Supplementary Appendix

Supplement to: Sperling RA, Donohue MC, Raman R, et al. Trial of solanezumab in preclinical Alzheimer's disease. N Engl J Med 2023;389:1096-107. DOI: 10.1056/NEJMoa2305032

This appendix has been provided by the authors to give readers additional information about the work.

Supplemental Appendix

Contents:

Collaborators

We would like to especially acknowledge the dedication of all the participants and their study partners. We are grateful to the A4 site investigators and staff, and all of the partnership team members who made the A4 Study possible. In particular, the authors wish to acknowledge the contributions of our faculty colleagues: Drs. Joshua Grill, Jason Karlawish, Neil Graff-Radford, Gregory Jicha, Stephen Salloway, Rebecca Amariglio, Katherine Papp, Aaron Schultz, Robert Rissman, and Mr. Gustavo Jimenez-Maggiora. We would like to thank the A4 Data and Safety and Monitoring Board (DSMB), chaired by Dr. Daniel Weintraub, and Dr. Laurie Ryan from the National Institute on Aging. We would also like to highlight the special contributions of individuals from the A4 coordinating center at ATRI: Sara Abdel-Latif, Alison Belsha, Stefania Bruschi, Paula Cohen, Devon Gessert, Karin Ernstrom, Renarda Jones, Oliver Langford, Gabriela Muranevici, Elizabeth Shaffer, Hongmei Qiu, Vedeline Torreon, Sarah Walter, and colleagues from Eli Lilly and Co.: Russell Barton, Cheryl Brown, Phyllis Ferrell, Dr. Eric Siemers, and Isabella Velona.

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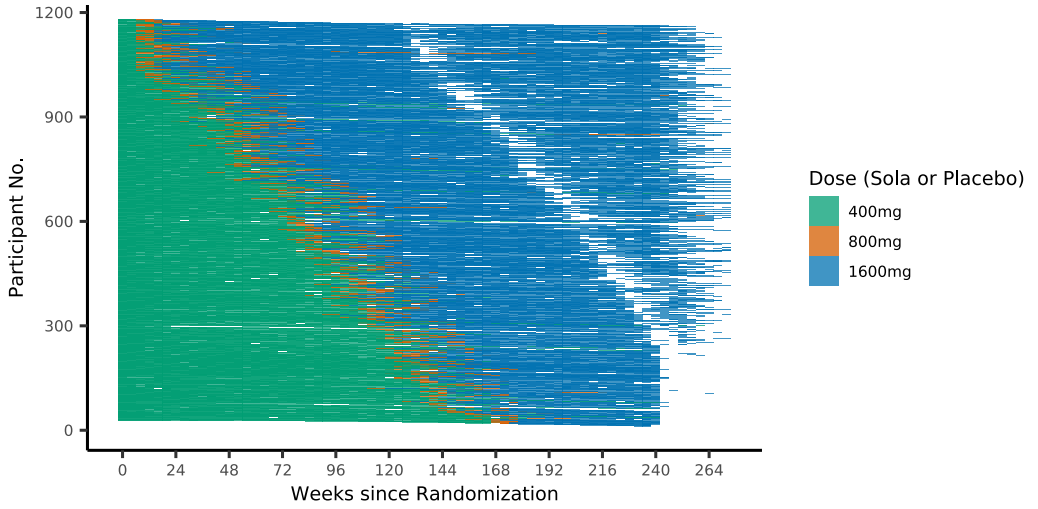
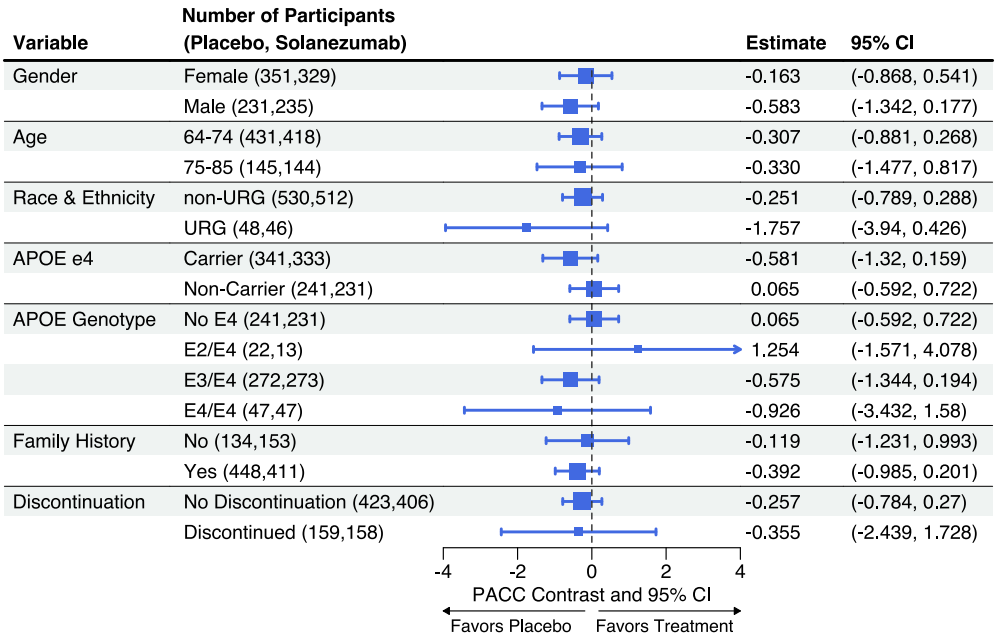
Supplemental Table 1. Representativeness of Study Participants.

Disease	Preclinical Alzheimer's disease
Sex and gender	AD is more common in women than men
Race or ethnic group	Increased risk and burden of dementia greater among African-American/Black and Hispanic/Latino individuals compared with non-Hispanic White individuals
Age	Prevalence increases steeply with age
Other considerations	Lower prevalence of amyloid accumulation in African-American/Black and Hispanic/Latino individuals confirmed during screening for A4. This finding is under investigation, but it may be an indication of increased risk of other dementia factors, such as vascular disease, in these groups.
Overall representativeness of this trial	The population studied in A4 is not representative of the population at risk for age-related cognitive decline or AD. Ongoing and future studies require major efforts to establish relationships of trust with diverse communities and minimize barriers to participation.



Supplemental Figure 1. Administered doses of solanezumab or placebo per participant and weeks since randomization. White spaces indicate missed doses or attrition. Participants who enrolled earlier and received fewer doses of 1600mg are depicted towards the bottom. Participants who enrolled later and received more doses of 1600mg are depicted towards the top. The hiatus in dosing due to the COVID19 pandemic is visible as the diagonal white band for all but the earliest enrolled participants.



Supplemental Figure 2. Subgroup Analyses of Primary Outcome

Forest plot of spline model adjusted randomized group difference in mean Preclinical Alzheimer Cognitive Composite (PACC) within the indicated subgroups. Confidence intervals (CI) which extend off of the plot are indicated with arrows. The natural cubic spline model includes effects for (i) two spline basis expansion terms for each subgroup, (ii) subgroup, (iii) PACC test version administered, (iv) age, (v) education, (vi) APOE4 Carrier Status (yes/no), and (vii) baseline florbetapir cortical SUVr. This model constrains the baseline treatment group means to be the same within each subgroup, but allow different baseline means for the subgroups. Redundant terms are dropped from the model in those cases in which the subgroup of interest is

overlapping with this general model (age and APOE subgroups). URG,

Underrepresented Group.

Supplemental Table 2: MMRM Analysis of Primary and Secondary Endpoints (Modified Intention-to-Treat Population).

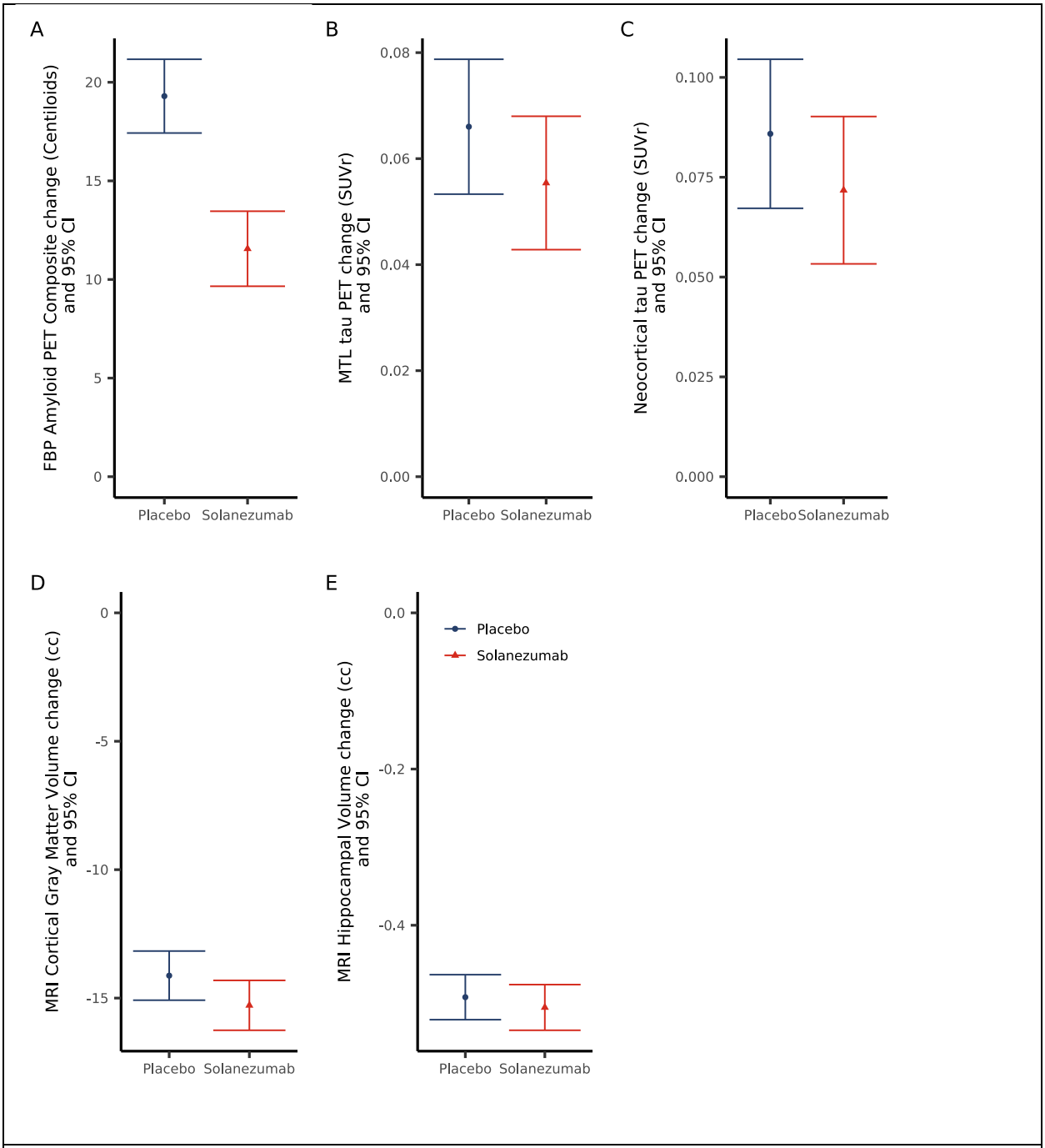
Endpoint		Solanezumab	Placebo
PACC	No. of participants evaluated*	401	423
	Adjusted mean change	-1.68	-1.34
	Adjusted mean difference vs. placebo (95% CI)	-0.34 (-0.94 to 0.27)	
CFI Combined	No. of participants evaluated*	403	416
	Adjusted mean change	1.84	1.30
	Adjusted mean difference vs. placebo (95% CI)	0.54 (-0.07 to 1.15)	
ADL Partner	No. of participants evaluated*	403	419
	Adjusted mean change	-2.59	-1.87
	Adjusted mean difference vs. placebo (95% CI)	-0.72 (-1.49 to 0.05)	
CDR-SB	No. of participants evaluated*	405	421
	Adjusted mean change	0.86	0.66
	Adjusted mean difference vs. placebo (95% CI)	0.20 (0.01 to 0.40)	

Adjusted mean and nominal 95% confidence intervals (CI) for the final visit derived from Mixed Model Repeated Measures (MMRM) analysis of Preclinical Alzheimer's Cognitive Composite (PACC), Cognitive Function Index (CFI) Participant and Partner, ADCS-Activities of Daily Living (ADL) Prevention Questionnaire Partner, and Clinical Dementia Rating - Sum of Boxes (CDR-SB).

Supplemental Table 3. Imaging Biomarker Endpoints.

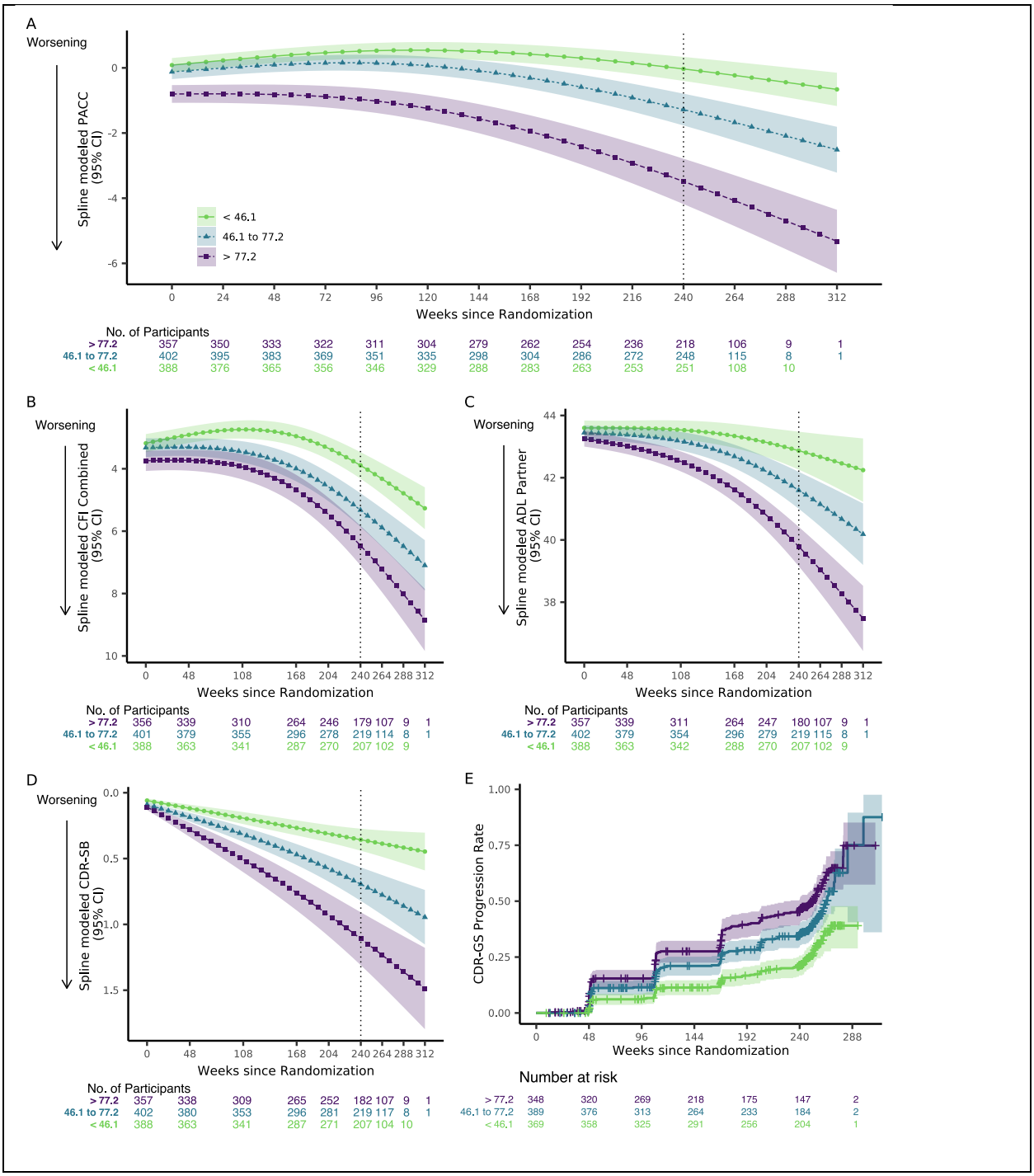
Endpoint		Solanezumab	Placebo
FBP Composite	No. of participants evaluated*	462	477
	Adjusted mean change	11.6	19.3
	Adjusted mean difference vs. placebo (95% CI)	-7.7 (-10 to -5.1)	
FTP MTL Composite	No. of participants evaluated*	172	168
	Adjusted mean change	0.0547	0.0665
	Adjusted mean difference vs. placebo (95% CI)	-0.012 (-0.03 to 0.006)	
FTP Neocortical Composite	No. of participants evaluated*	172	168
	Adjusted mean change	0.0720	0.0858
	Adjusted mean difference vs. placebo (95% CI)	-0.014 (-0.04 to 0.012)	
MRI Cortical Gray Matter	No. of participants evaluated*	394	408
	Adjusted mean change	-15.3	-14.1
	Adjusted mean difference vs. placebo (95% CI)	-1.2 (-2.5 to 0.19)	
MRI Hippocampal Volume	No. of participants evaluated*	394	408
	Adjusted mean change	-0.505	-0.492
	Adjusted mean difference vs. placebo (95% CI)	-0.013 (-0.054 to 0.027)	

The table provides model adjusted mean change and nominal 95% confidence intervals (CI) estimated from analysis of covariance models with age, APOE, treatment group, and baseline biomarker value as covariates. The 95% confidence intervals are not adjusted for multiple comparisons. Endpoints include florbetapir (FBP) amyloid positron emission tomography (PET) composite in centiloids, flortaucipir (FTP) tau PET medial temporal lobe (MTL) composite of amygdala, entorhinal, and parahippocampal standardized uptake value ratios (SUVr), FTP tau PET neocortical composite of fusiform, inferior temporal, middle temporal, inferior parietal SUVr, and magnetic resonance imaging (MRI) of hippocampal and total gray matter volume in cubic centimeters (cc).
*Some participants had delayed evaluations beyond 240 weeks due to the COVID pandemic.



Supplemental Figure 3. Imaging Biomarker Endpoints. All panels show model adjusted mean change and nominal 95% confidence intervals (CI) estimated from analysis of covariance models with age, APOE, treatment group, and baseline biomarker value as covariates. The 95% confidence intervals are not adjusted for multiple testing. Panel A shows florbetapir (FBP) amyloid positron emission tomography (PET) composite in centiloids. Panel B shows flortaucipir tau PET medial temporal lobe (MTL) composite of amygdala, entorhinal, and parahippocampal standardized uptake value ratios (SUVr). Panel C shows FTP tau PET neocortical composite of fusiform, inferior temporal, middle temporal, inferior parietal SUVr.

Panels D and E show magnetic resonance imaging (MRI) of total gray matter volume and hippocampal volume in cubic centimeters (cc).


A
Worsening
Spline modeled PACC (95% CI)
0
-2
-4
-6
< 46.1
46.1 to 77.2
> 77.2
0 24 48 72 96 120 144 168 192 216 240 264 288 312
Weeks since Randomization
No. of Participants
> 77.2 357 350 333 322 311 304 279 262 254 236 218 106 9 1
46.1 to 77.2 402 395 383 369 351 335 298 304 286 272 248 115 8 1
< 46.1 388 376 365 356 346 329 288 283 263 253 251 108 10
B
Worsening
Spline modeled CFI Combined (95% CI)
4
6
8
10
0 48 108 168 204 240 264 288 312
Weeks since Randomization
No. of Participants
> 77.2 356 339 310 264 246 179 107 9 1
46.1 to 77.2 401 379 355 296 278 219 114 8 1
< 46.1 388 363 341 287 270 207 102 9
C
Worsening
Spline modeled ADL Partner (95% CI)
44
42
40
38
0 48 108 168 204 240 264 288 312
Weeks since Randomization
No. of Participants
> 77.2 357 339 311 264 247 180 107 9 1
46.1 to 77.2 402 379 354 296 279 219 115 8 1
< 46.1 388 363 342 288 270 207 102 9
D
Worsening
Spline modeled CDR-SB (95% CI)
0.0
0.5
1.0
1.5
0 48 108 168 204 240 264 288 312
Weeks since Randomization
No. of Participants
> 77.2 357 338 309 265 252 182 107 9 1
46.1 to 77.2 402 380 353 296 281 219 117 8 1
< 46.1 388 363 341 287 271 207 104 10
E
CDR-GS Progression Rate
1.00
0.75
0.50
0.25
0.00
0 48 96 144 192 240 288
Weeks since Randomization
Number at risk
> 77.2 348 320 269 218 175 147 2
46.1 to 77.2 389 376 313 264 233 184 2
< 46.1 369 358 325 291 256 204 1

Supplemental Figure 4. Cognitive and functional scores by level of baseline amyloid.

All panels show results for the modified intention-to-treat population. The shaded regions represent nominal 95% confidence intervals that are not adjusted for multiple testing. Data are aggregated with respect to treatment groups and grouped instead by tertiles of baseline florbetapir amyloid positron emission tomography (PET). The Panel A shows the primary end point, the Preclinical Alzheimer Cognitive Composite (PACC). The PACC is the sum of four z-scores with higher scores indicating better cognitive performance. The adjusted means and 95% confidence (indicated by shaded regions) were estimated using a natural cubic spline model. The model allows amyloid group baseline means to be different and includes (i) two spline basis expansion terms for each amyloid group (six terms total), (ii) PACC test version administered, (iii) age, (iv) education, (v) APOE4 Carrier Status (yes/no), and (vi) baseline florbetapir cortical SUVr. Panels B and C show spline model adjusted mean Cognitive Function Index (CFI) Participant and Partner, ADCS-Activities of Daily Living (ADL) Prevention Questionnaire Partner. Panel D shows spline model adjusted mean Clinical Dementia Rating - Sum of Boxes (CDR-SB). Panel E shows Kaplan-Meier estimates of Global Score (CDR-GS) Progression stratified by amyloid group.

Supplemental Table 4. Adverse events.

	Solanezumab (N = 572)	Placebo (N = 591)
Events of special interest		
Any Treatment Emergent adverse event (TEAE)	560 (97.9)	577 (97.6)
TEAE definitely related to Solanezumab or Placebo	6 (1.0)	8 (1.4)
Treatment Emergent Serious Adverse event (TESAE)	172 (30.1)	158 (26.7)
Death	6 (1.0)	7 (1.2)
TEAE leading to discontinuation	28 (4.9)	34 (5.8)
ARIA, n (%)	167 (29.2%)	194 (32.8%)
ARIA-E, n (%)	1 (0.2%)	2 (0.3%)
ARIA-H, n (%)	167 (29.2%)	194 (32.8%)
Microhemorrhage, n (%)	158 (27.6%)	189 (32.0%)
Superficial siderosis, n (%)	19 (3.3%)	19 (3.2%)

Adverse event that occurred in ≥5% of participants in either group		
Upper respiratory tract infection	174 (30.4)	198 (33.5)
Fall	172 (30.1)	160 (27.1)
Nasopharyngitis	117 (20.5)	121 (20.5)
Arthralgia	116 (20.3)	119 (20.1)
Headache	113 (19.8)	118 (20.0)
Urinary tract infection	83 (14.5)	94 (15.9)
Dizziness	80 (14.0)	62 (10.5)
Diarrhoea	78 (13.6)	78 (13.2)
Back pain	78 (13.6)	78 (13.2)
Cataract	61 (10.7)	75 (12.7)
Sinusitis	59 (10.3)	74 (12.5)
Contusion	59 (10.3)	56 (9.5)
Hypertension	58 (10.1)	60 (10.2)
Fatigue	56 (9.8)	46 (7.8)
Rash	56 (9.8)	39 (6.6)
Osteoarthritis	55 (9.6)	63 (10.7)
Cognitive disorder	51 (8.9)	34 (5.8)
Bronchitis	50 (8.7)	63 (10.7)

Influenza	49 (8.6)	43 (7.3)
Pain in extremity	47 (8.2)	53 (9.0)
Basal cell carcinoma	47 (8.2)	53 (9.0)
Skin laceration	43 (7.5)	53 (9.0)
Muscle strain	43 (7.5)	37 (6.3)
Cough	43 (7.5)	50 (8.5)
Muscle spasms	40 (7.0)	33 (5.6)
Anxiety	38 (6.6)	34 (5.8)
Vertigo	35 (6.1)	29 (4.9)
Depression	35 (6.1)	38 (6.4)
Skin abrasion	34 (5.9)	28 (4.7)
Arthritis	34 (5.9)	37 (6.3)
Insomnia	34 (5.9)	36 (6.1)
Gastrooesophageal reflux disease	33 (5.8)	38 (6.4)
Nausea	33 (5.8)	31 (5.2)
Squamous cell carcinoma	33 (5.8)	30 (5.1)
Sciatica	33 (5.8)	22 (3.7)
Ligament sprain	31 (5.4)	40 (6.8)
Seasonal allergy	30 (5.2)	24 (4.1)
Cellulitis	29 (5.1)	30 (5.1)

Myalgia	29 (5.1)	23 (3.9)
Dermatitis contact	29 (5.1)	26 (4.4)
Viral upper respiratory tract infection	27 (4.7)	39 (6.6)
Atrial fibrillation	26 (4.5)	31 (5.2)
Pneumonia	26 (4.5)	33 (5.6)
Cerebral microhaemorrhage	22 (3.8)	41 (6.9)
Arthropod bite	21 (3.7)	30 (5.1)