A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease

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ABSTRACT

Objective: This randomized, double-blind, placebo-controlled, dose-ranging phase 2 study explored safety, efficacy, and biomarker effects of ELND005 (an oral amyloid anti-aggregation agent) in mild to moderate Alzheimer disease (AD).

Methods: A total of 353 patients were randomized to ELND005 (250, 1,000, or 2,000 mg) or placebo twice daily for 78 weeks. Coprimary endpoints were the Neuropsychological Test Battery (NTB) and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale. The primary analysis compared 250 mg (n = 84) to placebo (n = 82) after an imbalance of infections and deaths led to early discontinuation of the 2 higher dose groups.

Results: The 250 mg dose demonstrated acceptable safety. The primary efficacy analysis at 78 weeks revealed no significant differences between the treatment groups on the NTB or ADCS-ADL. Brain ventricular volume showed a small but significant increase in the overall 250 mg group ($p = 0.049$). At the 250 mg dose, scyllo-inositol concentrations increased in CSF and brain and CSF Aβx-42 was decreased significantly compared to placebo ($p = 0.009$).

Conclusions: Primary clinical efficacy outcomes were not significant. The safety and CSF biomarker results will guide selection of the optimal dose for future studies, which will target earlier stages of AD.

Classification of evidence: Due to the small sample sizes, this Class II trial provides insufficient evidence to support or refute a benefit of ELND005. *Neurology*® 2011;77:1253–1262

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–Cognitive subscale; **ADCS-ADL** = Alzheimer's Disease Cooperative Study–Activities of Daily Living; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **AE** = adverse event; **CDR-SB** = Clinical Dementia Rating–Sum of Boxes; **ISMC** = Independent Safety Monitoring Committee; **LTP** = long-term potentiation; **MedDRA** = Medical Dictionary for Regulatory Activities; **mITT** = modified intent-to-treat; **MMSE** = Mini-Mental State Examination; **MRS** = magnetic resonance spectroscopy; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; **NPI** = Neuropsychiatric Inventory; **NTB** = Neuropsychological Test Battery; **p-tau** = phospho-tau^{181}; **PI** = phosphatidyl-inositol; **PPS** = per protocol set; **SAE** = serious adverse event; **TEAE** = treatment-emergent adverse event.

Cortical deposition of amyloid plaques is one of the pathologic hallmarks of Alzheimer disease (AD).[1,2] Oligomers of Aβ peptides are hypothesized to exert toxic effects on neurons, initiating a cascade of events culminating in the classic "plaque and tangle" pathology characteristic of AD.

ELND005 (scyllo-inositol) is an endogenous inositol stereoisomer,[3] which is not directly involved in phosphatidyl-inositol (PI) signaling.[4,5] Although scyllo-inositol at pharmacologic doses may alter myo-inositol levels and indirectly affect PI signaling, its main effects are thought to be binding and inhibition of Aβ42 peptide aggregation and formation of Aβ fibrils.[5,6] In transgenic animals, scyllo-inositol reduced brain Aβ concentrations and plaque

Supplemental data at www.neurology.org

Supplemental Data

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The coinvestigators are listed in appendix e-2 on the *Neurology*® Web site at www.neurology.org.

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burden, preserved synaptic density, and improved learning deficits.[5,7] Scyllo-inositol also appears to neutralize toxic effects of Aβ oligomers,[6] including amelioration of oligomer-induced synaptic loss, LTP inhibition, and memory deficits.[8,9] A prior amyloid anti-aggregation agent failed to demonstrate efficacy in phase 3 trials,[10] but several other amyloid-targeted therapies are currently being studied.[11–13] ELND005 is an orally bioavailable small molecule, which achieves steady state in plasma within 5 days, and at 2,000 mg twice daily has shown CNS penetration in healthy volunteers.[14] This profile makes ELND005 an attractive candidate as a potential disease-modifying oral treatment for AD.

This study evaluated safety, efficacy, and biomarker effects of ELND005 across a wide dose range. The doses of ELND005 (250, 1,000, and 2,000 mg) administered twice daily (BID) were based on cumulative phase 1 safety/pharmacokinetic data. Brain imaging and CSF biomarkers were incorporated to assess potential effects of ELND005 on disease pathology.

METHODS

This double-blind, parallel-arm, randomized, placebo-controlled, multicenter safety and efficacy study was conducted at 58 sites in North America between December 2007 and May 2010.

Patients. The study enrolled patients 50–85 years of age with probable AD by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[15] Mini-Mental State Examination (MMSE)[16] score of 16–26, MRI scan consistent with AD and free of other pathologic findings, Rosen Modified Hachinski[17] score ≤4, and no significant neurologic, psychiatric, or medical illnesses. Medications with potential cognitive effects were not permitted, with the exception of stable dosages of acetylcholinesterase inhibitors or memantine.

Standard protocol approvals, registrations, and patient consents. The study protocol (ClinicalTrials.gov number NCT00568776) was approved by each site's institutional review board. Written informed consent was obtained from each patient (or legally authorized representative) and their study partners or caregivers.

Study design and treatment. Patients were randomly assigned to 1 of 4 treatment arms: placebo or ELND005 (250, 1,000, or 2,000 mg) administered orally BID. Random assignment was performed with an interactive voice response system using a computer-generated randomization list, which ensured that study site personnel had no knowledge of which group a given patient would be allocated to when making the determination of that patient's study eligibility. The randomization was stratified by MMSE score (16–21 vs 22–26), *APOE* ε4 carrier status (1 or 2 alleles vs none), and use of approved AD symptomatic medications (yes vs no). Cognitive, functional, and MRI assessments were performed at baseline and weeks 12 (no MRI), 24, 48, and 78. An Independent Safety Monitoring Committee (ISMC) reviewed ongoing and final study results. Administrative analyses were conducted after all patients had completed 24 and 48 weeks on study (see appendix e-1 for details). Based on the 48-week safety review, patients in the 1,000 and 2,000 mg groups were withdrawn; no changes were made to study conduct for patients in the 250 mg or placebo groups.

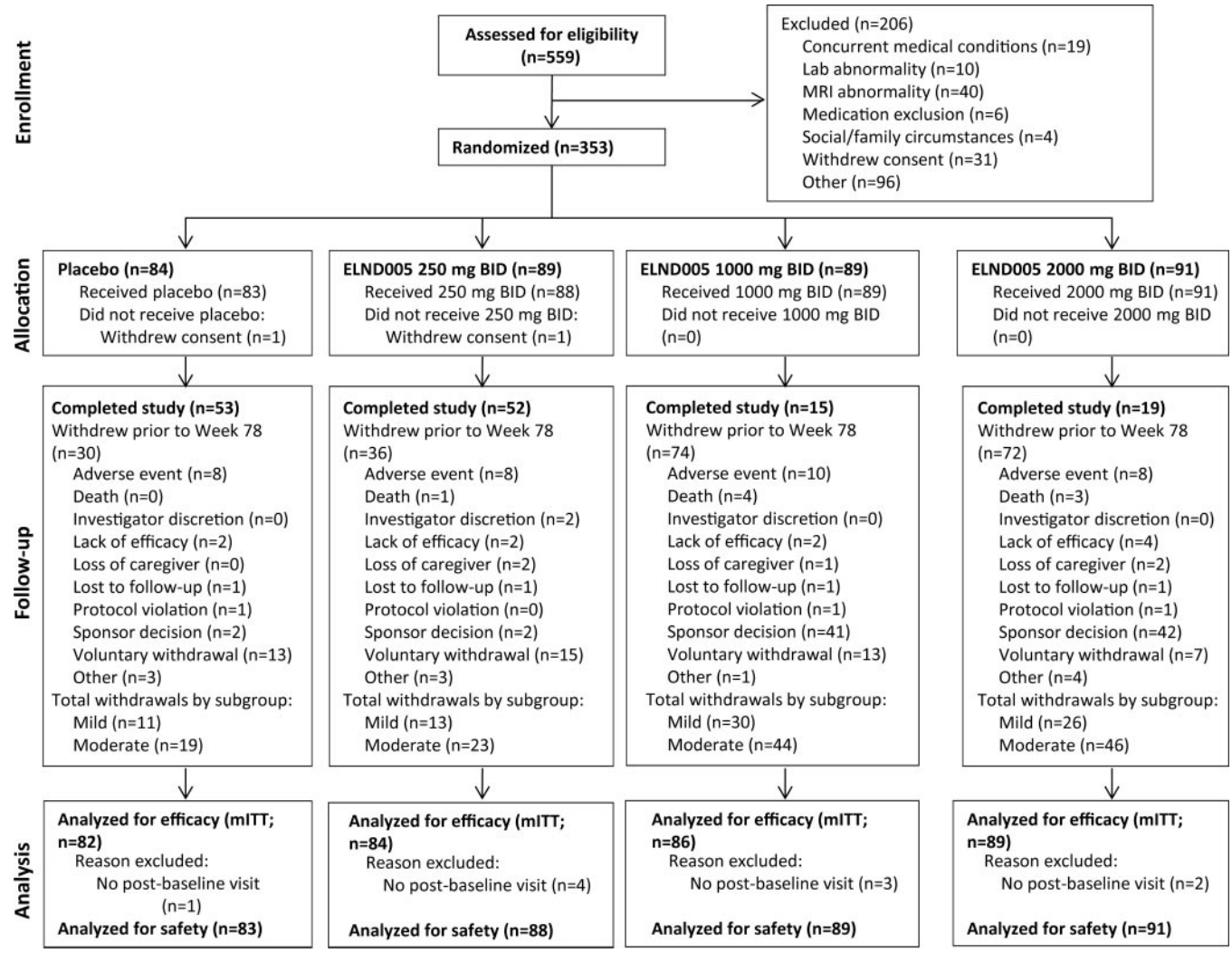
Safety measures. Safety assessments included adverse event (AE) monitoring, clinical laboratory tests, and electrocardiograms. MRI safety assessments included fluid-attenuated inversion recovery and gradient-echo MRI sequences[18] performed every 6 months in conjunction with volumetric MRI studies; results were interpreted by site-affiliated local radiologists.

Efficacy outcome measures. The coprimary efficacy endpoints were the changes from baseline to week 78 in Neuropsychological Test Battery (NTB)[19] *z* score and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) score.[20] Secondary clinical endpoints were the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog),[21] Clinical Dementia Rating–Sum of Boxes (CDR-SB),[22,23] and Neuropsychiatric Inventory (NPI) scores.[24] A 12-item ADAS-Cog version was used (75-point maximum score), including "concentration/distractibility" as the 12th item. Exploratory clinical outcomes were change from baseline to week 78 in MMSE[16] score and 3 responder analyses: proportion of patients having either 1) >0.3-point worsening in NTB *z* score, 2) <6-point worsening in ADAS-Cog score, or 3) no change or improvement in NTB *z* score or ADCS-ADL score. All efficacy endpoints were analyzed by modified Intent-to-Treat (mITT) population and per protocol set (PPS).

Biomarker outcome measures. The key imaging endpoint was change from baseline to week 78 in brain ventricular volume.[25,26] Whole brain volume, hippocampal volume, and cortical ribbon thickness were also measured. All volumetric MRI assessments were performed by NeuroRx Research (Montreal) using previously described methods.[27–29] All computer-generated results were reviewed and corrected as necessary. A subset of patients underwent magnetic resonance spectroscopy (MRS) for assessment of scyllo-inositol and myo-inositol brain levels. Lumbar punctures were performed on another subset of patients at baseline, week 24 (primary CSF biomarker endpoint), and week 78 for determination of CSF Aβx-40, Aβx-42, total tau, phospho-tau^{181} (p-tau),[30] and ELND005 concentrations.

Statistical analysis. Following the discontinuation of the 1,000 and 2,000 mg groups, the primary comparison was amended in the statistical analysis plan to include the 250 mg and placebo groups only. A repeated-measures model was used to compare the change from baseline between the 250 mg and placebo groups for all continuous efficacy and biomarker endpoints, with time included as a categorical variable; no assumptions or limitations were imposed on response trajectory (e.g., linearity). "Responder" proportions were analyzed using an exact unconditional version of Fisher exact test. The coprimary endpoints were tested at a significance level of 0.049 due to the administrative interim analyses performed by an independent statistical team and reviewed by sponsor personnel not involved in study conduct. All other statistical testing was performed at a significance level of 0.05. Analyses were carried out using SAS 9.1.3.

Figure 1 Patient disposition



mITT = modified intent-to-treat.

Analysis populations. The safety population consisted of 351 patients who received at least one dose of study drug. The mITT population included 341 patients who received at least one dose of study drug and one postbaseline efficacy assessment. The PPS included 130 mITT patients who met all inclusion/exclusion criteria, completed the week 78 visit, and took at least 80% of assigned study drug.

Prespecified subgroup analyses. Subgroup analyses specified in the protocol included mild AD (screening/baseline MMSE 23–26, in an attempt to define an even milder population), moderate AD (screening/baseline MMSE 16–22), and *APOE* ε4 carriers and noncarriers.

Safety analysis. AEs were coded using the Medical Dictionary for Regulatory Activities (v 13.0). Treatment-emergent AEs (TEAEs), serious AEs (SAEs), clinical laboratory, ECG, and vital signs data were summarized by treatment group.

Pharmacokinetic and pharmacodynamic analysis. ELND005 concentrations in plasma and CSF were summarized using descriptive statistics. Biomarkers were analyzed by repeated-measures analysis (see appendix e-1 on the *Neurology*® Web site at www.neurology.org for biomarker assay methodology).

Sample size. As originally designed, with a sample size of 85 in each of 4 groups (total n = 340) and a 0.050 level 2-sided *t* test of the average treatment effect of all 3 ELND005 groups vs placebo, the study had >90% power to detect differences of 0.2 on the NTB and 4.07 on the ADCS-ADL. Following discontinuation of the 2 highest dose groups, the study retained approximately 80% and 70% power to detect these same differences on the NTB and ADCS-ADL, respectively.

RESULTS

Patient disposition. Figure 1 depicts the disposition of all screened and randomized patients.

Demographics and baseline characteristics. A total of 353 patients were enrolled and randomized and 351 received at least one dose of study drug (figure 1). Baseline measures were well-balanced across all groups (table 1). After discontinuation of the 2

Table 1 Patient demographics and baseline characteristics

		ELND005		
Parameters[a] (safety population)	Placebo (n = 83)	250 mg BID (n = 88)	1,000 mg BID (n = 89)	2,000 mg BID (n = 91)
Age, y	73.4 (7.8)	73.4 (7.3)	73.4 (7.6)	72.2 (8.2)
Duration of AD, y	4.1 (2.4)	3.8 (2.1)	4.3 (2.5)	3.8 (2.3)
Years of education	14.1 (3.2)	13.9 (3.4)	13.8 (3.0)	14.2 (3.2)
Weight, kg	72.1 (11.6)	72.4 (15.3)	73.4 (14.9)	72.7 (15.5)
Gender, n (%) F	47 (56.6)	51 (58.0)	48 (53.9)	51 (56.0)
Race, n (%) white	81 (97.6)	85 (96.6)	86 (96.6)	87 (95.6)
AChEI/memantine use, n (%) yes	78 (94.0)	80 (90.9)	78 (87.6)	82 (90.1)
APOE ϵ4 genotype, n (%) carrier	53 (63.9)	55 (62.5)	56 (62.9)	58 (63.7)
MMSE stratum, n (%) high (22–26)	37 (44.6)	38 (43.2)	36 (40.5)	39 (42.9)

Baseline scores[a] (mITT population, n = 82)	Placebo (n = 82)	No.	250 mg BID (n = 84)	No.	1,000 mg BID (n = 86)	No.	2,000 mg BID (n = 89)
NTB	−0.047 (0.698)	84	0.067 (0.733)	86	0.013 (0.655)	88	−0.052 (0.596)
ADCS-ADL	62.8 (12.3)	84	62.9 (12.0)	86	61.7 (12.3)	88	61.4 (12.1)
ADAS-Cog (12-item)	23.6 (9.7)	79	23.1 (10.5)	85	23.5 (8.9)	87	23.6 (9.1)
CDR-SB	5.23 (2.93)	84	5.28 (2.73)	86	5.21 (2.67)	89	5.31 (2.47)
NPI Score	8.1 (8.4)	84	10.4 (12.6)	86	9.4 (9.5)	88	10.7 (11.1)
MMSE	20.5 (3.9)	84	20.5 (4.1)	86	20.3 (3.9)	86	20.4 (3.8)

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR-SB = Clinical Dementia Rating–Sum of Boxes; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; NTB = Neuropsychological Test Battery.
[a] All data are mean (SD) unless otherwise indicated.

high-dose groups, the primary analysis was based on 166 patients (n = 84 250 mg; n = 82 placebo).

Safety. The overall incidence of TEAEs was similar across the 4 dose groups. TEAEs were reported for 91.6% and 87.5% of patients in the placebo and 250 mg groups, respectively. The most common AEs in the 250 mg group are shown in table 2. The safety and tolerability profiles in *APOE* ϵ4 carriers and noncarriers were similar.

The incidence of withdrawals due to AE was higher in the 1,000 mg (16.9%) and 2,000 mg (13.2%) groups than in the 250 mg (10.2%) and placebo (9.6%) groups. The incidence of SAEs was also higher in the ELND005 groups compared with placebo (23.1, 22.5, 21.6, and 13.3%, in the 2,000 mg, 1,000 mg, 250 mg, and placebo groups, respectively). The incidence of respiratory tract infections was higher in the 1,000 mg and 2,000 mg groups than in the placebo and 250 mg groups, even when adjusted for duration of exposure to account for early termination of the high dose groups. The overall incidence of SAEs was similar in the mild and moderate subgroups, except for serious infections and neurologic and psychiatric SAEs, which were lower in the mild subgroup.

At the week 48 ISMC review, more SAEs of infection were found in the 2,000 mg group compared to other groups, and a disproportionate number of deaths was seen in the 2 high-dose groups, with 0, 1, 5, and 4 deaths in the placebo, 250, 1,000, and 2,000 mg groups, respectively. Nine of the 10 deaths were assessed as not related to study drug by the reporting investigator. The patients who died tended to be older, and 9 of the 10 were in the moderate AD stratum (table e-3). The sponsor electively discontinued the 1,000 and 2,000 mg groups with the concurrence of the ISMC. The 250 mg group showed an acceptable safety profile and was continued. No additional deaths occurred in the 250 mg or placebo groups. There were no clinically relevant changes in vital signs or laboratory measures except for a dose-dependent decrease in uric acid. The mild and moderate subgroups had similar TEAE profiles, except for confusional episodes (predominantly in moderate patients).

Efficacy. ***Primary endpoints.*** In the overall mITT population that included patients with mild and moderate AD (MMSE 16–26), the NTB *z* score difference was 0.033 (95% CI −0.140, 0.205) and the ADCS-ADL difference was −1.4 (95% CI −5.4, 2.6) (figure 2; table e-2). Neither of these differences was significant. In the overall PPS population, treatment differences on the NTB and the ADCS-ADL scores were also not significant.

Secondary and exploratory clinical endpoints. In the overall mITT population, patterns of change similar

Table 2 Treatment-emergent adverse events with frequency ≥5% in pooled ELND005 group (safety population)[a]

Preferred term	Placebo (n = 83)	ELND005 250 mg BID (n = 88)	ELND005 1,000 mg BID (n = 89)	ELND005 2,000 mg BID (n = 91)	ELND005 Pooled ELND005 (n = 268)
Fall	5 (6.0)	11 (12.5)	10 (11.2)	14 (15.4)	35 (13.1)
Diarrhea	6 (7.2)	9 (10.2)	8 (9.0)	12 (13.2)	29 (10.8)
Urinary tract infection	7 (8.4)	12 (13.6)	4 (4.5)	11 (12.1)	27 (10.1)
Depression	4 (4.8)	10 (11.4)	4 (4.5)	12 (13.2)	26 (9.7)
Nausea	4 (4.8)	8 (9.1)	3 (3.4)	14 (15.4)	25 (9.3)
Headache	12 (14.5)	4 (4.5)	11 (12.4)	8 (8.8)	23 (8.6)
Dizziness	7 (8.4)	4 (4.5)	6 (6.7)	11 (12.1)	21 (7.8)
Agitation	5 (6.0)	4 (4.5)	9 (10.1)	6 (6.6)	19 (7.1)
Fatigue	4 (4.8)	6 (6.8)	6 (6.7)	7 (7.7)	19 (7.1)
Vomiting	3 (3.6)	5 (5.7)	3 (3.4)	8 (8.8)	16 (6.0)
Confusional state	3 (3.6)	7 (8.0)	4 (4.5)	4 (4.4)	15 (5.6)
Upper respiratory tract infection	5 (6.0)	9 (10.2)	3 (3.4)	3 (3.3)	15 (5.6)
Insomnia	5 (6.0)	3 (3.4)	2 (2.2)	8 (8.8)	13 (4.9)

[a] Data are number (%) of patients with treatment-emergent adverse events, sorted by descending order of frequency in the pooled ELND005 column; preferred terms coded using MedDRA version 13.0.

to the primary outcomes were noted for CDR-SB, NPI, ADAS-Cog, and MMSE (table e-2), none of which achieved significance. The proportion of "responders" who did not decline on either primary endpoint was 38% in the 250 mg and 32% in placebo groups. When the 2 high-dose groups were discontinued, <25% of patients in those 2 groups had completed week 78, and clinical assessments of discontinuing patients were partially unblinded (investigators were aware that they were in the high-dose groups). Observed treatment effects at the 1,000 and 2,000 mg doses were not significant in comparison to the 250 mg dose or placebo on the primary endpoints (summary statistics of observed values are presented in appendix e-1).

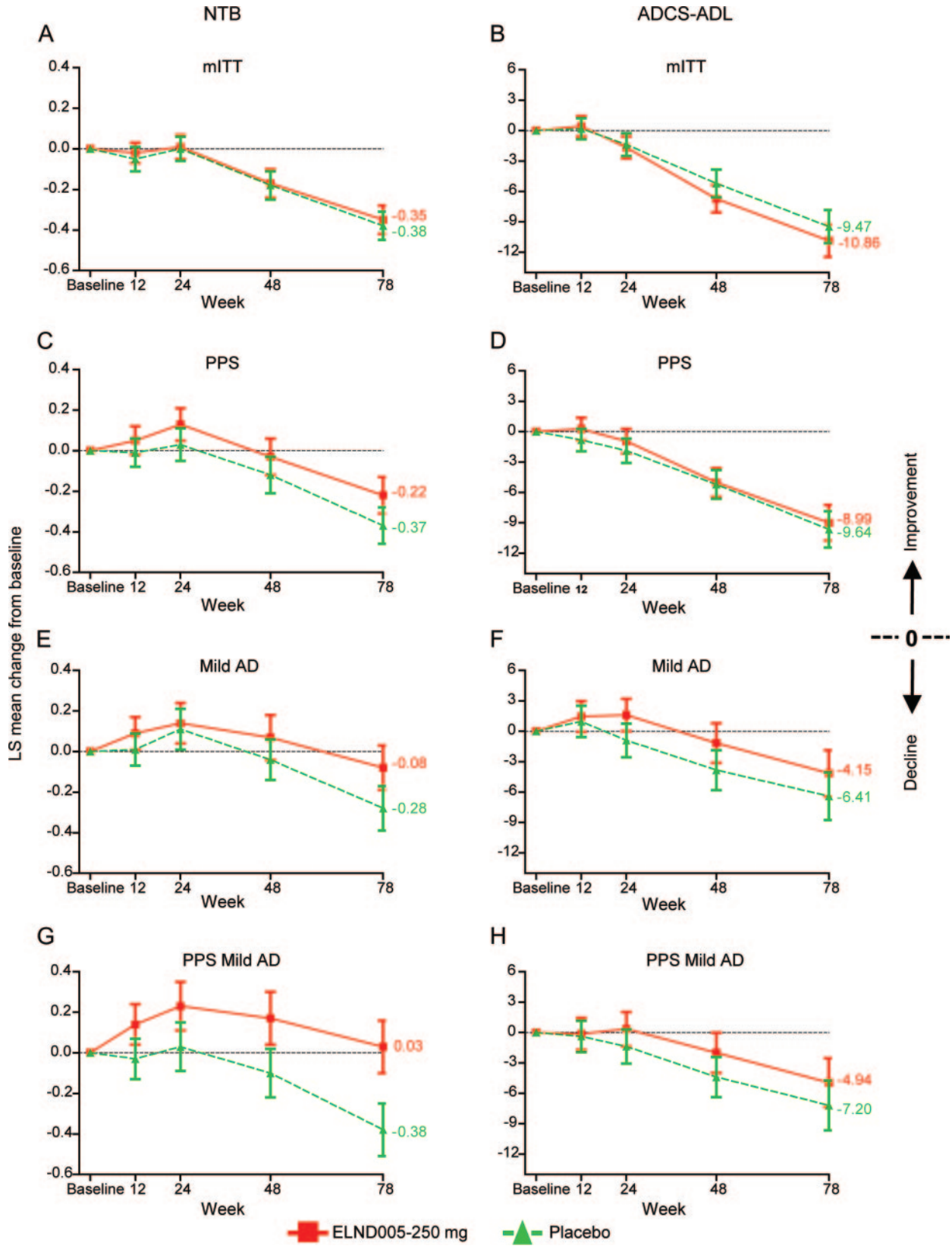
Prospectively defined subgroup analyses. Demographic characteristics for the subgroups analyzed were generally balanced (table e-1). *APOE* ϵ4 carrier status had no consistent effect on treatment outcomes. No significant treatment differences were seen in the moderate subgroup. As shown in table e-2, differences between 250 mg and placebo in the mITT analysis of the mild subgroup were 0.200 on the NTB (95% CI −0.046, 0.446; $p = 0.110$) and 2.3 on the ADCS-ADL (95% CI −3.4, 7.9; $p = 0.426$). In the PPS analysis of the mild subgroup, treatment–placebo difference of 0.403 (95% CI 0.111, 0.695) on the NTB was significant ($p = 0.007$), but the ADCS-ADL difference of 2.3 (95% CI −3.8, 8.3) was not ($p = 0.459$). The CDR-SB treatment differences of 0.87 (95% CI −0.44, 2.19) in the mild mITT ($p = 0.189$) and 0.95 (95% CI −0.50, 2.40) in the mild PPS ($p = 0.195$) were not significant, but were directionally consistent with the NTB (figure 2; table e-2). The ADAS-Cog treatment difference was not significant. Exploratory responder analyses in the mild subgroup favored treatment over placebo and were statistically significant in the PPS, but not mITT analysis (see table e-2).

Imaging biomarker endpoints. In the overall mITT population, the change from baseline in ventricular volume was greater (3.2 mL; 95% CI 0.01, 6.4; $p = 0.049$) in the 250 mg group (14.1 mL; 95% CI 11.7, 16.4) compared to the placebo group (10.9 mL; 95% CI 8.6, 13.2). Whole brain volume, hippocampal volume, and cortical ribbon thickness treatment differences were not significant (not shown).

CSF biomarkers. At the week 24 (primary) time point, changes from baseline in Aβ40, Aβ42, tau, and p-tau concentrations were not significant. The week 78 samples from 20 patients showed a significant reduction in Aβ42 in the 250 mg group compared to placebo (−191.3 pg/mL [95% CI −329.6, −53.0; $p = 0.009$]). The decrease in tau (−39.9, 95% CI −160.7, 80.9; $p = 0.497$) was not significant (figure 3).

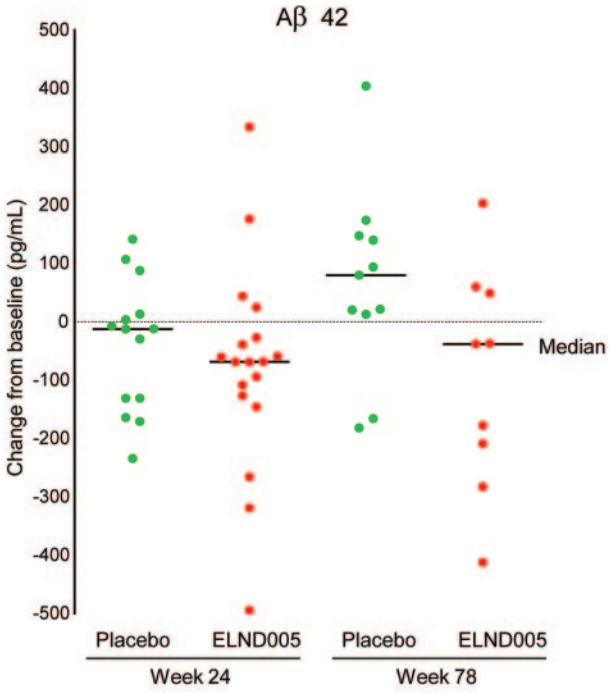
Plasma and CSF pharmacokinetics of ELND005. Plasma concentrations increased proportionately with dose and reached steady state between weeks 2 and 12 (not shown). CSF concentrations at week 24 were 13.8 μg/mL (95% CI 12.3, 315.4; n = 19) in the 250 mg group, 31.4 μg/mL (95% CI 28.5, 34.4; n = 16) in the 1,000 mg group, and 35.1 μg/mL (95% CI 28.7, 41.5; n = 15) in the 2,000 mg group. MRS showed a dose-dependent increase in brain scyllo-inositol levels (data not shown).

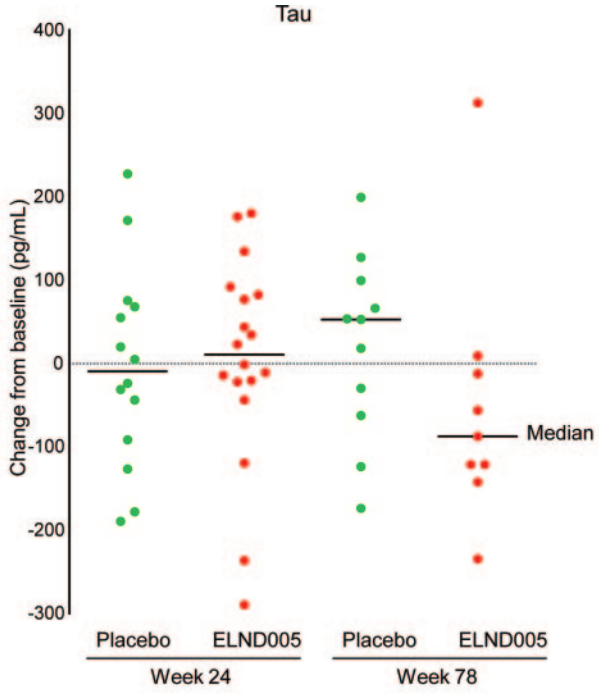
Figure 2 Primary outcome measures: Changes from baseline



Least squares (LS) mean changes from baseline for the coprimary outcome measures (Neuropsychological Test Battery [NTB] and Alzheimer's Disease Cooperative Study–Activities of Daily Living [ADCS-ADL]) in overall (Mini-Mental State Examination [MMSE] 16–26) modified intent-to-treat (mITT) (A, B) and per protocol set (PPS) (C, D) populations, and for mild Alzheimer disease (AD) subgroup (MMSE 23–26) mITT (E, F) and PPS (G, H) populations. For all panels: upward (positive) direction represents better performance, downward direction (negative) indicates worse performance. Changes from baseline to week 78 in the ELND005 (purple) and placebo (green) treatment groups noted on graph.

Figure 3 CSF biomarker changes from baseline





		Placebo	ELND005	Δ	p-value
Mean baseline values	N	14	19		
	Mean	707.19	717.82		
	SD	195.18	353.84		
CBL at Wk 24	N	14	18		
	LS mean	-26.9	-71.2	-44.4	0.374
	Median	-12.4	-68.7	-56.3	0.414
CBL at Wk 78	N	11	9		
	LS mean	70.4	-120.9	-191.3	0.009
	Median	79.8	-38.1	-117.9	0.068

		Placebo	ELND005	Δ	p-value
Mean baseline values	N	14	19		
	Mean	785.11	689.65		
	SD	318.70	419.52		
CBL at Wk 24	N	14	18		
	LS mean	2.8	-0.8	-3.6	0.936
	Median	-9.5	10.7	20.2	0.506
CBL at Wk 78	N	11	9		
	LS mean	13.6	-26.3	-39.9	0.497
	Median	52.6	-87.5	-140.1	0.129

Baseline values and change from baseline (CBL) to weeks 24 and 78 for CSF Aβx-42 (left) and tau (right). Least squares (LS) means were compared using a repeated-measures analysis; median values were compared using Wilcoxon rank-sum test.

DISCUSSION The imbalance in the number of deaths and serious infections at the week 48 administrative analysis resulted in discontinuation of the 2 highest dose groups. The overall number and causes of death and the nature of infections were similar to rates reported in epidemiologic studies[31,32] and in AD trials of similar duration.[33] The mechanistic relationship, if any, between high doses and increase in infections remains unclear but is under investigation. The 250 mg group displayed an acceptable safety profile, which was not affected by patients' *APOE* ϵ4 carrier status. There were no reports of cerebral vasogenic edema[18] at any dose, as assessed by local site radiologists.

The differences between the 250 mg and placebo groups (overall mITT, n = 166) were not significant for the coprimary (NTB and ADCS-ADL) or secondary endpoints. In the prespecified subgroup analyses, there were no consistent efficacy trends in the moderate AD or *APOE* ϵ4 carrier or noncarrier subgroups.

In the prespecified subgroup of mild patients who completed the study and were compliant (PPS analysis), the 250 mg dose showed a significant and clinically relevant treatment effect on the NTB. The CDR-SB treatment difference of 0.95, although not significant, was directionally consistent with the NTB. The rate of CDR-SB decline on placebo (2.17 points over 78 weeks) was similar to that observed in the ADNI mild AD cohort (1.6 points over 52 weeks).[34]

The ADAS-Cog treatment–placebo difference was not significant but was directionally opposite to the NTB. The ADAS-Cog treatment–placebo difference was largely driven by minimal decline on placebo (2 points over 78 weeks), which is one-third the

rate from the ADNI mild AD cohort (4.3 points over 52 weeks).[34] The low rate of placebo worsening on ADAS-Cog was also inconsistent with the rates of placebo worsening on the NTB, CDR-SB, and ADCS-ADL in this study.

The NTB was chosen as the study's primary cognitive outcome measure because of its greater sensitivity in patients with mild AD.[19,35] The ADAS-Cog is most sensitive to change in patients with moderate disease.[36,37] Since the NTB captures changes in delayed memory and executive function which are not well-covered by the ADAS-Cog, our findings support the choice of the NTB for studies in mild AD.

There is a growing consensus that amyloid-targeted agents may provide more meaningful benefit when introduced at early stages of the disease.[38] The positive cognitive trends in compliant mild patients are consistent with the preclinical effects of ELND005. In TgCRND8 mice, scyllo-inositol showed a more robust reduction of plaque accumulation when treatment was started at an earlier age.[7]

In patients with mild to moderate disease, the ventricular volume increase was significantly larger in the 250 mg group but was of small magnitude. In the mild group, the increase in ventricular volume was smaller and not significantly different from placebo. Although counterintuitive, similar findings were observed with other amyloid-targeted therapies.[39,40] The observed ventricular enlargement could be due to inositol-related osmotic effects, to blockage of the arachnoid villi during the process of amyloid clearance, or could reflect "ex vacuo" changes due to amyloid clearance leading to a decrease in brain volume.

The 250 mg dose achieved CSF concentrations similar to those associated with improved learning in animal models.[7] This dose also demonstrated a significant reduction of CSF Aβ42 at 78 weeks, which may reflect a gradual reduction of brain amyloid pathology consistent with findings in transgenic animals.[5,7] In contrast to the CSF Aβ42 decline that is associated with greater plaque burden during the early stages of AD, the anti-aggregation effects of ELND005 are thought to result in clearance of soluble Aβ peptides and in decreased brain amyloid burden. The decrease in amyloid burden may be reflected in lower CSF Aβ42 levels, and possibly in larger ventricular volume at week 78.

The study's limitations include the decreased power to test the coprimary endpoints due to discontinuation of 2 dose groups and the small sample size of the prespecified subgroups and the CSF substudy. There were no statistical corrections for the multiple analyses.

Despite the limitations, and the fact that the study did not achieve its primary objective, these results will inform the design of future studies. The safety findings at the highest doses helped define the AEs to be carefully monitored in future studies. The 250 mg dose demonstrated acceptable safety and tolerability, CNS penetration, and target engagement (Aβ42 reduction), and showed potential cognitive benefit in patients with mild disease. These results will help optimize the dose range and choice of biomarkers, and will aid the selection of the appropriate patient population. Our findings support the concept that amyloid-targeted therapies may have their greatest benefit in patients at earlier stages of AD.

AUTHOR CONTRIBUTIONS

Dr. Salloway: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Sperling: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Keren: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Porsteinsson: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. van Dyck: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Tariot: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Gilman: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Arnold: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Abushakra: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis, study supervision. Dr. Hernandez: study concept or design, analysis or interpretation of data acquisition of data, statistical analysis. Dr. Crans: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. Dr. Liang: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Quinn: drafting/revising the manuscript, analysis or interpretation of data. Dr. Bairu: drafting/revising the manuscript, analysis or interpretation of data, study supervision, obtaining funding. Dr. Pastrak: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision. Dr. Cedarbaum: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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DISCLOSURE

Dr. Salloway serves on the scientific advisory boards of Elan Corporation, sanofi-aventis, Pfizer Inc, and Bristol-Myers Squibb; served on the scientific advisory for Eisai Inc.; serves as Associate Editor for *Journal of Neuropsychiatry and Clinical Neurosciences*; receives publishing royalties for *The Frontal Lobes and Neuropsychiatric Illness* (American Psychiatric Press Inc., 2001), *The Neuropsychiatry of Limbic and Subcortical Disorders* (American Psychiatric Press Inc., 1997), and *Vascular Dementia* (Humana Press, 2004); receives honoraria from Eisai Inc., Pfizer Inc, Novartis, Forest Laboratories, Inc., Elan Corporation, and Athena Diagnostics, Inc.; holds corporate appointments with Merck Serono and Medivation, Inc.; receives research support from Elan Corporation, Janssen Alzheimer's Immunotherapy, Bayer Schering Pharma, Wyeth, Bristol-Myers Squibb, Pfizer Inc, and Eisai Inc.; received research support from Myriad Genetics, Inc., GlaxoSmithKline, Neurochem-Alzhemed, Cephalon, Inc., Forest Laboratories Inc., and Voyager; and receives research support from the NIH/NIA, the Norman and Rosalie Fain Family Foundation, the Champlin Foundation, and the

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