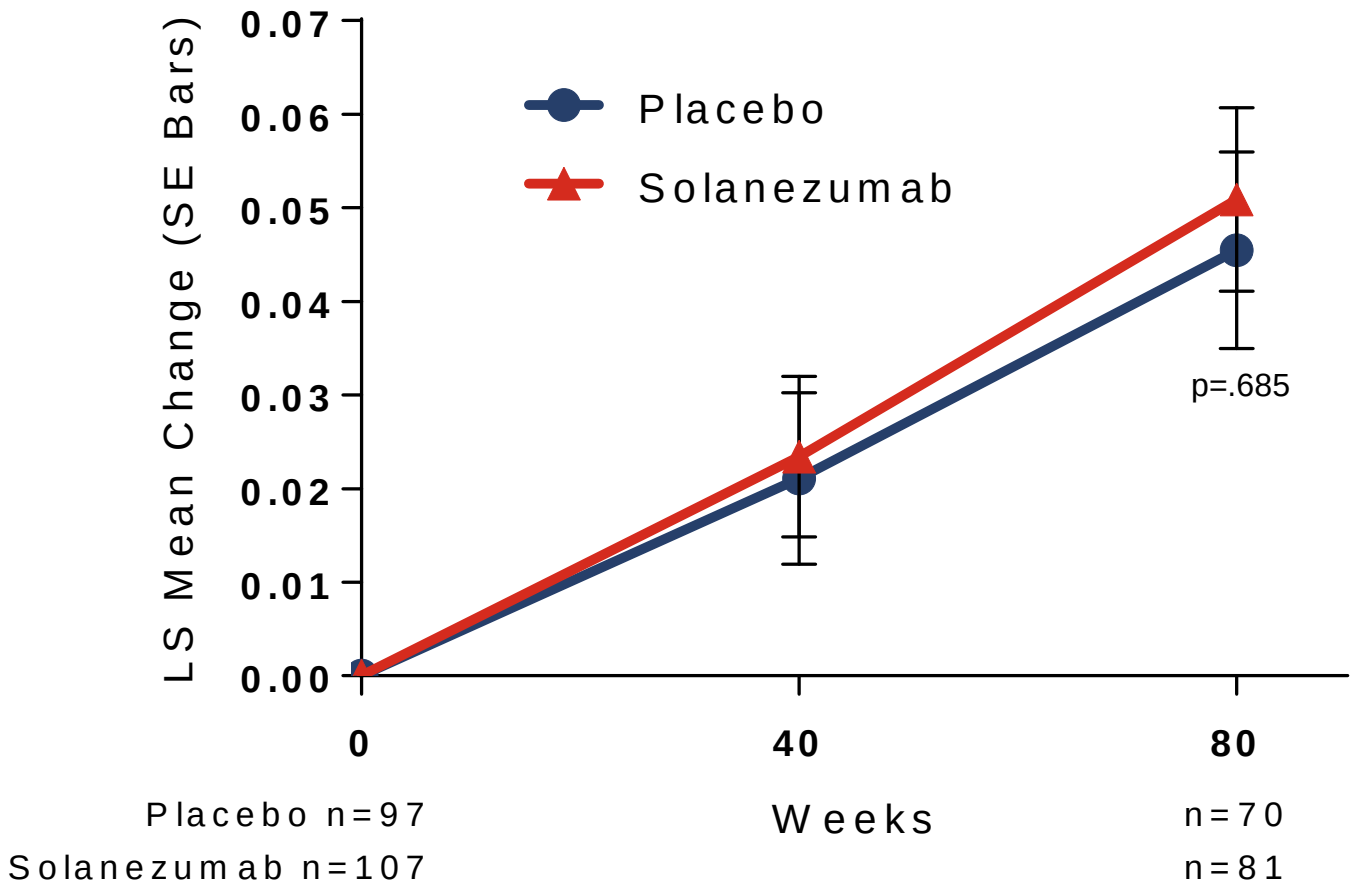
Flortaucipir PET Changes in Tau Deposition



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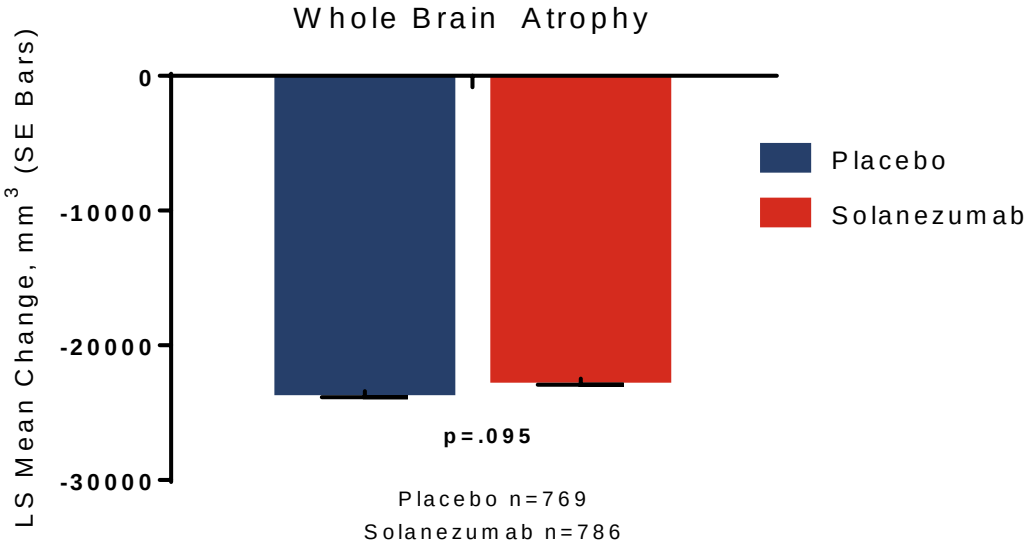
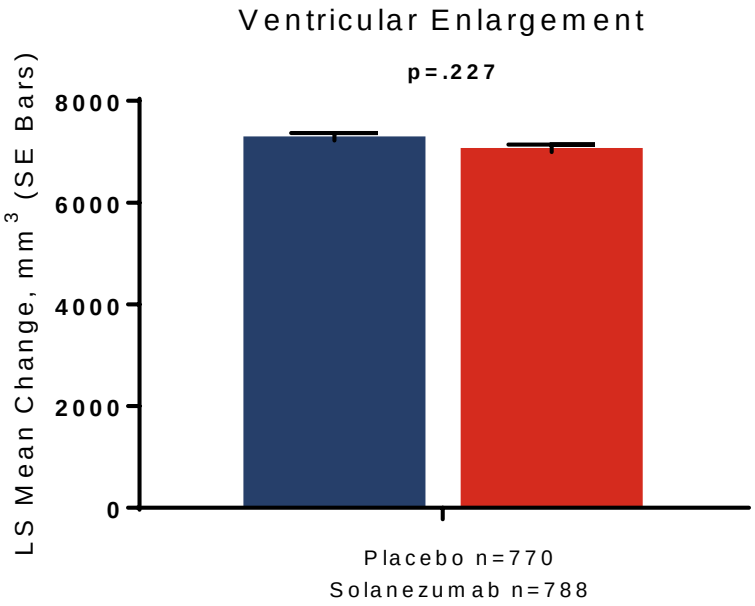
MRI Whole Brain Atrophy/Ventricular Enlargement





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Adverse Events Overview

Category, n (%)	Placebo N=1067	Solanezumab N=1054	p-value
SAE	202 (18.9%)	175 (16.6%)	.173
Death	16 (1.5%)	9 (0.9%)	.227
TEAE	890 (83.4%)	891 (84.5%)	.515
Discontinuation due to AE	39 (3.6%)	48 (4.5%)	.325

Abbreviations: AD=Alzheimer's disease; AE=adverse event; n=number; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

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Treatment Emergent AE Differences (p≤.05)

Preferred Term, n (%)	Placebo N=1067	Solanezumab N=1054	p-value
TEAE (≥1)	890 (83.4%)	891 (84.5%)	.515
Events more frequent in solanezumab treatment group			
Vitamin D Deficiency	6 (0.6%)	15 (1.4%)	.050
Nasal Congestion	4 (0.4%)	13 (1.2%)	.029
Spinal Osteoarthritis	4 (0.4%)	12 (1.1%)	.047
Dysuria	2 (0.2%)	9 (0.9%)	.037
Events more frequent in placebo treatment group			
Gait Disturbance	18 (1.7%)	4 (0.4%)	.004
Somnolence	13 (1.2%)	2 (0.2%)	.007

Abbreviations: AD=Alzheimer's disease; AE=adverse event; n=number; TEAE=treatment-emergent adverse event.

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EXPEDITION3 Conclusions

- Did not meet primary endpoint of decreasing cognitive decline
- Several secondary clinical endpoints directionally favored solanezumab, but the magnitudes of treatment differences were small
- Amyloid PET and CSF tau did not show significant treatment differences
- Factors possibly relevant to interpretation of study results include drug target, disease stage studied, and dosage of drug delivered

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Acknowledgements

Many thanks to the patients and their families, and the investigators and clinical trial staff, for their time and commitment to the EXPEDITION3 study

Thank you to the EXPEDITION3 Steering Committee and Study Team

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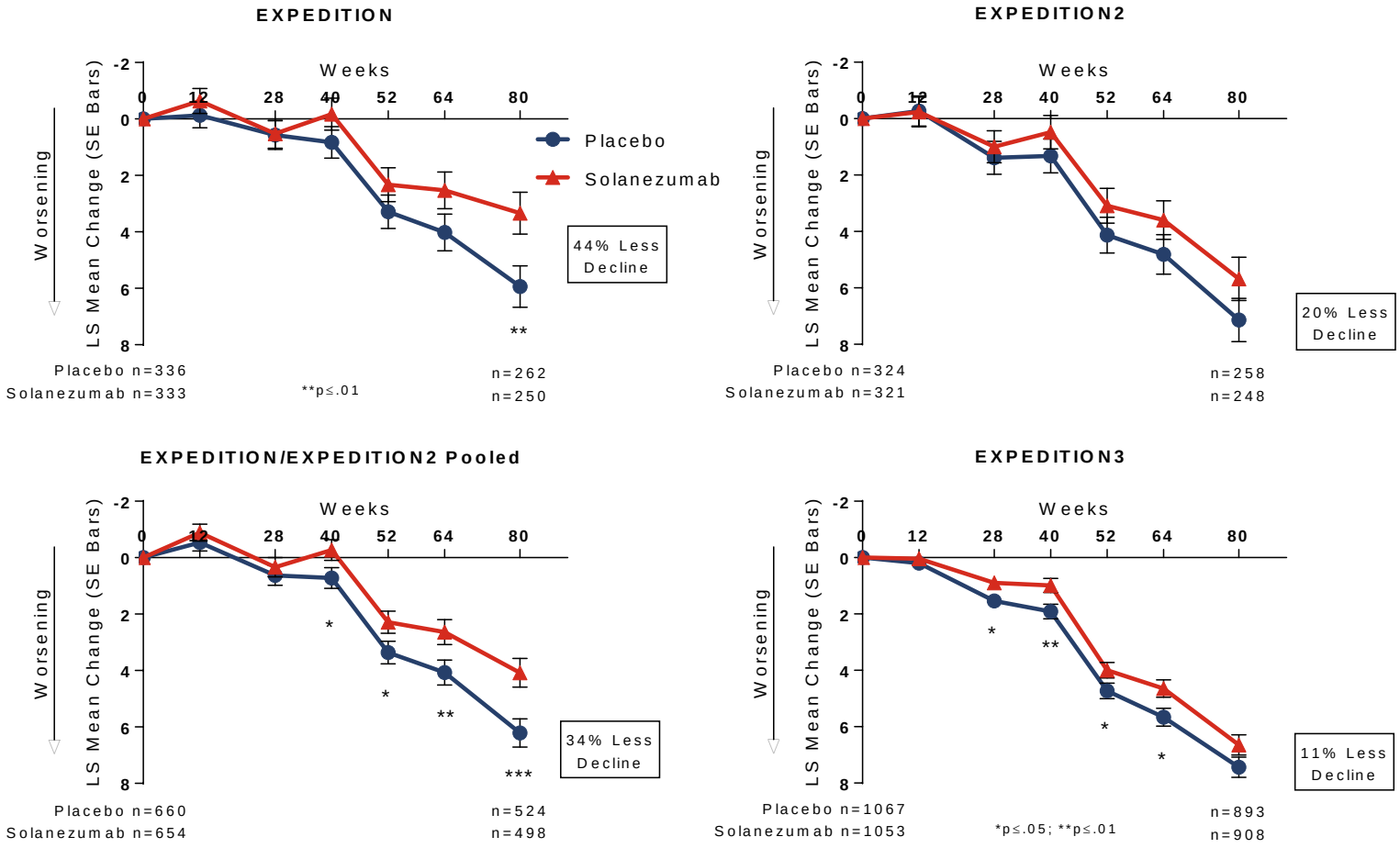
Panel Discussion

Lawrence S. Honig, MD, PhD, Columbia University Medical Center, New York, NY
Paul Aisen, MD, University of Southern California, San Diego, CA
Maria Carrillo, PhD, Alzheimer's Association, Chicago, IL
Bruno Vellas, MD, PhD, University Hospital of Toulouse, France
Eric Siemers, MD, Eli Lilly and Company, Indianapolis, IN

EXP, EXP2, Pooled, EXP3: Solanezumab Initiated in Mild AD Dementia

Change in Cognition - ADAS-Cog$_{14}$



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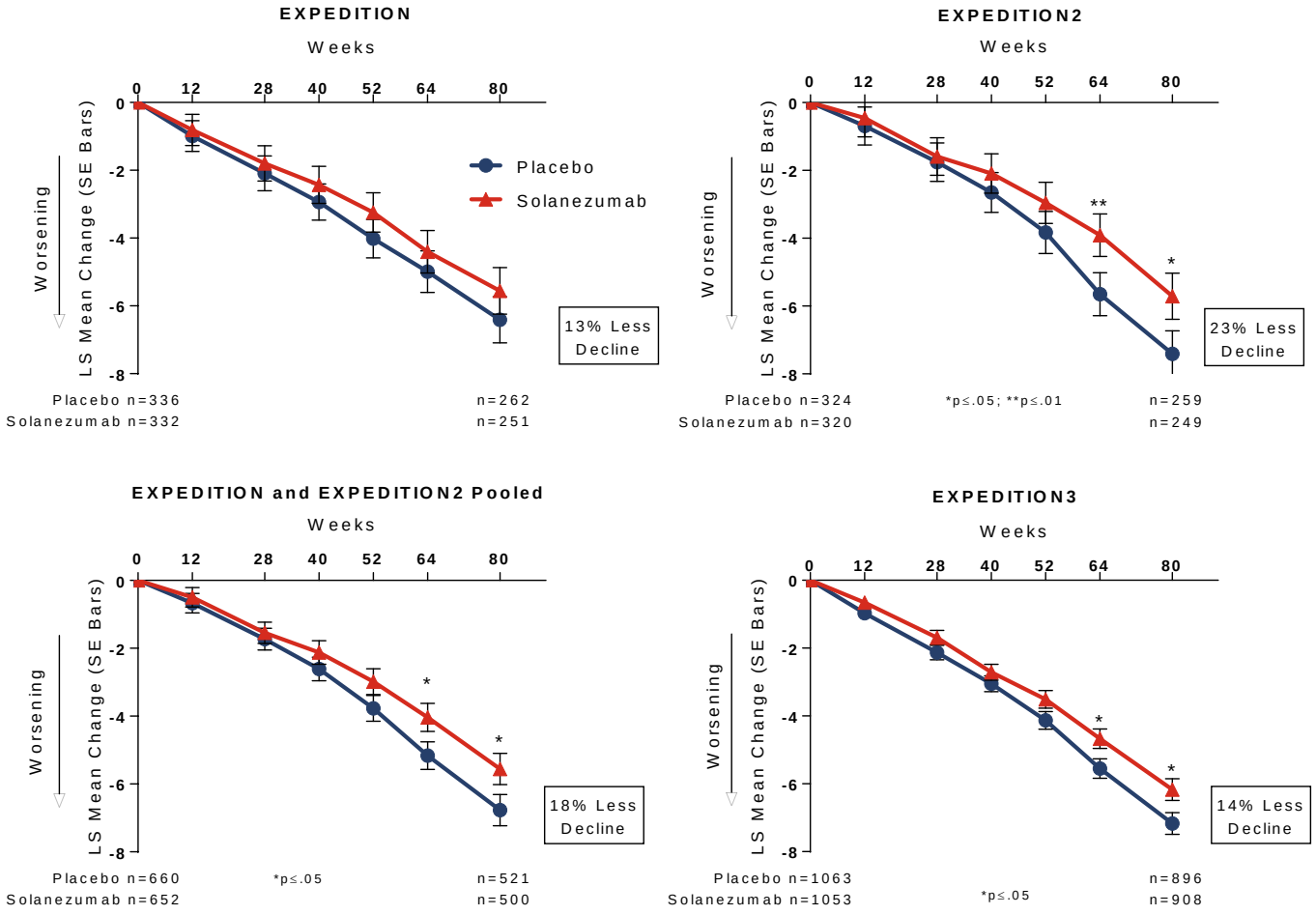

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