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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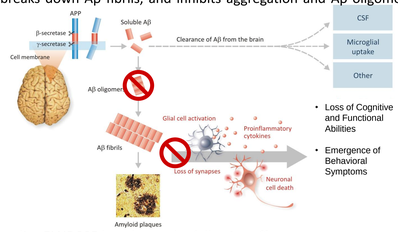
#P2-499

BACKGROUND

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



- In preclinical studies ELND005 has shown the following effects:
- Aβ anti-aggregation effects in vitro (*McLaurin et al, J Biol Chem 2000;275:18495-502*)
- Protection from Aβ 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, astrocytosis, 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

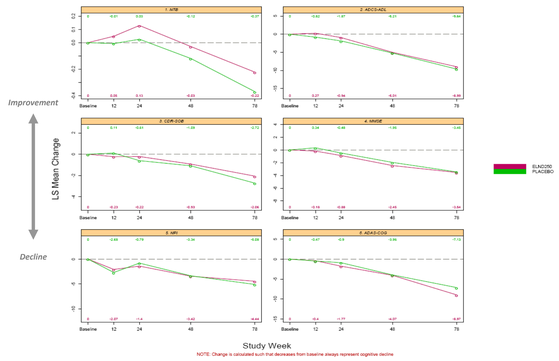
- Mild/Moderate (M/M) study population did not achieve significance on co-primary endpoints of NTB in m-ITT or PPS (see Table 2 and figure 1)
- Moderate AD group (MMSE 16-22, inclusive) and ApoE4 carriers and non-carriers showed no consistent positive or negative trends. Moderate AD results were similar 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 of Mild/Moderate & Moderate Groups

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

Study ELND005-AD201 Test Score Least Squares Mean Changes over Time by Treatment Group

All Subjects in PPS Population



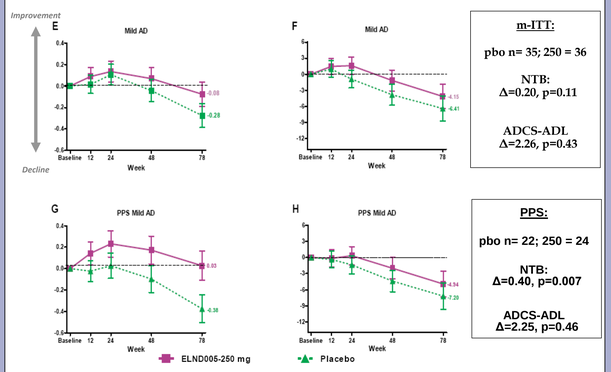
NOTE: Change is calculated such that decreases from baseline always represent cognitive decline

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	Δ= 0.03 P = 0.71	Δ=-1.40 P = 0.49	Δ= 0.29 P = 0.54	Δ=- 2.56 P = 0.18
Moderate N=48/47	Δ= -0.10 P = 0.39	Δ=-4.3 P = 0.10	Δ= -0.20 P = 0.76	Δ=- 1.28 P = 0.61

Results of Pre-specified Mild Group

Figure 2: Results of NTB (Left) and ADCS-ADL (Right)



m-ITT:

pbo n= 35; 250 = 36

NTB: Δ=0.20, p=0.11

ADCS-ADL Δ=2.26, p=0.43

PPS:

pbo n= 22; 250 = 24

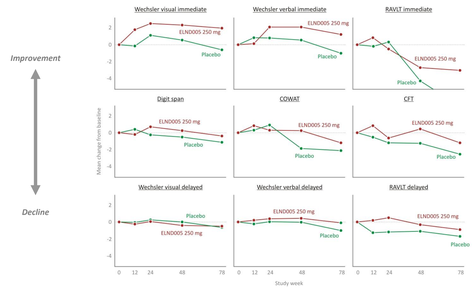
NTB: Δ=0.40, p=0.007

ADCS-ADL Δ=2.25, p=0.46

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

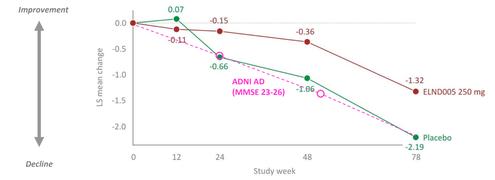
Results of Pre-specified Mild Group *(Cont'd)*

Figure 3: Sub-items of NTB (PPS)



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

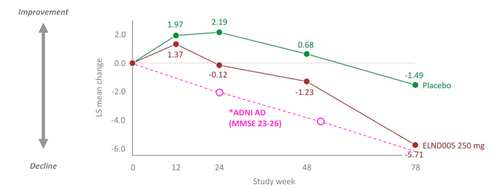
Figure 4: Mild AD Results of CDR-SB, m-ITT (m-ITT: Δ=0.87, p=0.19; PPS: =0.95, p=0.20)



% 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: Δ= - 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

SAFETY: Overall Mild/Moderate

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%)

Safety in Mild/Moderate & Mild AD

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

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

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

Table 5: Most Common TEAEs (≥5%) in 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)*

CONCLUSIONS

- 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

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