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Imaging & Cerebrospinal Fluid Biomarker Results of a Phase 2 Dose-Ranging Study of ELND005 (Scyllo-inositol) in Mild/Moderate AD

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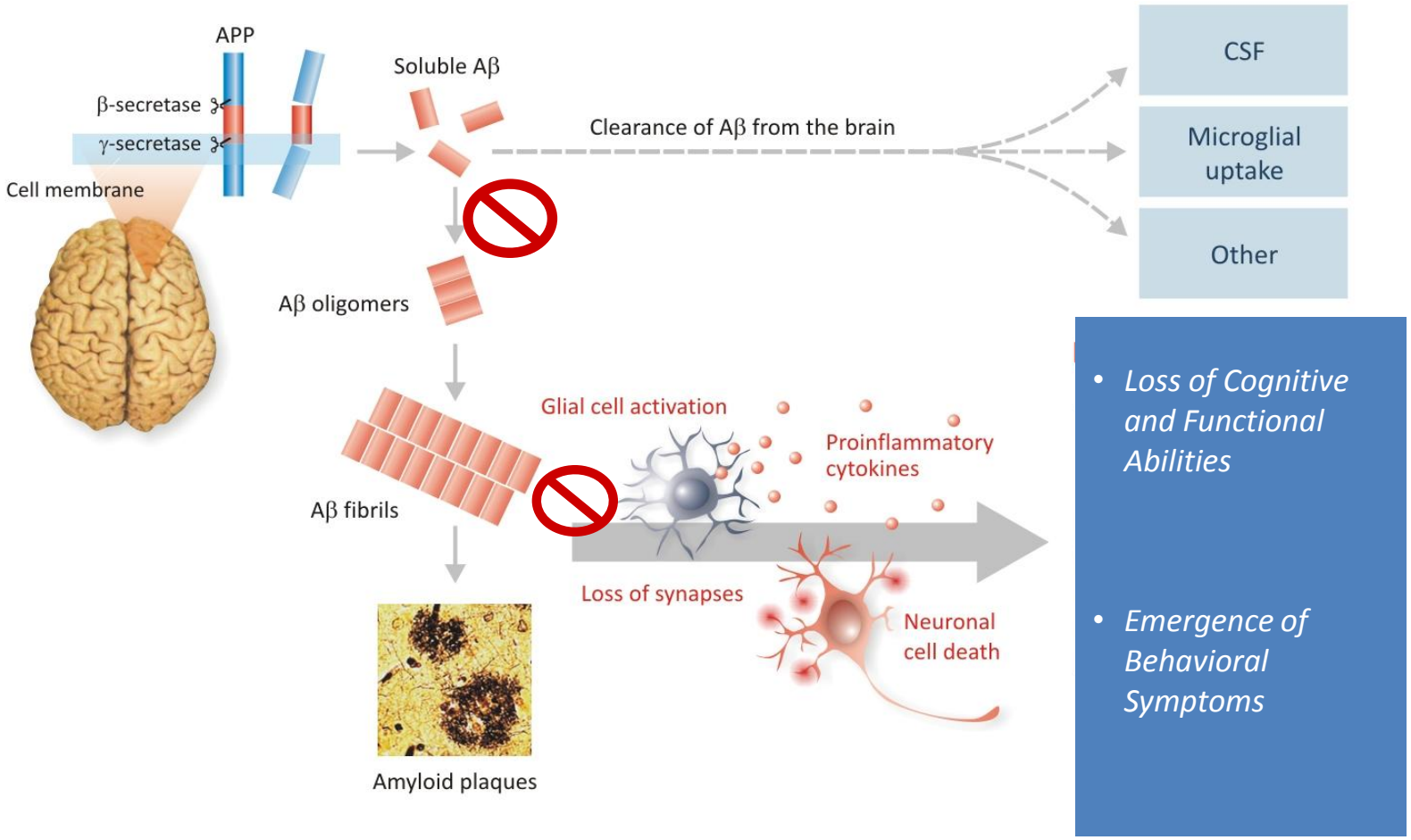
On behalf of Study ELND005-AD201 Investigators

Preclinical Pharmacology: ELND005 (Scyllo-inositol) is an Aβ Aggregation Inhibitor



- In vitro anti-aggregation effects: *McLaurin et al, J Biol Chem 2000;275:18495*
- Protection from Aβ oligomer induced LTP inhibition & dendritic spine loss: *Shankar et al, J Neurosci 2007;27:2866; Townsend et al, Ann Neurol 2006;60:668*
- Amyloid lowering and learning benefits in TgCRND8 mice: *McLaurin et al., Nature Med 2006;12:801*

Phase 2 Study AD201: Objectives & Study Design

Objective:

- Evaluate dose-related safety and efficacy of 3 oral dosages of ELND005 (250mg, 1000mg and 2000mg, all given bid) versus placebo in Mild/Moderate AD (MMSE: 16-26)
    - Included v-MRI and CSF biomarkers (in a subset) to evaluate disease modifying potential

Design:

- RCT parallel-arm study at 58 sites in North America; Co-primary endpoints; NTB and ADCS-ADL
- With 85 per am, powered to detect differences of 0.2 on NTB, 4 points on ADCS-ADL
- Total 353 randomized for 78 week of treatment: 351 dosed, 341 (m-ITT)
- Main efficacy and biomarker analyses were based on placebo and 250mg only
    - 1000mg and 2000mg groups discontinued before study end due to safety findings
    - Pre-planned subgroup analyses: Mild, moderate AD, ApoE4 carrier and non-carrier
    - MMSE definition for Mild: 23-26; Moderate: 16-22

Biomarker Measures:

- Imaging biomarkers: volumetric MRI (v-MRI) at baseline and every 24 weeks
    - Ventricular volume at 78 weeks was key imaging biomarker
    - Others: Brain Volume, hippocampal volume, and cortical ribbon thickness
- CSF biomarkers: Aβ42 , Aβ40; tau, and phospho-tau_{181} at baseline , 24, and 78 weeks

Methods

Volumetric-MRI Assessments:

- All MRI measures were evaluated by NeuroRx Research, Montreal

- Ventricular volume (VV): *L*ateral ventricles were segmented manually on baseline scans, and vv changes were estimated using longitudinal edge motion detection of the ventricular CSF boundary [1]

- Brain volume (BV): Brain volume, normalized for subject head size, was estimated using SIENAX. Subsequent two-time point percentage brain volume change was estimated using SIENA [1].

- Hippocampal volume: utilized automatic nonlinear image matching and anatomical labeling, combined with template fusion [2]

- Cortical ribbon thickness : utilized a variation of SIENA [3]

1. Smith SM, Zhang Y et al. NeuroImage 2002;17:479-489.
2. Collins DL , J Pruessner. NeuroImage 2010; 52: 1355-1366
3. Chen JT, Narayanan S. et al. NeuroImage 2004;23:1168-1175

Methods: CSF Biomarkers

***CSF Assays**:*

- *Week 24 assessments were considered the main analysis time point*
  - *All assays performed at Elan's Bio-analytical Laboratory*

- Aβ42 , Aβ40: validated Meso-Scale Discovery Electrochemiluminescence (ECLA). Lower limit of Quantitation (LLQ):
  - Aβ42: 100 pg/ml
  - Aβ40: 100 pg/ml

- Tau, and Phospho-tau$_{181}$ (P-tau): validated ELISA using commercial kit from Innogenetics. LLQ:
  - Tau: 37.5 pg/ml
  - P-tau : 15.6 pg/ml

***Statistical Analysis**:*

- *All clinical and biomarker analyses used a repeated measure mixed effect model (MMRM)*
- *Exploratory analyses of the 4 dose groups used observed values with no MMRM*

v-MRI Summary: Placebo versus 250 mg BID Change from Baseline to 78 weeks (MMRM)

- **Overall Mild/Moderate Population (Mean MMSE 20.5)**

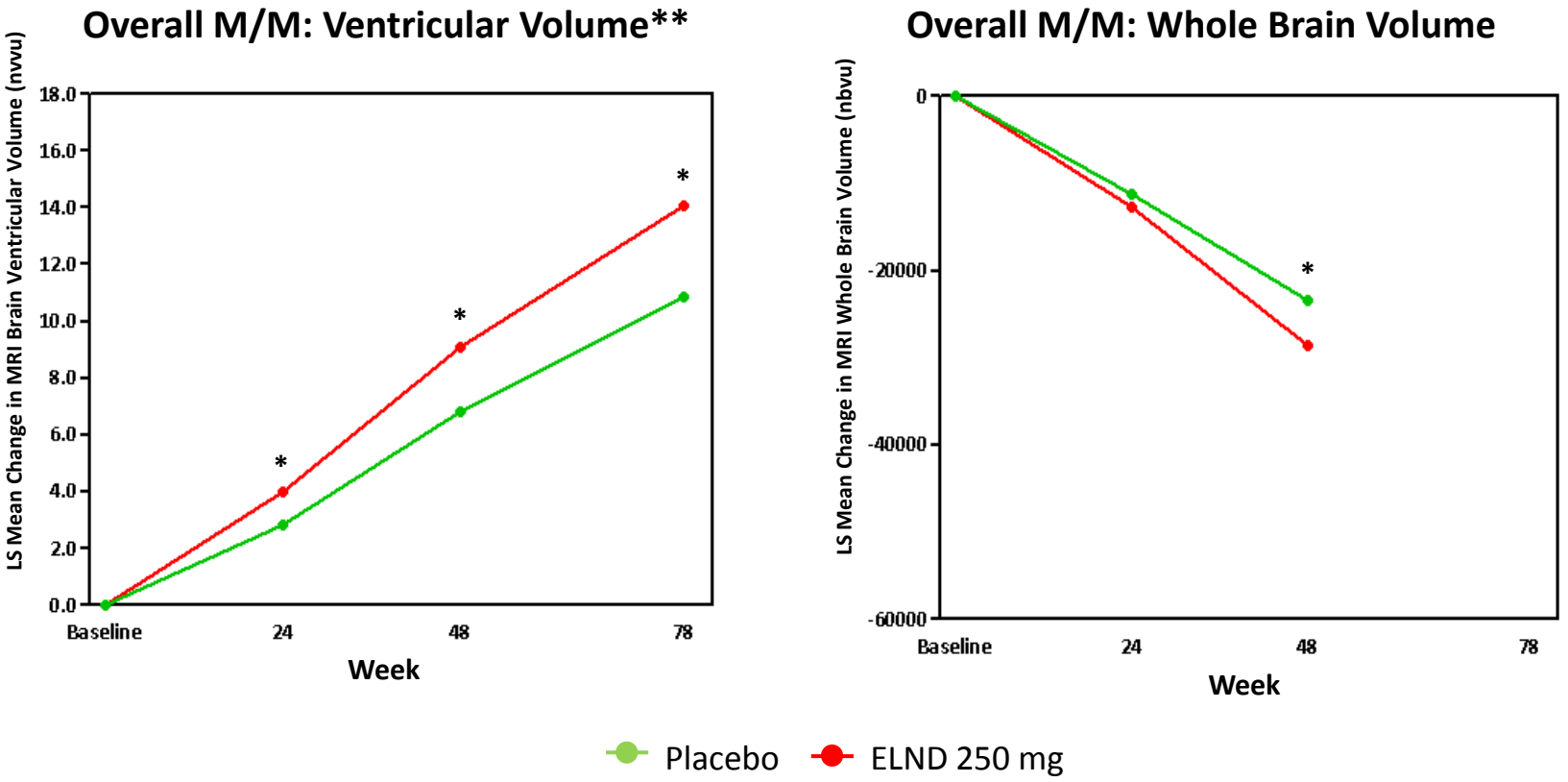
Population (N Placebo/250 mg)	*Ventricular Volume (cc)	Whole brain volume (mm3)	Average hippocampal volume (mm3)	Cortical ribbon thickness (mm)
m-ITT N=82/84	3.206 **(p=0.049)**	-4904 (p=0.208)	-0.025 (p=0.283)	-0.002 (p=0.738)

- **Subgroups (Mean MMSE): Mild (24.0); Moderate (17.9)**

Mild N=35/36	0.256 (p=0.908)	-2015 (p=0.696)	0.000 (p=0.999)	-0.002 (p=0.833)
Moderate N=47/48	5.835 **(p=0.007)**	-7936 (p=0.113)	-0.048 (p=0.139)	-0.002 (p=0.748)

- *Designated key imaging biomarker; shown are LS means of difference between drug and placebo
- Mild AD: MMSE 23-26 is the pre-specified subgroup that showed a positive trend on the NTB in the Per Protocol Analysis (PPS): Δ= 0.40, p= 0.007. In the m-ITT: Δ= 0.20, p= 0.110
- Moderate AD (MMSE 16-22 inclusive). This group showed no significant treatment effect or trend on the NTB in m-ITT or PPS. NTB (in PPS): Δ= -0.08, p= 0.591; NTB (m-ITT): Δ= -0.100, p= 0.392

Time Course of Changes in Ventricular and Brain Volume: Placebo versus 250 mg BID at 24, 48, and 78 weeks (MMRM Analysis)

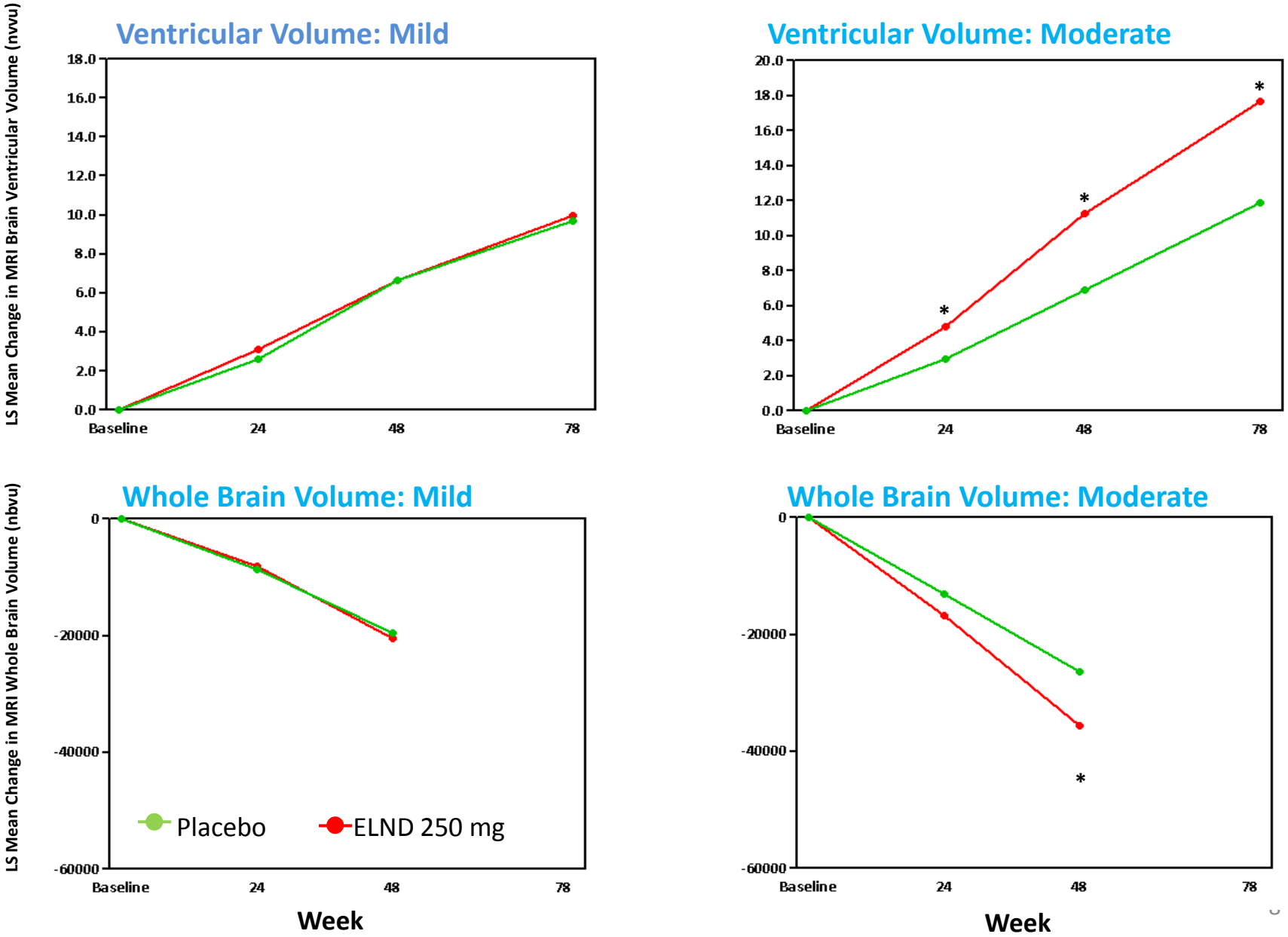


Note: The LS mean for the Week 78 change in whole brain volume was reported as "not estimable" by Model

*Indicates $p < 0.05$

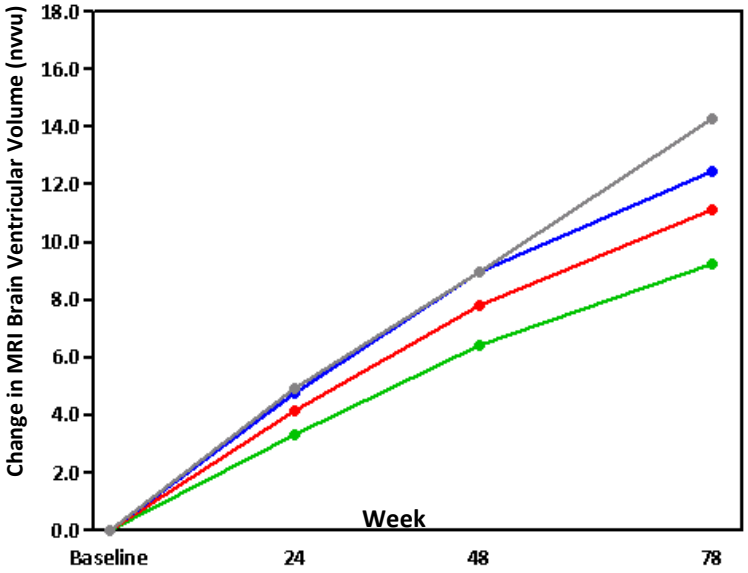
** Key Imaging biomarker

Ventricular and Brain Volume Changes in Mild and Moderate Subgroups: Placebo versus 250 mg BID (MMRM)

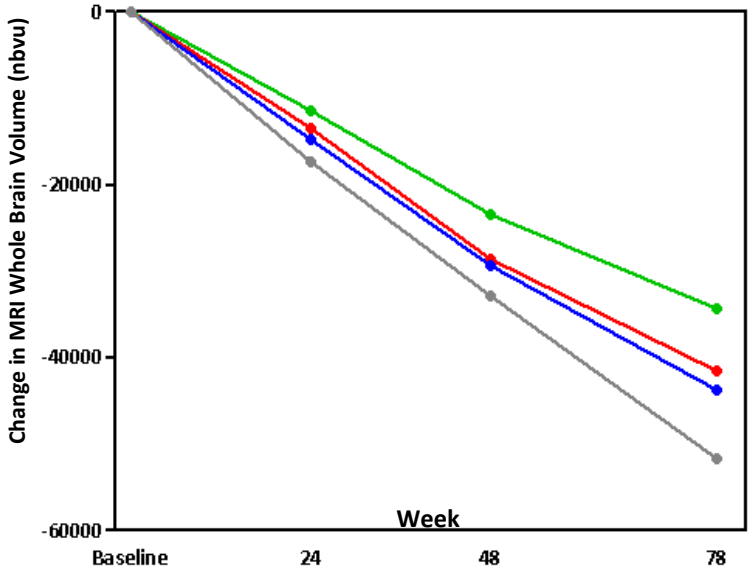


All Dose Groups: Ventricular and Brain Volume Changes in Overall M/M Population (Observed Values, OC)

Ventricular Volume



Whole Brain Volume



Placebo ELND 250 mg ELND 1000 mg ELND 2000 mg

Note:

•For the 2 high dose groups: only 15 and 19 patients completed wk 78 visit. For other patients , mean time in study was ~73 weeks, last visits that occurred between wks 63 and 77 were mapped to wk 78 visit.

•This analysis was based on actual or observed values, and did not use MMRM

CSF Biomarker Summary: Placebo versus 250 mg BID Change from Baseline (Mild/Moderate Population)

Overall CSF Population: Pbo/250mg, N= 14/19 at baseline; N= 11/9 at wk 78

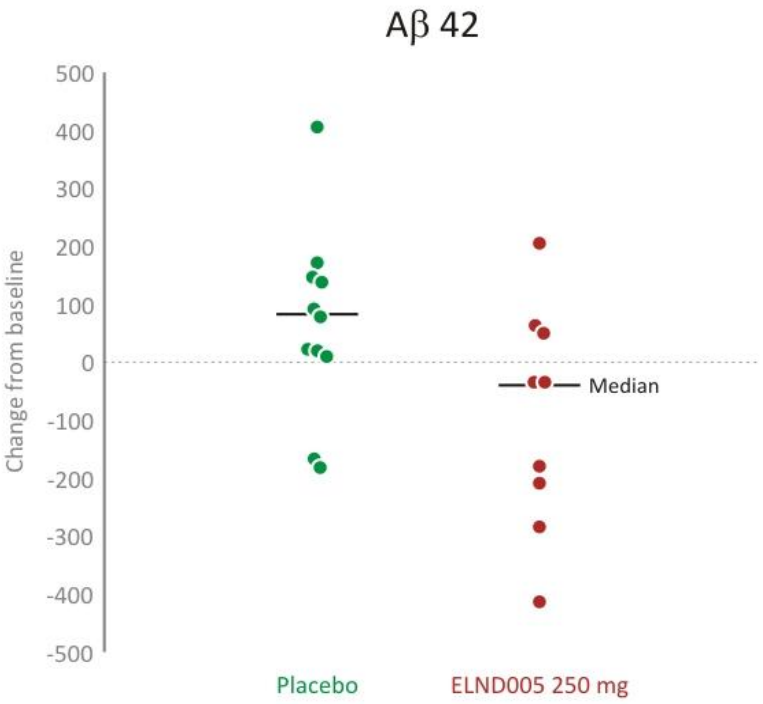
Time Point	**Aβ42 (pg/ml)**	**Aβ40 (pg/ml)**	**Tau (pg/ml)**	**p-Tau (pg/ml)**
Baseline Mean Pbo/250mg	707/718	9256/8558	785/690	121/101
CSF population 24 wks*	-44 (p=0.374)	-1259 (p=0.168)	-3.60 (p=0.936)	0.813 (p=0.832)
CSF population 78 wks	**-191** (p=0.009)**	-1320 (p=0.152)	-39.89 (p=0.497)	11.43 (p=0.334)

*Designated primary CSF analysis time point , Comparison of LS means using MMRM

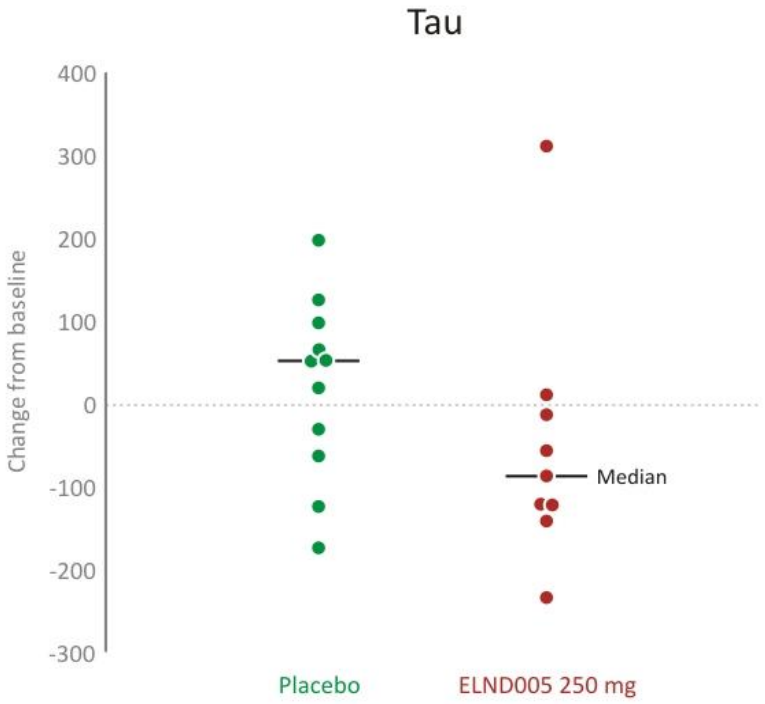
Similar results for completers (PPS) for **Aβ42: Δ-173, p=0.036

CSF Aβ42 and TAU: Changes from Baseline to Week 78

Placebo N= 11; 250mg BID N= 9 at week 78



	Placebo	ELND005	Δ	p-value
N	11	9		
LS mean	70.4	-120.9	-191.3	0.009
Median	79.8	-38.1	-117.9	0.068

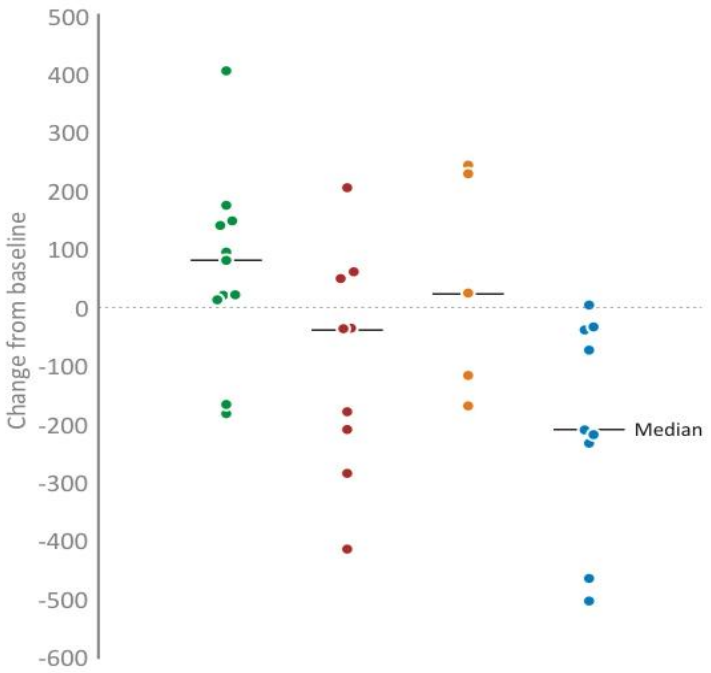


	Placebo	ELND005	Δ	p-value
N	11	9		
LS mean	13.6	-26.3	-39.9	0.497
Median	52.6	-87.5	-140.1	0.129

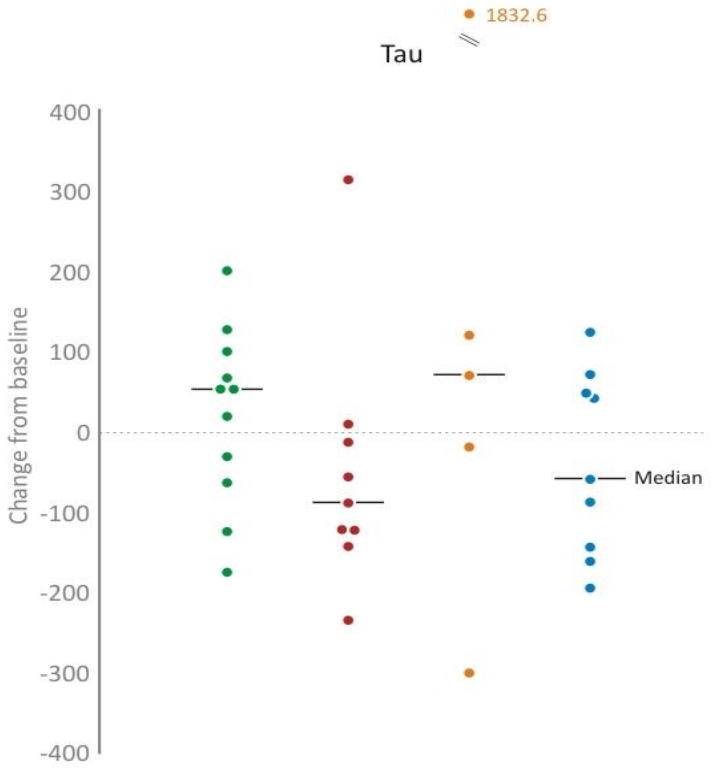
- Comparison of LS means using MMRM
- Comparison of median values using Wilcoxon's Rank Sum
- Note: Significant correlations between Aβ42/ Aβ40 ratio reduction & drug exposure metrics **(0.42-0.50 , $p < 0.05$)**

All Dose Groups: CSF Aβ42 and Tau Changes at wk 78

Placebo N = 11; 250mg N = 9; 1000mg N = 5; 2000mg N = 9



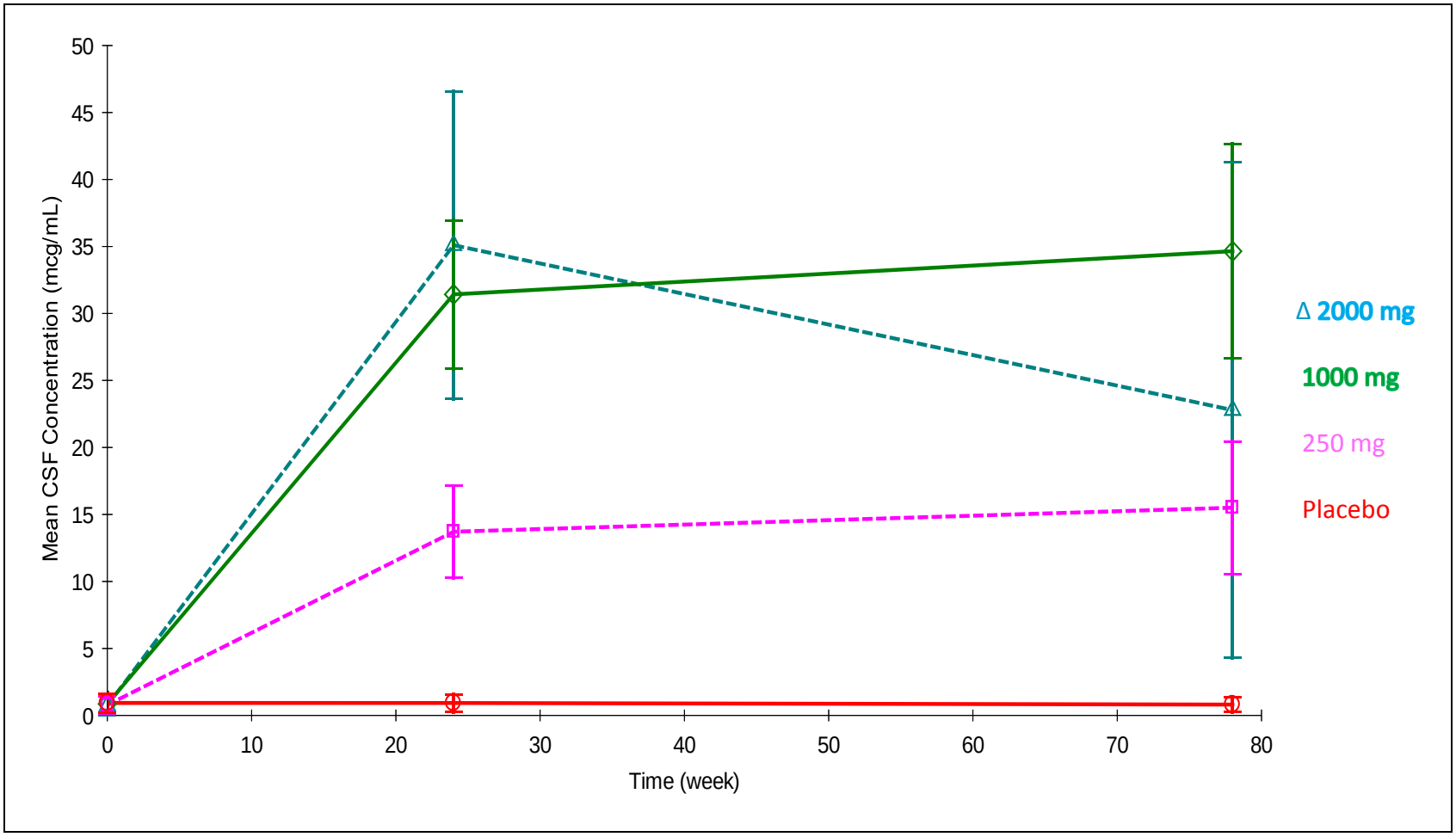
	Placebo	250 mg	1000mg	2000mg
N	11	9	5	9
Mean	67.9	-94.0	41.7	-196.3
Median	79.8	-38.1	23.3	-209.3



	Placebo	250 mg	1000mg	2000mg
N	11	9	5	9
Mean	20.5	-50.5	340.9	-39.8
Median	52.6	-87.5	70.7	-58.0

- Actual observed data, not MMRM analysis

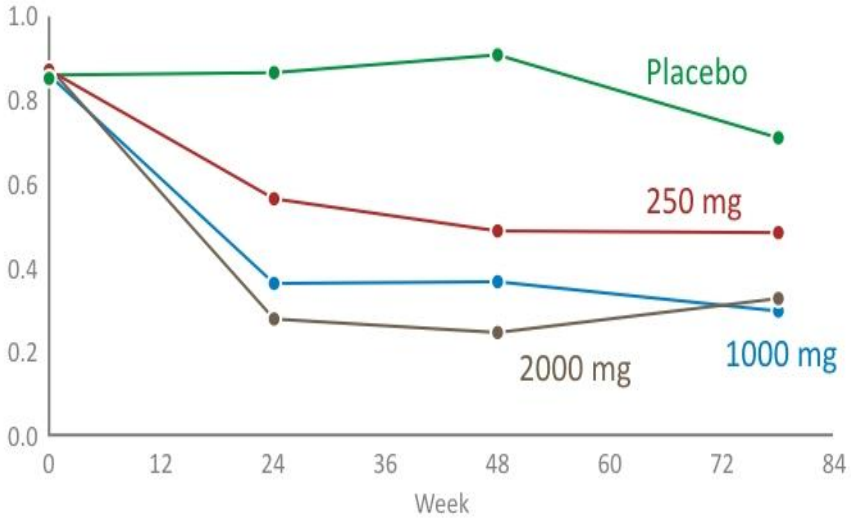
ELND005 CSF Concentrations at 3 Dosages (µg/ml)



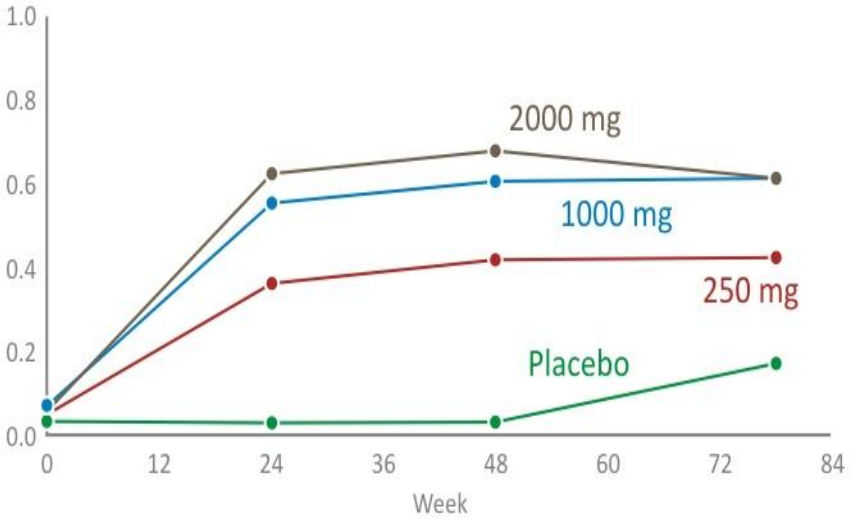
CSF ELND005 levels approach saturation at doses ≥ 1000mg bid

Brain Myo-inositol and *Scyllo*-inositol levels by Proton-MRS (Molar ratio to creatine, in overall MRS population)

Myo-inositol



Scyllo-inositol

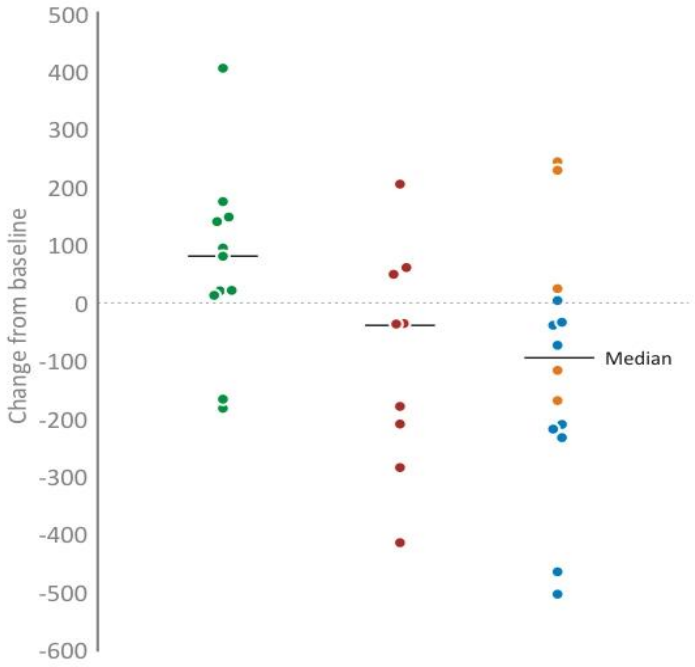


Brain levels (molar ratio to creatine) also approach saturation at doses ≥ 1000mg bid

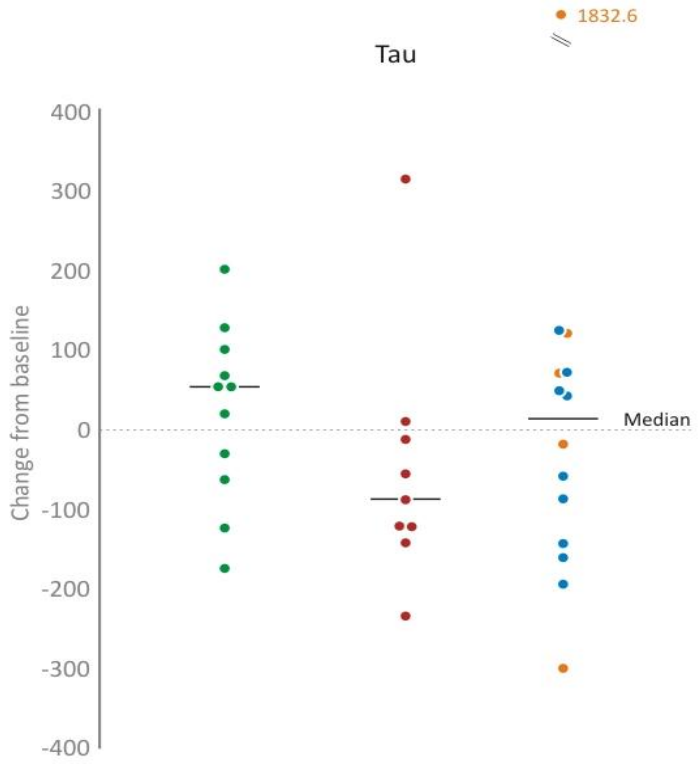
CSF/brain PK allows pooling of 2 high dose groups for CSF biomarker effects

Pooled Highest Dose Groups: CSF Aβ42 and Tau Changes at wk 78

Placebo N = 11; 250mg N = 9; Combined 2 high dose groups N = 14



	Placebo	250 mg	Higher doses
N	11	9	14
Mean	67.9	-94.0	-111.3
Median	79.8	-38.1	-94.9



	Placebo	250 mg	Higher doses
N	11	9	14
Mean	20.5	-87.5	96.2
Median	52.6	-50.5	11.3

Conclusions

- In Mild/Moderate AD, ELND005 was associated with significant increases in ventricular volume, and numerical decreases in whole brain volume at 78 weeks
- The brain volume effects were minimal and not significant, compared to placebo, in the Mild subgroup which had a beneficial cognitive trend on 250mg bid dose (NTB, p= 0.007 in compliant completers)
- In the CSF subset: At 250mg bid there was significant reduction of CSF Aβ42 (~27%), and a numerical reduction of tau (NS due to an outlier); significant only at 78 weeks
- Observed case analyses of the 3 dose groups suggest dose-dependent effects on brain volume measures and on CSF Aβ42 reduction
- Above results, taken together, may reflect a gradual reduction of brain Amyloid pathology by ELND005 , consistent with its preclinical effects in the Tg CRND8 model of AD
- The 250mg bid dose demonstrated relevant biological activity , and together with the clinical efficacy/safety profile*, support its choice for future development in AD

* In Press: Neurology 2011, Salloway et al. Also ICAD poster presentation on July 18, 2011