



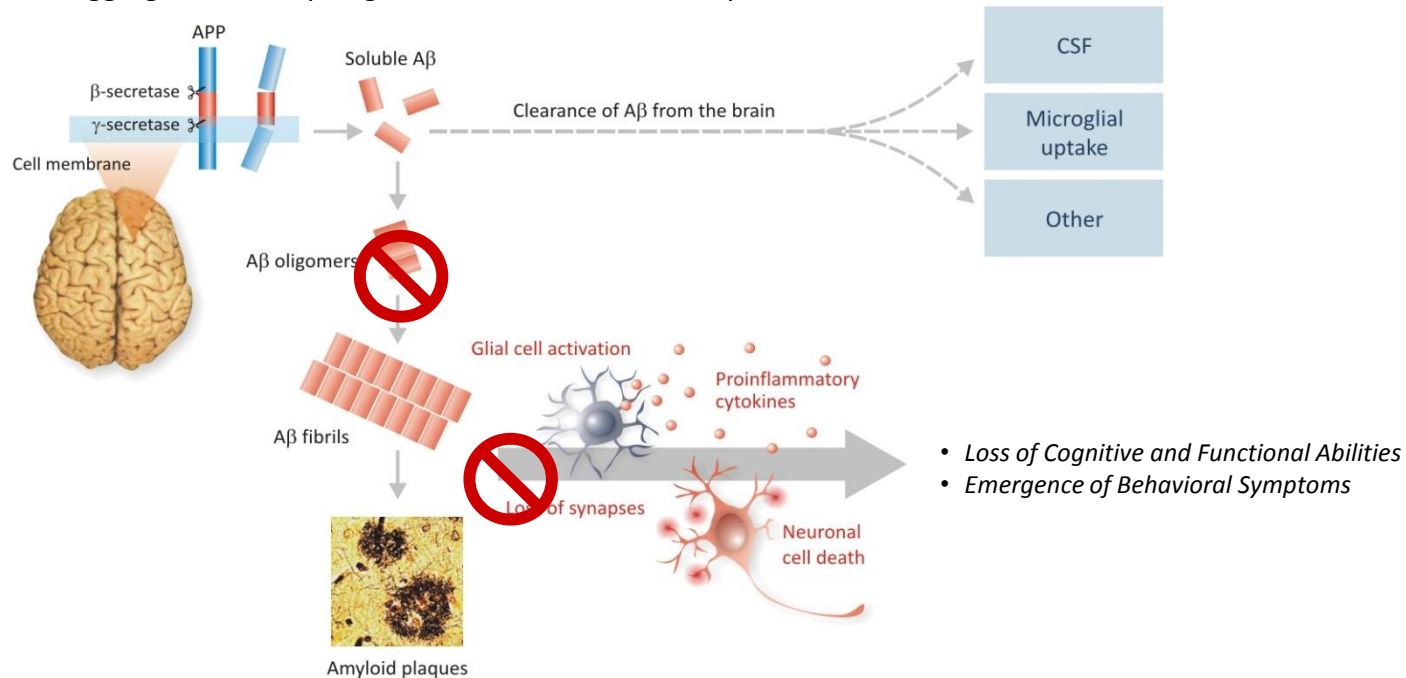
Safety and Efficacy Results of a Phase 2 Randomized, Placebo-Controlled, Dose-Ranging Study of ELND005 (Scyllo-inositol) in Mild to Moderate Alzheimer's Disease

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BACKGROUND

- In preclinical studies, ELND005 (Scyllo-inositol) was shown to be an A β aggregation inhibitor that breaks down A β fibrils, and inhibits aggregation and A β oligomer-induced neurotoxicity



- In preclinical studies ELND005 has shown the following effects:
- A β anti-aggregation effects in vitro (*McLaurin et al, J Biol Chem 2000;275:18495-502*)
- Protection from A β oligomer induced LTP inhibition and dendritic spine loss (*Shankar et al, J Neurosci 2007;27:2866-75; Townsend et al, Ann Neurol 2006;60:668-76*)
- In TgCRND8 mice (*McLaurin et al., Nature Med 2006;12:801*) :
 - Decrease in amyloid burden, vascular amyloid, astrogliosis, and microgliosis
 - Improvement in Morris Water Maze performance, with early and late intervention models
- This 78-week, Phase 2 study evaluated efficacy and safety of 3 ELND005 doses; CSF and MRI biomarkers were included to support a potential disease modifying profile (to be presented on Wednesday July 20)

METHODS

- Randomized, placebo-controlled, parallel-arm study at 58 N. American sites
- ELND005 doses: 250mg bid, 1000mg bid, 2000mg bid and placebo
- 353 mild to moderate AD patients enrolled for treatment duration of 18 months
- AT 85 per arm (target enrollment= 340) study was powered to detect mean differences of *0.2 on NTB and 4 points on ADCS-ADL*; target enrollment 340
- The primary efficacy analysis was based on 250-mg bid and placebo groups (Mixed Effect Repeated Measure method)
- Stratification by ApoE4 carrier status & AD severity (Mild: 22-26, Moderate (16-21))
- Co-primary efficacy endpoints: NTB and ADCS-ADL
- Secondary efficacy endpoints: CDR-SB, ADAS-Cog, NPI; MMSE (exploratory endpoint)
- Pre-planned subgroup analyses:
 - Mild (23-26) and Moderate (16-22) subgroups
 - ApoE4 carrier vs. non-carrier
- There was no correction for multiplicity testing in the secondary/exploratory analyses

RESULTS

Study Populations and Demographics

Table 1: Demographics of Randomized Patients

	Placebo N=83	250 mg BID N=88	1000 mg BID N=89	2000 mg BID N=91
Age (mean/med)	73.4 / 75	73.4 / 74.5	73.4 / 75	72.2 / 74
Gender (% female)	57%	58%	54%	56%
Race (% Caucasian)	98%	97%	97%	96%
AD duration (yrs, mean/med)	4/4	4/3	4/4	4/3
ApoE4 Carrier	64%	62.5%	63%	64%
MMSE (mean/med)	20.5 / 21	20.6 / 21	20.4 / 20	20.5 / 20
% Mild (MMSE 22-26)	45%	43%	40%	43%
% Moderate (MMSE 16-21)	54%	57%	60%	57%
Education (yrs, mean/med)	14 / 14	14 / 13	14 / 14	14 / 14
AD medication	94%	91%	88%	90%

- *Randomized: N=353; safety population: N=351; modified intent-to-treat (m-ITT): N=341; per protocol set (PPS): N=130; PPS = study completers who received at least 80% of study drug*

Study AD201 Overview of Clinical Results

- Mild/Moderate (M/M) study population did not achieve significance on co-primary endpoints of NTB in m-ITT or PPS (see Table 2 and figure 1)
- Moderate AD group (MMSE 16-22, inclusive) and ApoE4 carriers and non-carriers showed no consistent positive or negative trends. Moderate AD results were similar in m-ITT/PPS
- *Mild AD group (MMSE 23-26, inclusive) showed encouraging trends on NTB, CDR-SB, and ADCS-ADL, but not on ADAS-cog, details shown in figures 2-5*

RESULTS

Results of Mild/Moderate & Moderate Groups

Figure 1: Clinical Outcomes in Overall M/M, PPS (N=47/49)
 (NTB: $\Delta=0.15$, $p=0.17$; ADCS: $\Delta=0.65$, $p=0.77$)

Study ELND005-AD201 Test Score Least Squares Mean Changes over Time by Treatment Group
 All Subjects in PPS Population

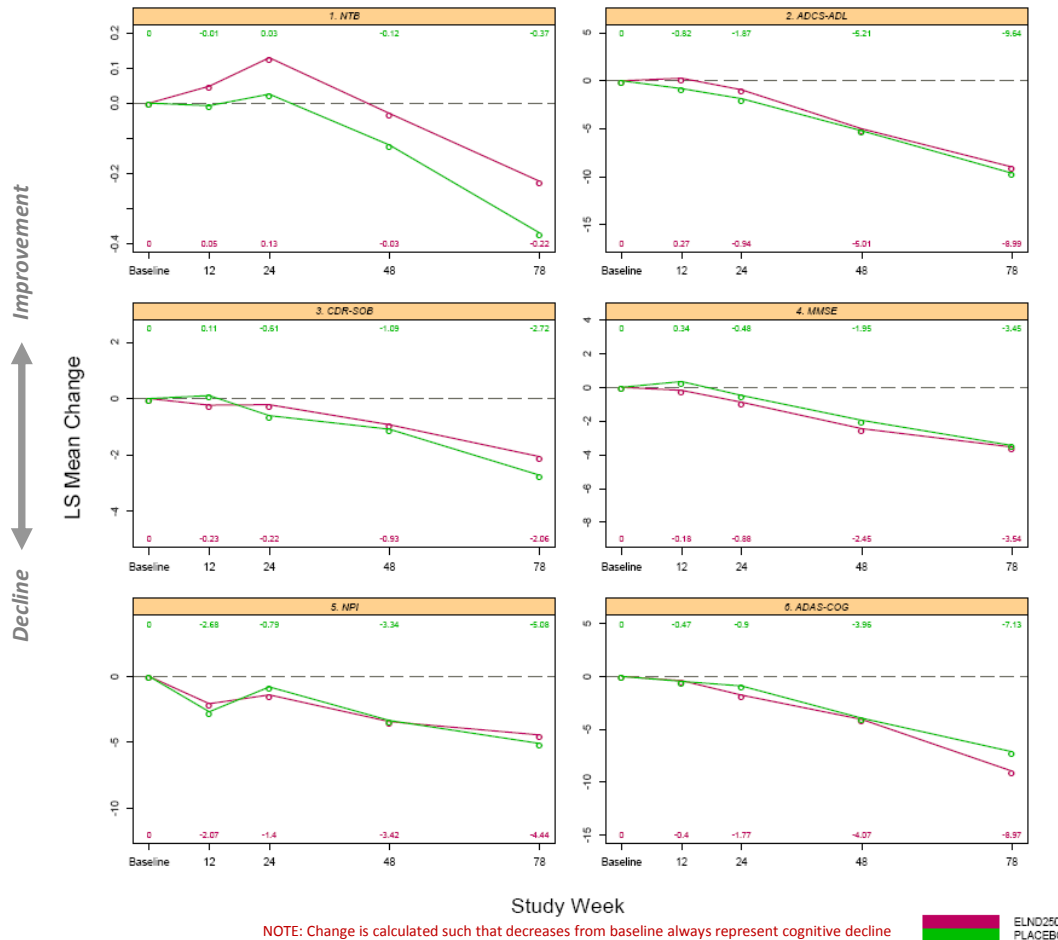


Table 2: Clinical Outcomes in Overall M/M and Moderate AD (m-ITT Analysis)

Population N= Pbo/250mg	NTB	ADCS-ADL	CDR-SB	ADAS-cog
Overall Mild/Moderate N=82/84	$\Delta= 0.03$ P = 0.71	$\Delta=-1.40$ P = 0.49	$\Delta= 0.29$ P = 0.54	$\Delta=- 2.56$ P = 0.18
Moderate N=48/47	$\Delta= -0.10$ P = 0.39	$\Delta=-4.3$ P = 0.10	$\Delta= -0.20$ P = 0.76	$\Delta=- 1.28$ P = 0.61

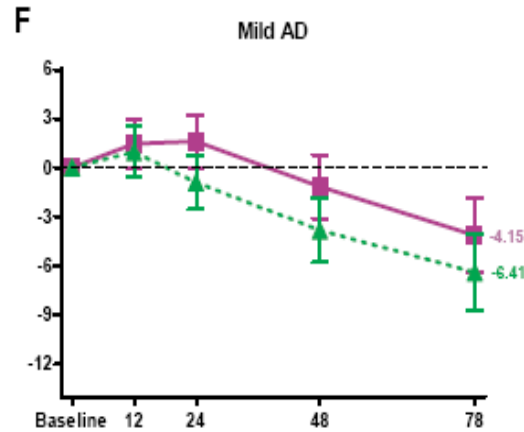
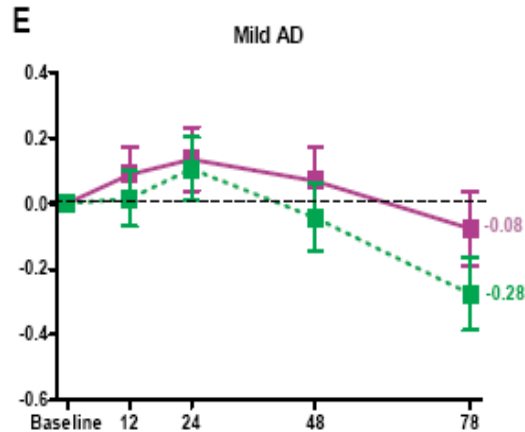
NOTE: Change is calculated such that decreases from baseline always represent cognitive decline

ELND250
PLACEBO

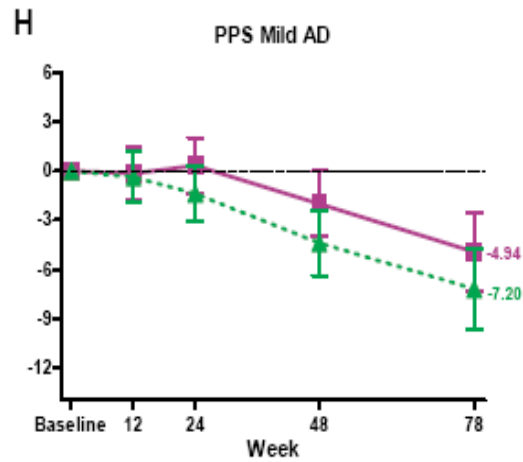
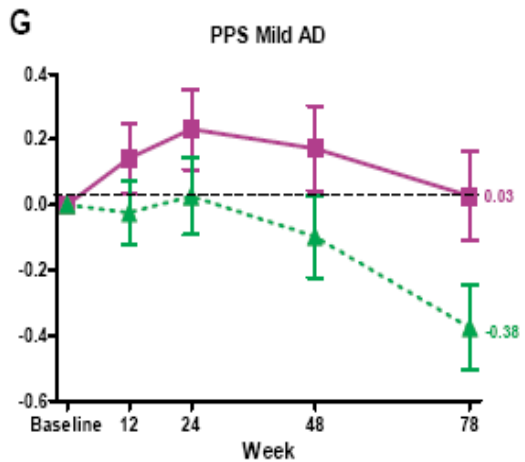
RESULTS

Results of Pre-Specified Mild Group

Figure 2: Results of NTB (left) and ADCS-ADL (right)



m-ITT:
 pbo n= 35; 250 = 36
 NTB:
 $\Delta=0.20$, $p=0.11$
 ADCS-ADL
 $\Delta=2.26$, $p=0.43$



PPS:
 pbo n= 22; 250 = 24
 NTB:
 $\Delta=0.40$, $p=0.007$
 ADCS-ADL
 $\Delta=2.25$, $p=0.46$

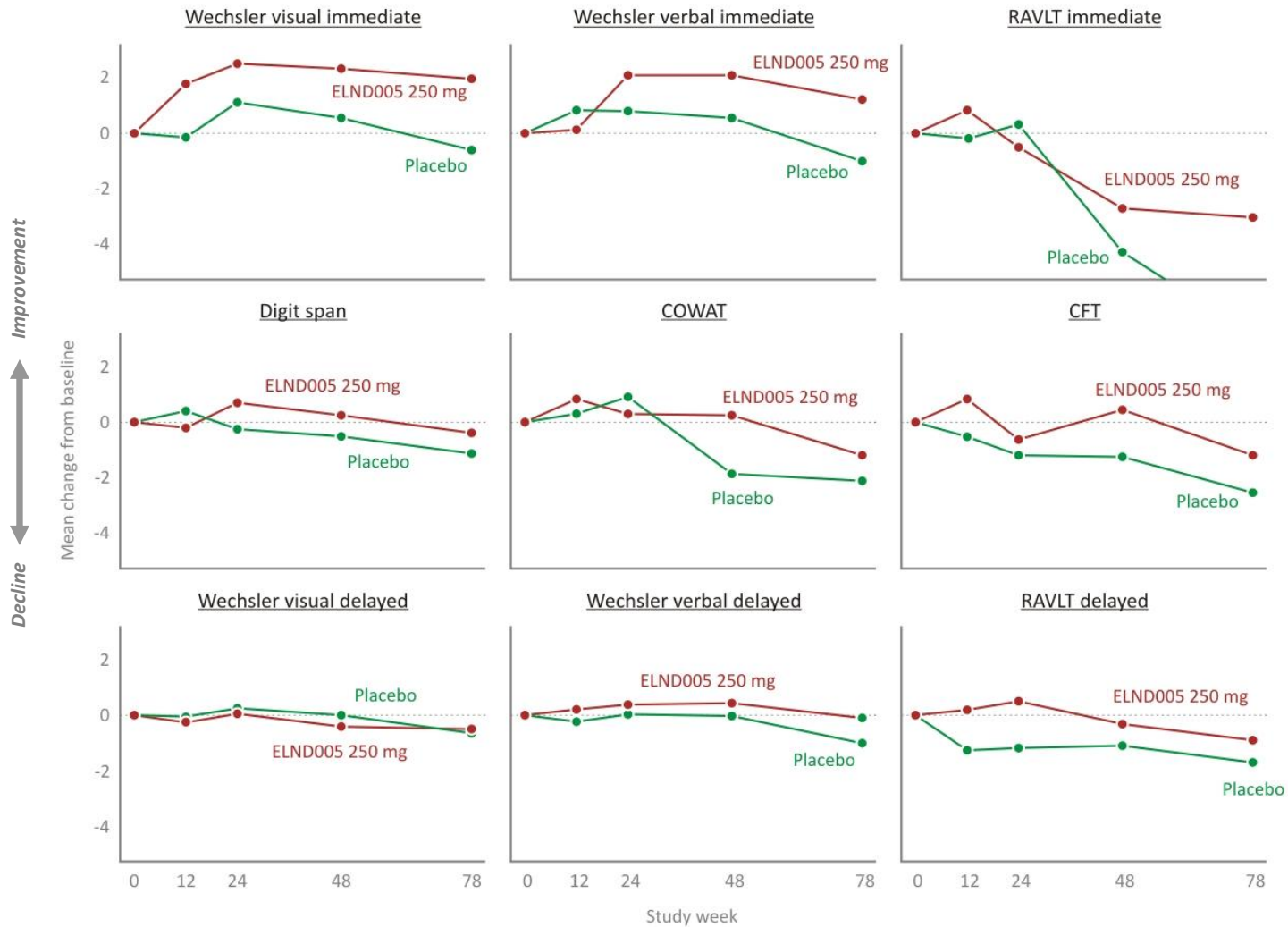
■ ELND005-250 mg ▲ Placebo

mITT: % drug effect relative to placebo = 71.4% on NTB; 35.3% on ADCS-ADL
 PPS: % drug effect relative to placebo > 100% on NTB; 31% on ADCS-ADL

RESULTS

Results of Pre-Specified Mild Group (continued)

Figure 3: Sub-Items of NTB (PPS)

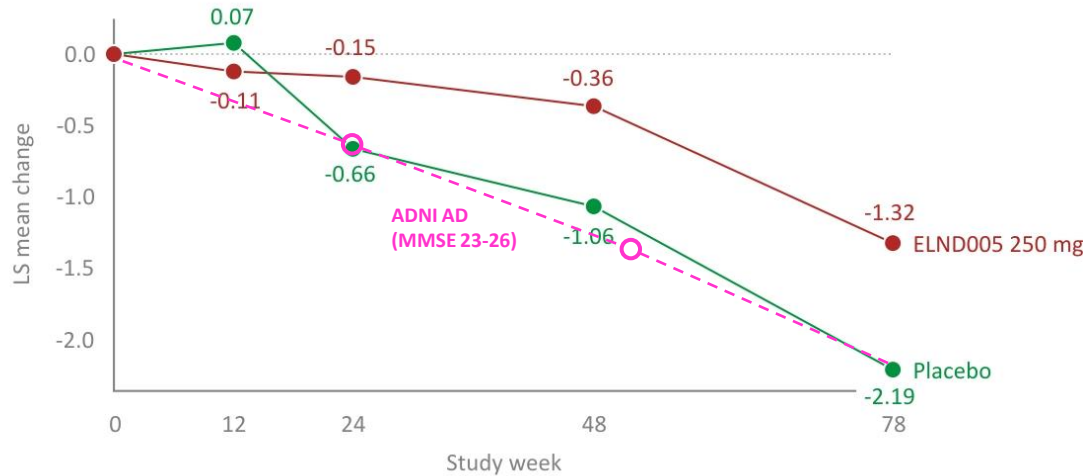


The sub-items of Immediate Memory and Executive Function show potential drug effects

RESULTS

Results of Pre-Specified Mild Group (continued)

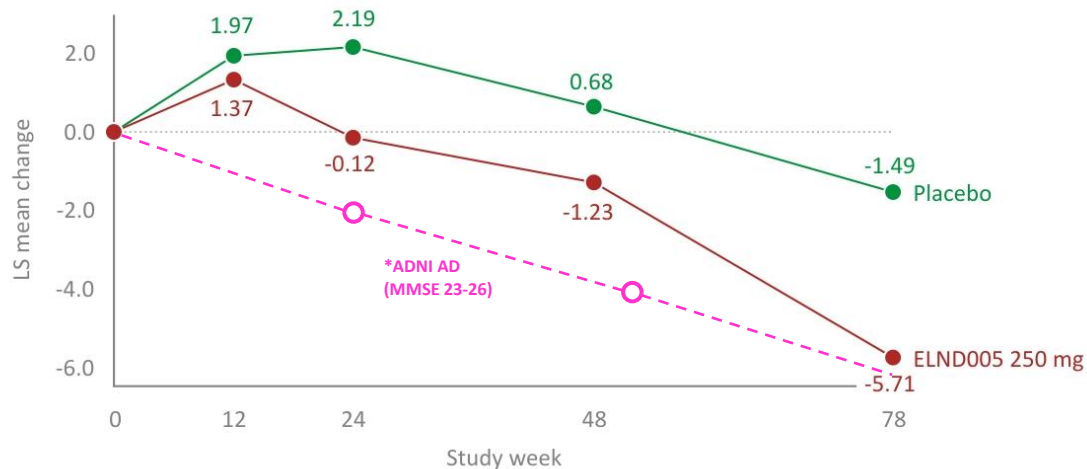
Figure 4: Mild AD Results of CDR-SB, m-ITT (m-ITT: $\Delta=0.87$, $p=0.19$; PPS: $=0.95$, $p=0.20$)



% drug effect relative to placebo in m-ITT = 40% and in PPS: 43%

The sub-items that showed potential drug effects were: cognitive (Memory and Orientation), and functional (Community Affairs and Personal Care)

Figure 5: Mild AD Results of ADAS-Cog, m-ITT (m-ITT: $\Delta= -4.22$, $p=0.11$; PPS: $=-4.11$, $p=0.18$)



Only 1 of 12 sub-items showed potential benefit in favor of placebo: Word Recognition

*Placebo decline is not consistent with expected decline from ADNI Mild population

Overall Mild/Moderate AD

Table 3: Overview of TEAEs in Mild/Moderate AD

No. Patients (%)	Placebo n=83	250 mg BID n=88	1000 mg BID n=89	2000 mg BID n=91
Any TEAE	76 (91.6%)	77 (87.5%)	78 (87.6%)	82 (90.1%)
TEAE related to study drug	28 (33.7%)	29 (33.0%)	34 (38.2%)	29 (31.9%)
D/C due to TEAE	8 (9.6%)	9 (10.2%)	15 (16.9%)	12 (13.2%)
Severe TEAE	5 (6.0%)	10 (11.4%)	11 (12.4%)	10 (11.0%)
Life- threaten. TEAE (CTCAE)	2 (2.4%)	1 (1.1%)	0 (0%)	1 (1.1%)
SAE	11 (13.3%)	19 (21.6%)	20 (22.5%)	21 (23.1%)
SAE related to study drug	2 (2.4%)	2 (2.3%)	6 (6.7%)	2 (2.2%)
Deaths*	0 (0%)	1 (1.1%)	5 (5.6%)	4 (4.4%)

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SAFETY

Mild/Moderate AD

Table 4: Most Common TEAEs (≥5%) by Preferred Term (PT) in M/M

Preferred Term	Placebo (N=83)	ELND005			Pooled ELND005 (N=268)
		250 mg BID (N=88)	1000 mg BID (N=89)	2000 mg BID (N=91)	
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)

Note: Adverse events are presented in the frequency that each event was reported in the pooled ELND005 group. 5% is with respect to the total number of patients in the safety set.

- Serious AE (SAE):
 - The overall incidence of SAEs was higher in the 3 ELND005 groups: 21.6%, 22.5%, and 23.1% in the 250-mg, 1000-mg, and 2000-mg groups than in placebo (13.3%)
 - Treatment-related SAEs were highest in 1000-mg group (6.7%) versus: Placebo (2.4%), 250-mg (2.3%), and 2000-mg (2.2%) groups
 - The most frequent SAEs were infections (respiratory and urinary), and were highest at 2 top doses (placebo = 1.2%, 250 mg = 1.1%, 1000 mg = 4.5%, 2000 mg = 8.8%)
 - Placebo and 250mg groups had 1 infection SAE each (Placebo: UTI, 250mg: viral infection)
- Deaths (total 10):
 - The 9 deaths in the 2 high dose groups were preceded by : aspiration pneumonia/pneumonia (2/2), respiratory failure (1), sudden death in setting of hypokalemia (1), sudden death after AD progression (1), failure to thrive/AD progression (1/1)
 - 8 of 9 deaths in 2 high dose groups were patients who had Moderate AD
 - 1 death in 250mg: due to frontal cerebral hemorrhage in an ApoE4 carrier, had evidence of prior hemorrhage on baseline MRI
- Vasogenic edema: None reported by local radiologist assessments

SAFETY

Mild AD

Table 5: Most Common TEAEs (≥5%) by Mild AD* by PT

	Placebo (N=45)	250 mg BID (N=46)
Preferred Term	n (%)	n (%)
Diarrhea	4 (8.9)	7 (15.2)
Upper respiratory tract infection	2 (4.4)	7 (15.2)
Depression or depressive Symptoms*	4 (8.9)	6 (13.0)
Nausea	1 (2.2)	5 (10.9)
Fatigue	2 (4.4)	5 (10.9)
Urinary tract infection	4 (8.9)	5 (10.9)
Fall	2 (4.4)	3 (6.5)
Arthralgia	2 (4.4)	3 (6.5)
Pain in extremity	1 (2.2)	3 (6.5)
Headache	7 (15.6)	3 (6.5)
Hypertension	1 (2.2)	3 (6.5)
Atrial fibrillation	3 (6.7)	2 (4.3)
Cataract	3 (6.7)	2 (4.3)

* Safety profile of 250mg bid in the Target Mild AD population for future studies (MMSE 22-26)

CONCLUSION

SAFETY

- The safety and tolerability profile of 250-mg bid is deemed acceptable, the independent safety committee concurred with this assessment
 - The 2 high dose groups were electively discontinued due to imbalance of infections and deaths due to various causes

EFFICACY

- In Mild/Moderate group, the treatment effects were not significant (NTB or ADCS-ADL)
- In Pre-specified analyses of Mild group, there were encouraging trends on cognition (NTB: $p=0.007$ in compliant patients who completed the study)
- The positive NTB trends were observed on both memory and executive function
- In Mild AD, the ADCS-ADL and CDR-SB effects of ELND005, though not significant, were of clinically relevant magnitude: > 30% less decline than placebo

Above results , and the CSF biomarker results, helped select an appropriate dose for further development of ELND005 in Mild AD

ACKNOWLEDGEMENTS

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