

SHORT REPORT

Magnetic resonance imaging measures of brain volumes across the EXPEDITION trials in mild and moderate Alzheimer's disease dementia

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Abstract

Introduction: Solanezumab is a monoclonal antibody that preferentially binds soluble amyloid beta and promotes its clearance from the brain. The aim of this post hoc analysis was to assess the effect of low-dose solanezumab (400 mg) on global brain volume measures in patients with mild or moderate Alzheimer's disease (AD) dementia quantified using volumetric magnetic resonance imaging (vMRI) data from the EXPEDITION clinical trial program.

Methods: Patients with mild or moderate AD (EXPEDITION and EXPEDITION2) and mild AD (EXPEDITION3), were treated with either placebo or solanezumab (400 mg) every 4 weeks (Q4W) for 76 weeks. vMRI scans were acquired at baseline and at 80 weeks from 427 MRI facilities using a standardized imaging protocol. Whole brain volume (WBV) and ventricle volume (VV) changes were estimated at 80 weeks using either boundary shift integral (EXPEDITION and EXPEDITION2) or tensor-based morphometry (EXPEDITION3).

Results: The pooled cohort used for this study consisted of participants with vMRI at baseline and week 80 across the three trials. Analyzed patient subgroups comprised full patient cohort ($N = 2933$), apolipoprotein E (APOE) $\epsilon 4^+$ carriers ($N = 1835$), and patients with mild ($N = 2497$) or moderate AD dementia ($N = 428$). No significant effect (all P -values $\geq .05$) of treatment was observed in the pooled sample, individual trials, or subgroups of patients with mild or moderate AD or APOE $\epsilon 4$ carriers, in either WBV or VV change.

Discussion: Analysis of patients with mild or moderate AD dementia from baseline to 80 weeks using vMRI measures of WBV and VV changes suggested that low-dose solanezumab was not linked to changes in volumes at 80 weeks. Analysis of the pooled cohort did not demonstrate an effect on brain volumes with treatment. Evaluation

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KEYWORDS

Alzheimer's disease, amyloid, atrophy, magnetic resonance imaging, solanezumab, volumetric magnetic resonance imaging

1 | INTRODUCTION

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disease, characterized by accumulation of amyloid beta ($A\beta$) plaques and neurofibrillary tangles of hyperphosphorylated tau.¹ Current treatments include acetylcholinesterase inhibitors and the non-competitive N-methyl-D-aspartate receptor antagonist memantine, which provide partial symptomatic relief.¹ The anti-amyloid antibody, Aduhelm, was recently approved for treatment of patients with mild cognitive impairment or mild dementia due to AD.²

A number of $A\beta$ immunotherapies have shown promise in Phase 2 and 3 trials.^{3–8} Solanezumab is a monoclonal antibody designed to slow progression of AD by preferentially binding soluble $A\beta$.⁹

In patients with mild-to-moderate AD dementia (EXPEDITION and EXPEDITION2), low-dose solanezumab (400 mg), every 4 weeks (Q4W) for 76 weeks, did not yield a treatment benefit.⁷ In a secondary analysis of the mild AD dementia population, less decline was seen on some cognitive and functional measures.¹⁰ In EXPEDITION3, in patients with mild AD and evidence of amyloid pathology, there was no significant difference at week 80 between solanezumab and placebo-treated patients on the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog14).⁸ Although solanezumab had no significant effect on the primary outcome in this study, solanezumab was favored across multiple other measures.⁸ The anti-amyloid treatment in asymptomatic AD study (NCT02008357) is currently exploring high-dose solanezumab (1600 mg Q4W) in preclinical AD patients.¹¹

Volumetric magnetic resonance imaging (vMRI) and atrophy assessments are essential tools in characterizing effects of candidate treatments on brain volume in AD trials. Inclusion of imaging endpoints is useful in assessing treatment safety and efficacy.¹² Rates of whole brain volume (WBV) and ventricular volume (VV) changes are sensitive markers of neurodegeneration and used as biomarker outcome measures in trials of potential disease-modifying therapies.¹² Prior anti-amyloid therapies have been associated with increased volume changes or atrophy.^{13–17} In EXPEDITION3, solanezumab did not significantly alter WBV change in mild AD compared to placebo, although patients treated with solanezumab showed numerically less WBV change than placebo.¹⁸

The aim of this post hoc analysis was to investigate the effects of solanezumab on global brain volume measures in patients with mild or moderate AD, using vMRI data from EXPEDITION, EXPEDITION2, EXPEDITION3, and a pooled EXPEDITION dataset.

2 | METHODS

2.1 | Study design

EXPEDITION (NCT00905372), EXPEDITION2 (NCT00904683), and EXPEDITION3 (NCT01900665) were multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies comparing 400 mg solanezumab to placebo, given as an intravenous infusion Q4W for 76 weeks in patients with mild-to-moderate AD (EXPEDITION and EXPEDITION2), and mild AD (EXPEDITION3). Full details of each trial have been reported previously.^{7,8}

2.2 | Study population

Participants at least aged 55 years with AD, meeting National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.¹⁹ In EXPEDITION3, florbetapir F18 positron emission tomography imaging or cerebrospinal fluid biomarkers confirmed amyloid pathology in eligible patients. Participants were randomized, in a double-blind manner, to receive intravenous infusions of 400 mg solanezumab or placebo Q4W up to and including week 76. Stable concomitant drug and nondrug AD treatments were allowed, ensuring patients continued to receive AD standard of care. vMRI assessments occurred at baseline and 80 weeks in EXPEDITION3 and additionally at 12, 28, and 52 weeks in EXPEDITION and EXPEDITION2; or at early discontinuation visit. Results are presented for participants whose baseline and week 80 vMRI scans passed image quality control: full cohort, apolipoprotein E ϵ 4 (APOE ϵ 4⁺) subpopulation, and subpopulations of participants with mild (all trials) and moderate AD dementia (EXPEDITION and EXPEDITION2 only). All study participants provided written informed consent before participation in the studies.

2.3 | Magnetic resonance imaging

There were 110 imaging sites contributing to EXPEDITION and EXPEDITION2, and 217 sites that contributed to EXPEDITION3. Sites were distributed across Asia, Australia, Europe, and North and South America. All facilities were trained on study procedures by the central imaging laboratory (Bioclinica) and implemented a standardized

imaging protocol on their MRI scanners. Both 1.5T and 3T scanners (General Electric, Philips, and Siemens) were used. Scanner performance was assessed during site qualification and monitored throughout using American College of Radiology phantoms.

The 3DT1 data consisted of sagittal 3D magnetization-prepared rapid gradient-echo (Siemens), sagittal 3D turbo-field echo (Philips), or coronal 3D fast spoiled gradient-recalled (General Electric) sequences with 1.2-mm-thick slices and a $1.25 \times 1.25 \text{ mm}^2$ in-plane resolution.

WBV and VV change, measured in cm^3 , were estimated at 80 weeks using either boundary shift integral (BSI)²⁰ (EXPEDITION and EXPEDITION2) or tensor-based morphometry (TBM)²¹⁻²³ (EXPEDITION3). BSI uses signal changes at the boundary between cerebrospinal fluid and brain tissue between baseline and follow-up scans to determine change in brain volume, hence requiring two segmentations to generate the brain/ventricular boundary across visits.²⁰ TBM measures change globally within a region of interest defined at baseline.²⁴

Volume measures from all trials were pooled after confirming strong agreement (Lin's concordance correlation coefficient; between 0.81 and 0.98) between the two methods in a subanalysis of 113 participants from EXPEDITION2. This strong concordance corroborates previous results from Alzheimer's Disease Neuroimaging Initiative data.²⁵

WBV and VV changes were prespecified as the primary vMRI endpoints for analysis of treatment effects on brain volume changes. The images were parcellated using FreeSurfer v5.3 (cross-sectional pipeline) and the Desikan atlas²⁶ for region-of-interest definition. Given the analysis methodology, for BSI, segmentations from both visits were needed, while for TBM, the baseline segmentation was sufficient to derive volume changes. The results were not normalized for intracranial volume because the primary outcomes compared across arms were change from baseline and there were no significant differences in intracranial volume across arms (data not shown). Upon visual inspection of analysis results, it is occasionally the case that rejected whole brain results are rejected due to peripheral, motion-related artifacts (ringing). Despite this, signal at the center of the image (ventricles) is often preserved and the related results are therefore worth reporting.

2.4 | Statistical analysis

For analyses of brain volume changes, analysis of covariance (ANCOVA) models were used with factors for treatment, baseline volume (whole brain or ventricular), sex, baseline age, acetylcholinesterase inhibitors and/or memantine use, and study (pooled analysis only). Effect sizes were estimated using least squares mean differences and root mean square errors. Percentage reduction in brain volumes was relative to changes in placebo-treated patients, estimated using the calculation: $([\text{LS Mean atrophy of placebo} - \text{LS Mean atrophy of solanezumab}] / [\text{LS Mean atrophy of placebo}]) * 100$, such that positive values indicate less volume change in the solanezumab group.

RESEARCH IN CONTEXT

- **Systematic Review:** The authors reviewed the literature using traditional sources (e.g., PubMed), meeting abstracts, and presentations. Recent publications describing the results of experimental anti-amyloid therapies in late-phase clinical trials and their effects on brain volume are appropriately cited.
- **Interpretation:** Our findings demonstrate that low-dose solanezumab is not associated with changes in whole brain volume (WBV) or ventricular volume (VV) relative to placebo after approximately 80 weeks of treatment. Furthermore, no consistent changes in relative percent change in WBV or VV were observed across all studies or patient subpopulations examined. Results were in line with a previous report examining EXPEDITION3 only.
- **Future Directions:** Evaluation of a higher dose of solanezumab in the preclinical stage of Alzheimer's disease is currently being undertaken.

3 | RESULTS

3.1 | Effects of solanezumab on rates of brain volume and ventricular enlargement

There was no difference in WBV or VV changes between treatment groups or across studies in the full participant cohort (WBV $n = 2499$, VV $n = 2627$; Figure 1A and B), the APOE $\epsilon 4^+$ cohort (WBV $n = 1574$, VV $n = 1647$; Figure 1C and D) or participants with mild (WBV $n = 2153$, VV $n = 2236$; Figure 1E and F) or moderate AD dementia (WBV $n = 338$, VV $n = 383$; Figure 1G and H and Table 1).

3.2 | Relative percentage change in brain volume and ventricular enlargement

An overview of the relative percentage change in WBV and VV is provided in Table 1. In most measures analyzed, participants treated with solanezumab demonstrated less WBV and VV changes compared to those treated with placebo. Effects were not statistically significant.

4 | DISCUSSION

Analysis of vMRI outputs across the EXPEDITION program indicates that low-dose solanezumab is not associated with changes in WBV or VV relative to placebo after 76 weeks of treatment. This was observed in the full participant cohort and in subpopulations evaluated. No significant changes in relative percentage reduction in WBV or VV were

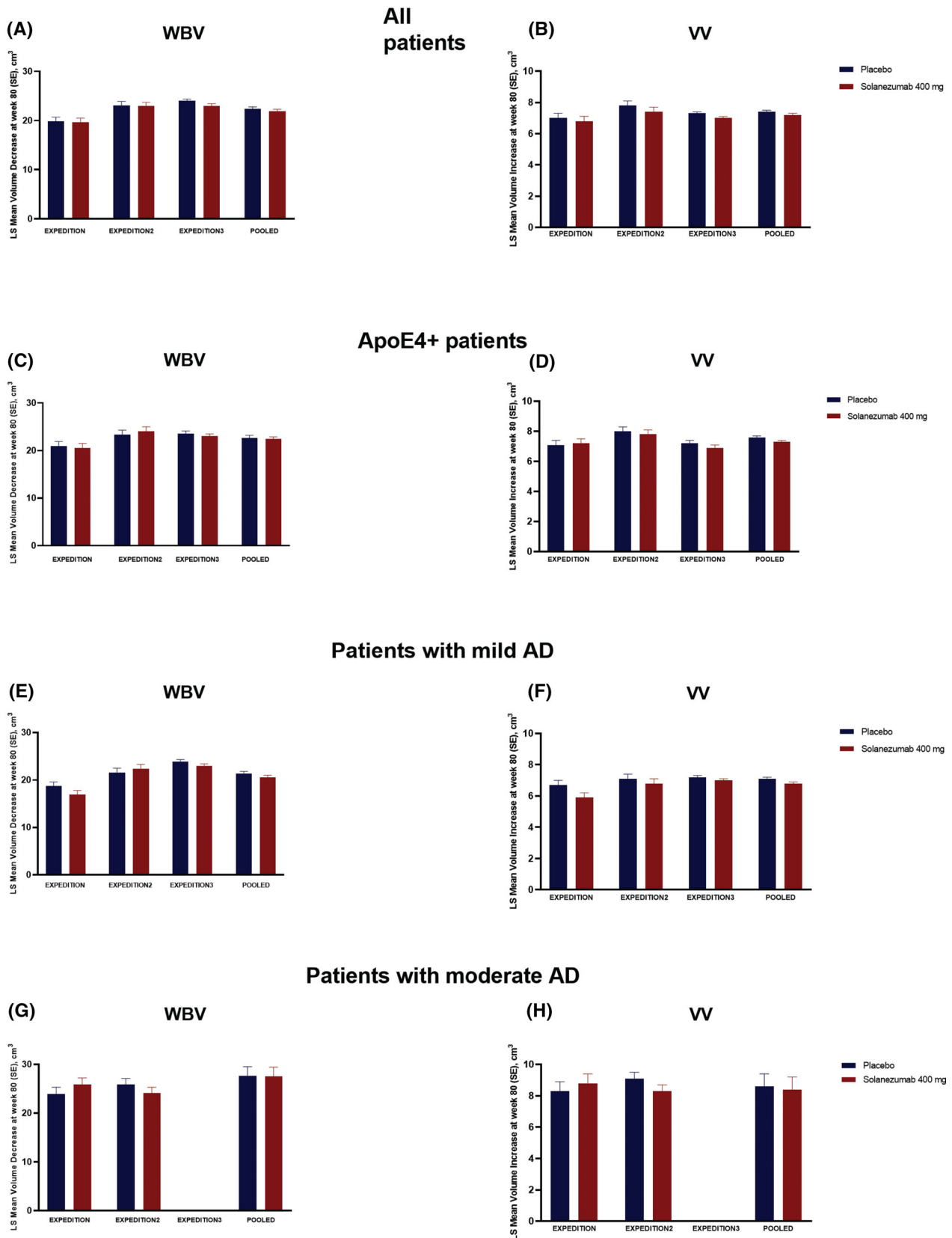


FIGURE 1 LS mean whole brain volume decrease and ventricular enlargement at week 80 for placebo and solanezumab-treated groups in all patients (A and B); APOE $\epsilon 4^+$ patients (C and D), patients with mild AD (E and F); and patients with moderate AD (G and H). Error bars represent standard error. AD, Alzheimer's disease; APOE $\epsilon 4^+$, apolipoprotein E $\epsilon 4^+$; LS, least squares; SE, standard error; VV, ventricular volume; WBV, whole brain volume.

TABLE 1 Relative decrease in WBV and VV (ANCOVA)

Relative percentage decrease in whole brain volume (WBV)*	EXPEDITION	EXPEDITION2	EXPEDITION3	POOLED SAMPLE
All subjects, N (PBO, SOL)	(239, 252)	(256, 270)	(732, 750)	(1227, 1272)
Relative % decrease in WBV	1.3	0.3	3.5	2.3
Effect size (P-value)	-0.020 (0.827)	-0.006 (0.942)	-0.071 (0.171)	-0.042 (0.290)
APOE ε4+ subjects, N (PBO, SOL)	(152, 150)	(142, 145)	(476, 509)	(770, 804)
Relative % decrease in WBV	4.1	-3.2	2.4	1.5
Effect size (P-value)	-0.063 (0.586)	0.054 (0.650)	-0.048 (0.456)	-0.027 (0.599)
Mild subjects, N (PBO, SOL)	(175, 174)	(163, 169)	(727, 745)	(1065, 1088)
Relative % decrease in WBV	10.6	-4.5	3.4	3.2
Effect size (P-value)	-0.156 (0.148)	0.077 (0.487)	-0.069 (0.185)	-0.056 (0.192)
Moderate subjects, N (PBO, SOL)	(62, 78)	(93, 100)	N/a	(158, 180)
Relative % decrease in WBV	-8.6	6.7	N/a	0.4
Effect size (P-value)	0.172 (0.315)	-0.150 (0.299)	N/a	-0.010 (0.929)
Relative percentage increase in ventricular volume (VV)*	EXPEDITION	EXPEDITION2	EXPEDITION3	POOLED SAMPLE
All subjects, N (PBO, SOL)	(269, 280)	(296, 297)	(733, 752)	(1298, 1329)
Relative % increase in VV	3.6	6.2	2.7	3.6
Effect size (P-value)	-0.052 (0.542)	-0.107 (0.193)	-0.054 (0.303)	-0.064 (0.099)
APOE ε4+ subjects, N (PBO, SOL)	(172, 166)	(163, 159)	(476, 511)	(811, 836)
Relative % increase in VV	0.9	2.4	4.6	3.6
Effect size (P-value)	-0.013 (0.902)	-0.043 (0.699)	-0.092 (0.149)	-0.067 (0.172)
Mild subjects, N (PBO, SOL)	(193, 192)	(189, 187)	(728, 747)	(1110, 1126)
Relative % increase in VV	12.5	4.2	2.8	4.4
Effect size (P-value)	-0.193 (0.060)	-0.067 (0.519)	-0.055 (0.294)	-0.079 (0.063)
Moderate subjects, N (PBO, SOL)	(74, 88)	(107, 109)	N/a	(184, 199)
Relative % increase in VV	-6.5	9.5	N/a	3.3
Effect size (P-value)	0.105 (0.510)	-0.189 (0.168)	N/a	-0.057 (0.577)

Abbreviations: ANCOVA, analysis of covariance; APOE ε4+, apolipoprotein E ε4; LS, least squares; N, number of subjects; PBO, placebo; SOL, solanezumab; VV, ventricular volume; WBV, whole brain volume.

*Relative % decrease was calculated using the formula: $([LS \text{ Mean atrophy of placebo} - LS \text{ Mean atrophy of LY}] / [LS \text{ Mean atrophy of placebo}]) * 100$. Effect size was calculated using the formula: $([LS \text{ Mean atrophy of solanezumab} - LS \text{ Mean atrophy of placebo}] / [\text{standard deviation}])$ at week 80.

observed across studies or participant subpopulations. Results were in line with a previous report examining EXPEDITION3.¹⁸

Increased VV changes with anti-amyloid immunoglobulin therapy may be a class effect, particularly for those agents with significant early amyloid changes.¹⁵⁻¹⁷ It should be noted that low-dose solanezumab has not demonstrated amyloid removal or brain volume changes. To what extent volume changes are related to changes in amyloid or total dose of immunoglobulin is unknown. Effects on brain volume vary across trials of passive anti-amyloid therapies. Other anti-amyloid studies have demonstrated volume changes related to therapy. In Phase 3 placebo-controlled studies of bapineuzumab, brain volume changes were quantified at 78 weeks in patients with mild-to-moderate AD, both APOE ε4 carriers and non-carriers. Initial studies reported no treatment-related differences.²⁷ A follow-up study on the pooled cohort at 71 weeks revealed significantly increased VV

changes for APOE ε4 carriers and non-carriers on bapineuzumab compared to non-carriers on placebo.¹⁶ In a Phase 3 trial of gantenerumab, in patients with prodromal AD, no treatment-related differences in WBV, VV, and hippocampal volume changes were observed for any dose.²⁸ In a Phase 2b trial of lecanemab, a slightly greater total hippocampal volume reduction was observed at 10 mg/kg biweekly compared to placebo without nominal significance. WBV and VV results reflect increased volume decline in the treatment groups compared to placebo.⁶ In the aducanumab Phase 3 study, an increase in change from baseline in lateral ventricle volume was observed in both doses relative to placebo.²⁹ Data from a donanemab Phase 2 study also showed reduction in WBV, increase in VV, but no change in hippocampal volume compared to placebo.⁵

As demonstrated in this analysis, data from the EXPEDITION program demonstrates no significant effect of solanezumab on brain

volume changes although the low-dose explored here equates to <6 mg/kg compared to 10–20 mg/kg monthly with agents most likely associated with volume loss. Investigations are under way evaluating a higher dose of solanezumab in the preclinical stage of AD.¹¹ It remains to be seen whether amyloid load and/or brain volumes will show significant changes with a higher dose.

Limitations of this analysis should be considered. First, in this analysis solanezumab did not appreciably change amyloid,¹⁰ which may contribute to the lack of volumetric changes seen here. This analysis should be re-explored at higher doses that may have a more appreciable effect on amyloid. Second, EXPEDITION3 had different inclusion criteria than EXPEDITION and EXPEDITION2 (confirmed amyloid pathology). This led to the APOE ϵ 4 substudy as a proxy for amyloid positivity. Third, across the three trials, different measurement methods were used—BSI for EXPEDITION and EXPEDITION2 and TBM for EXPEDITION3. Fourth, we did not include field strength as a covariant in our model, as the randomization is done at the site level; thus, there is an expectation that there is an equivalent number of scans performed on the various field strengths and manufacturers across treatments. Fifth, as this was a post hoc analysis, cross-sectional FreeSurfer derived images were used to compare baseline and follow-up in EXPEDITION and EXPEDITION2. Finally, hippocampal volume was not assessed in this analysis as it was only evaluated cross-sectionally at each session in EXPEDITION and EXPEDITION2.

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CONFLICTS OF INTEREST

Diana O. Svaldi, Ixavier A. Higgins, Karen C. Holdridge, Roy Yaari, Michael Case, Sergey Shcherbinin, and John R. Sims are all employees and minor shareholders of Eli Lilly and Company. Diana O. Svaldi has received support from Eli Lilly and Company for attending meetings and/or travel. Luc Bracoud and David Scott have nothing to report.

AUTHOR CONTRIBUTIONS

Karen C. Holdridge and John R. Sims were involved in the conception of the work. Roy Yaari and John R. Sims were involved in design of the work. Ixavier A. Higgins, Michael Case, and David Scott were involved in acquisition of data for the work. Diana Otero Svaldi, Ixavier A. Higgins, Michael Case, Luc Bracoud, and David Scott were involved in analysis of data for the work. Diana Otero Svaldi, Ixavier A. Higgins, Karen C. Holdridge, Roy Yaari, Michael Case, Sergey Shcherbinin, and John R. Sims were involved in interpretation of data for the work. Diana Otero Svaldi, Ixavier A. Higgins, and Roy Yaari were involved in drafting the manuscript. David Scott, Ixavier A. Higgins, Michael Case, Roy Yaari, Luc Bracoud, David Scott, Sergey Shcherbinin, and John R. Sims

were involved in critical revision of the work for important intellectual content. All authors approved the final version of the manuscript.

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