

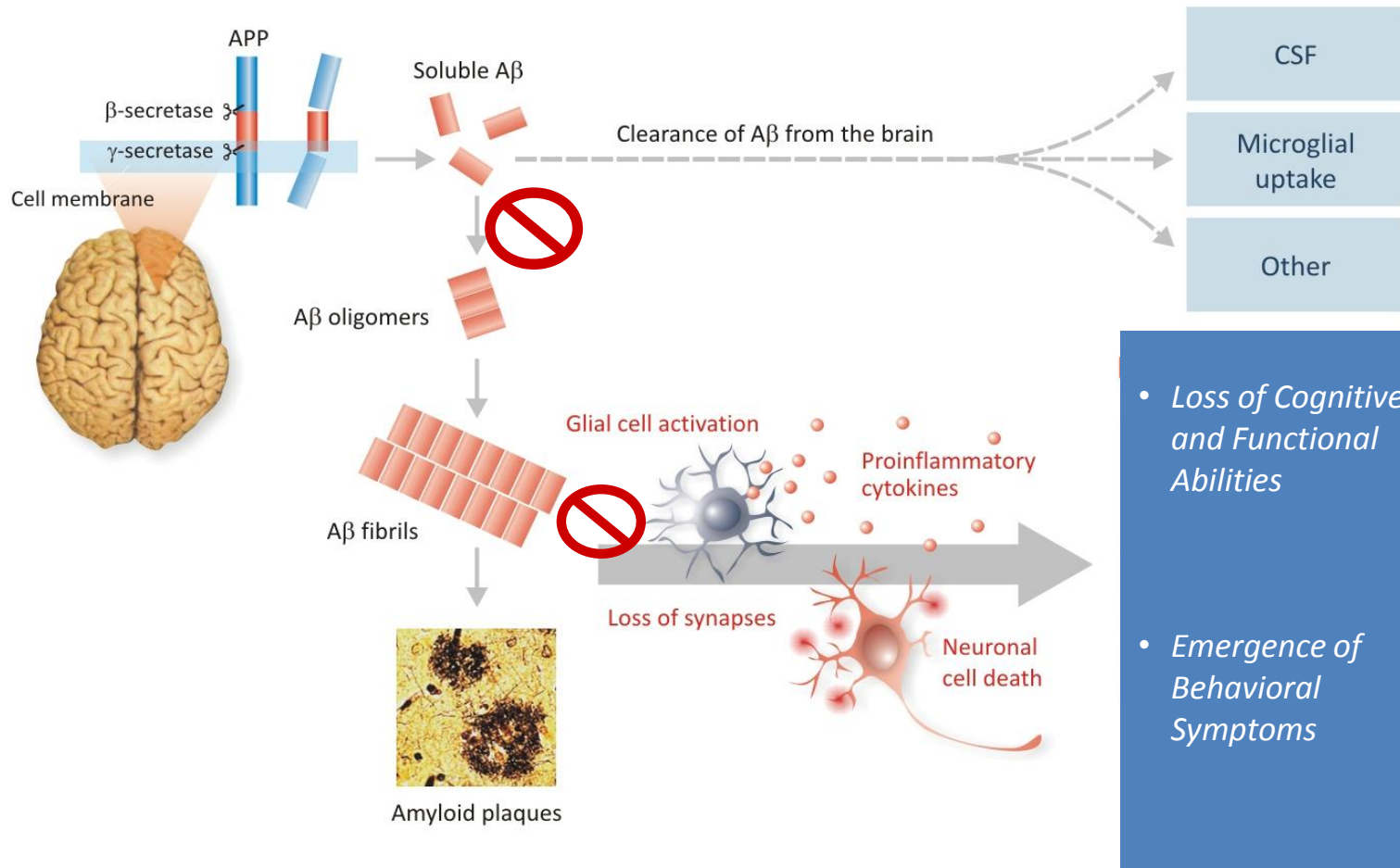
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Imaging & Cerebrospinal Fluid Biomarker Results of a Phase 2 Dose-
Ranging Study of ELND005 (Scyllo-inositol) in Mild/Moderate AD

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On behalf of Study ELND005-AD201 Investigators

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



- ❖ In vitro anti-aggregation effects: *McLaurin et al, J Biol Chem 2000;275:18495*
- ❖ Protection from A β 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 arm, 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: A β 42 , A β 40; tau, and phospho-tau₁₈₁ at baseline , 24, and 78 weeks

Methods

Volumetric-MRI Assessments:

- All MRI measures were evaluated by NeuroRx Research, Montreal
- Ventricular volume (VV): Lateral 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*
- *A β 42 , A β 40: validated Meso-Scale Discovery Electrochemiluminescence (ECLA). Lower limit of Quantitation (LLQ):*
 - *A β 42: 100 pg/ml*
 - *A β 40: 100 pg/ml*
- *Tau, and Phospho-tau₁₈₁ (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)**

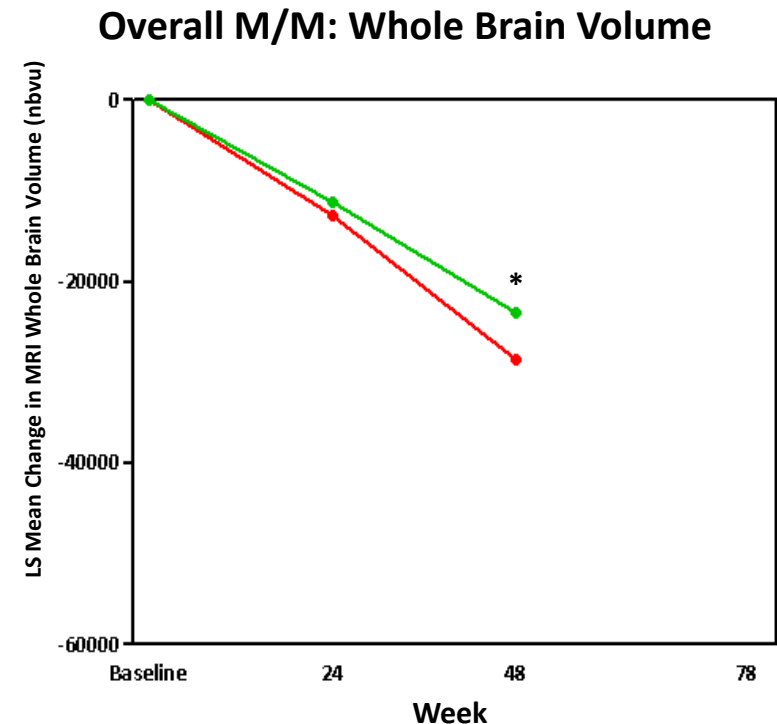
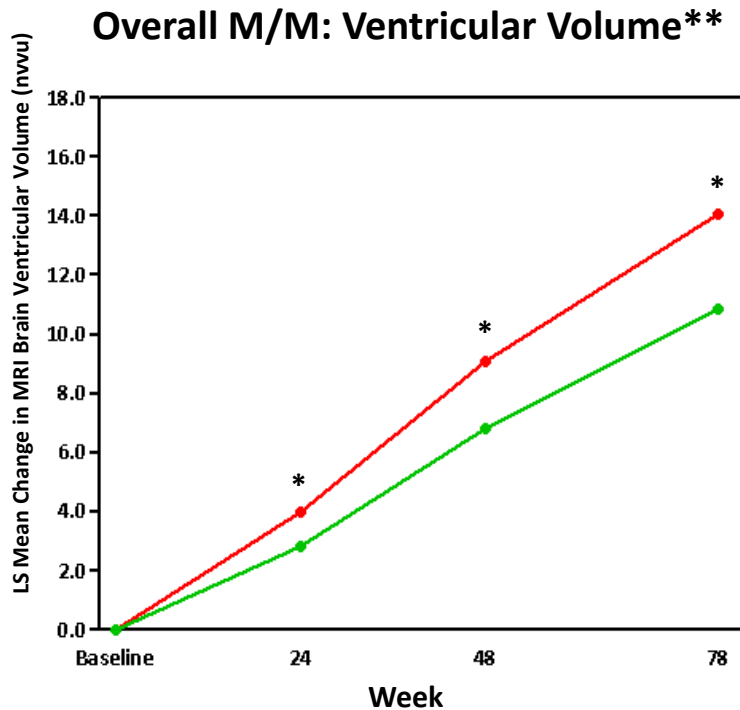
Population (N Placebo/250 mg)	*Ventricular Volume (cc)	Whole brain volume (mm ³)	Average hippocampal volume (mm ³)	Cortical ribbon thickness (mm)
m-ITT N=82/84	3.206 (p=0.049)	-4904 (p=0.208)	-0.025 (p=0.283)	-0.002 (p=0.738)

- **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): $\Delta = 0.40$, $p = 0.007$. In the m-ITT: $\Delta = 0.20$, $p = 0.110$
- 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): $\Delta = -0.08$, $p = 0.591$; NTB (m-ITT): $\Delta = -0.100$, $p = 0.392$

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



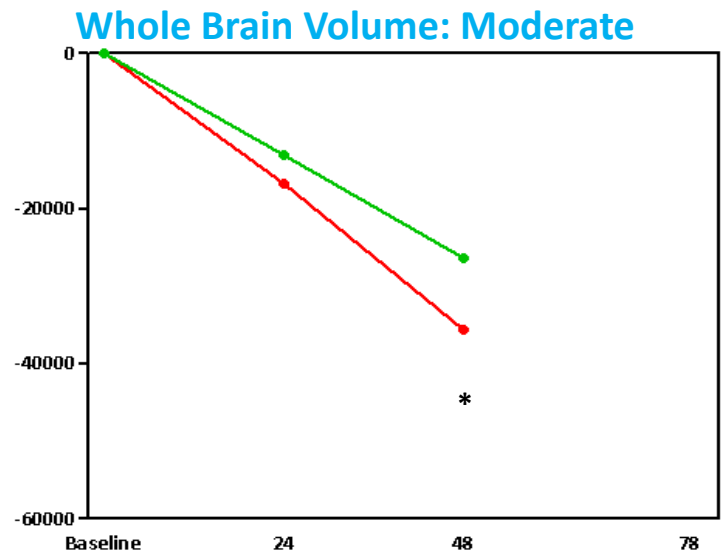
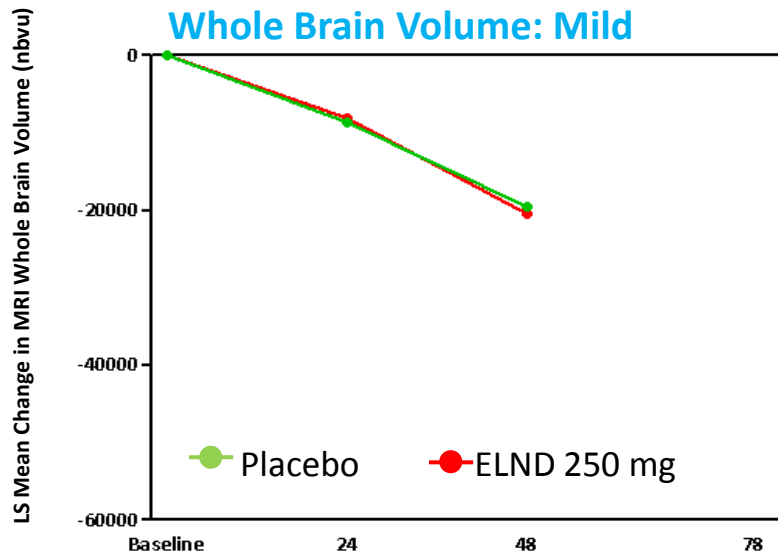
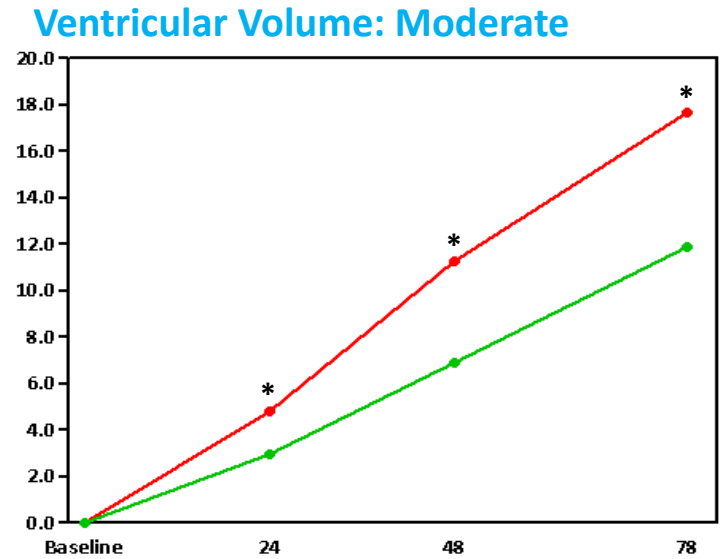
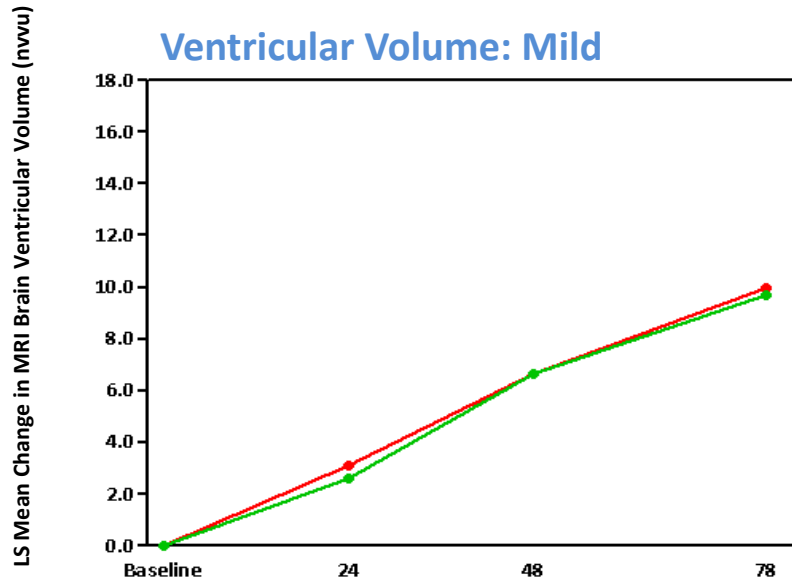
● Placebo ● ELND 250 mg

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

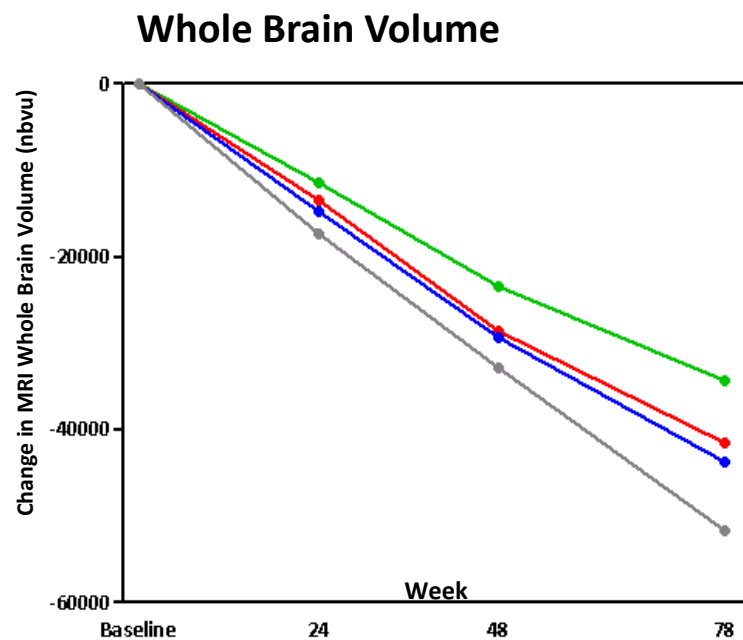
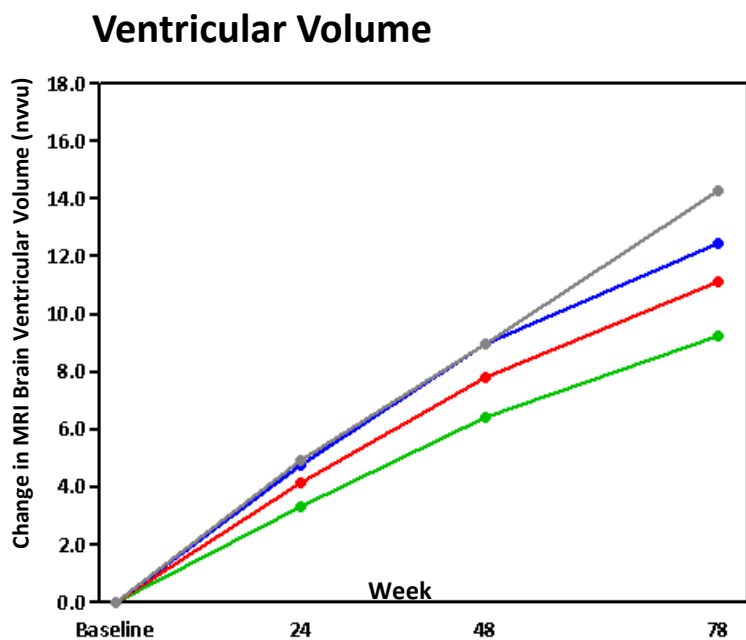
Ventricular and Brain Volume Changes in Mild and Moderate Subgroups: Placebo versus 250 mg BID (MMRM)



Week

Week

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



● 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

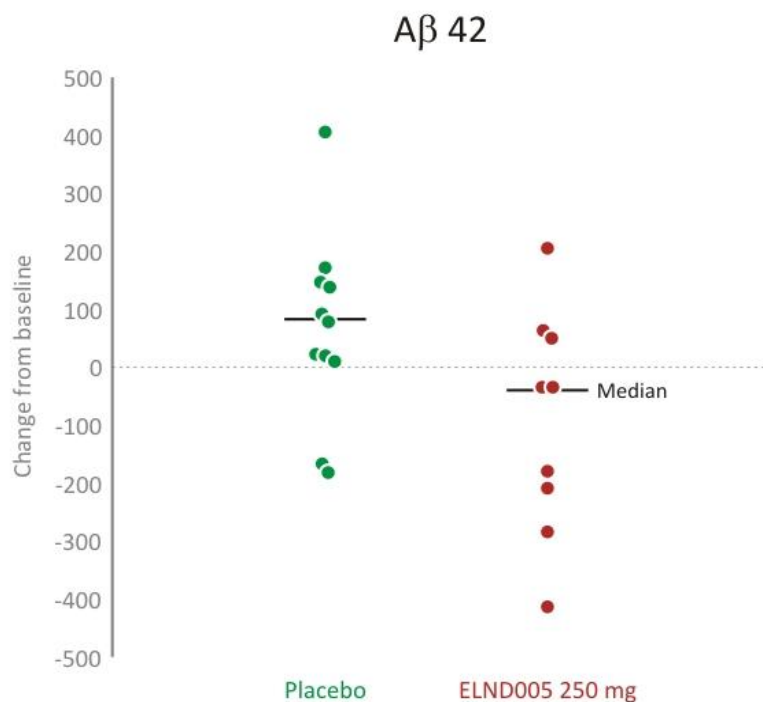
Time Point	Aβ42 (pg/ml)	Aβ40 (pg/ml)	Tau (pg/ml)	p-Tau (pg/ml)
Baseline Mean Pbo/250mg	707/718	9256/8558	785/690	121/101
CSF population 24 wks*	-44 (p=0.374)	-1259 (p=0.168)	-3.60 (p=0.936)	0.813 (p=0.832)
CSF population 78 wks	-191** (p=0.009)	-1320 (p=0.152)	-39.89 (p=0.497)	11.43 (p=0.334)

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

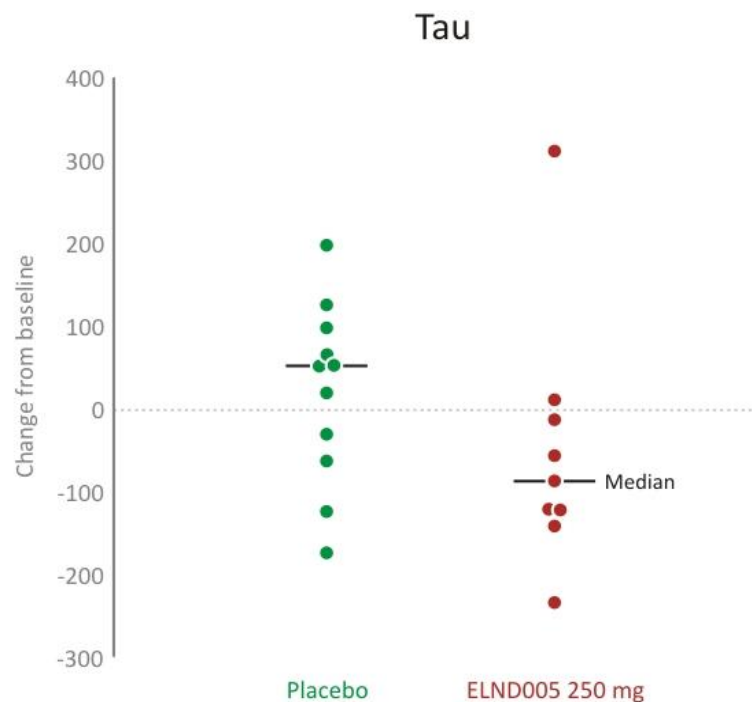
Similar results for completers (PPS) for **A β 42: Δ -173, p=0.036

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

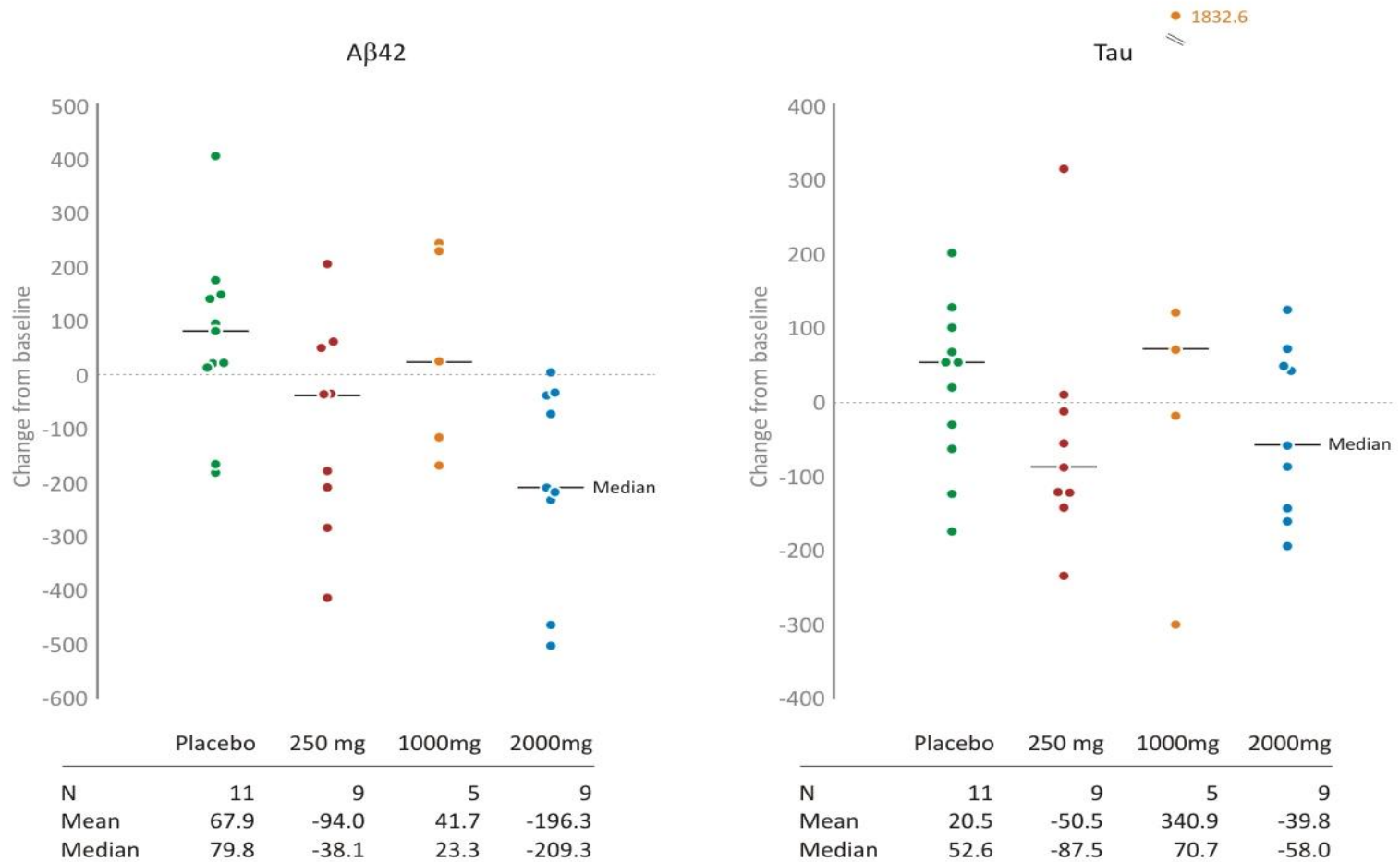


	Placebo	ELND005	Δ	p-value
N	11	9		
LS mean	13.6	-26.3	-39.9	0.497
Median	52.6	-87.5	-140.1	0.129

- 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**)

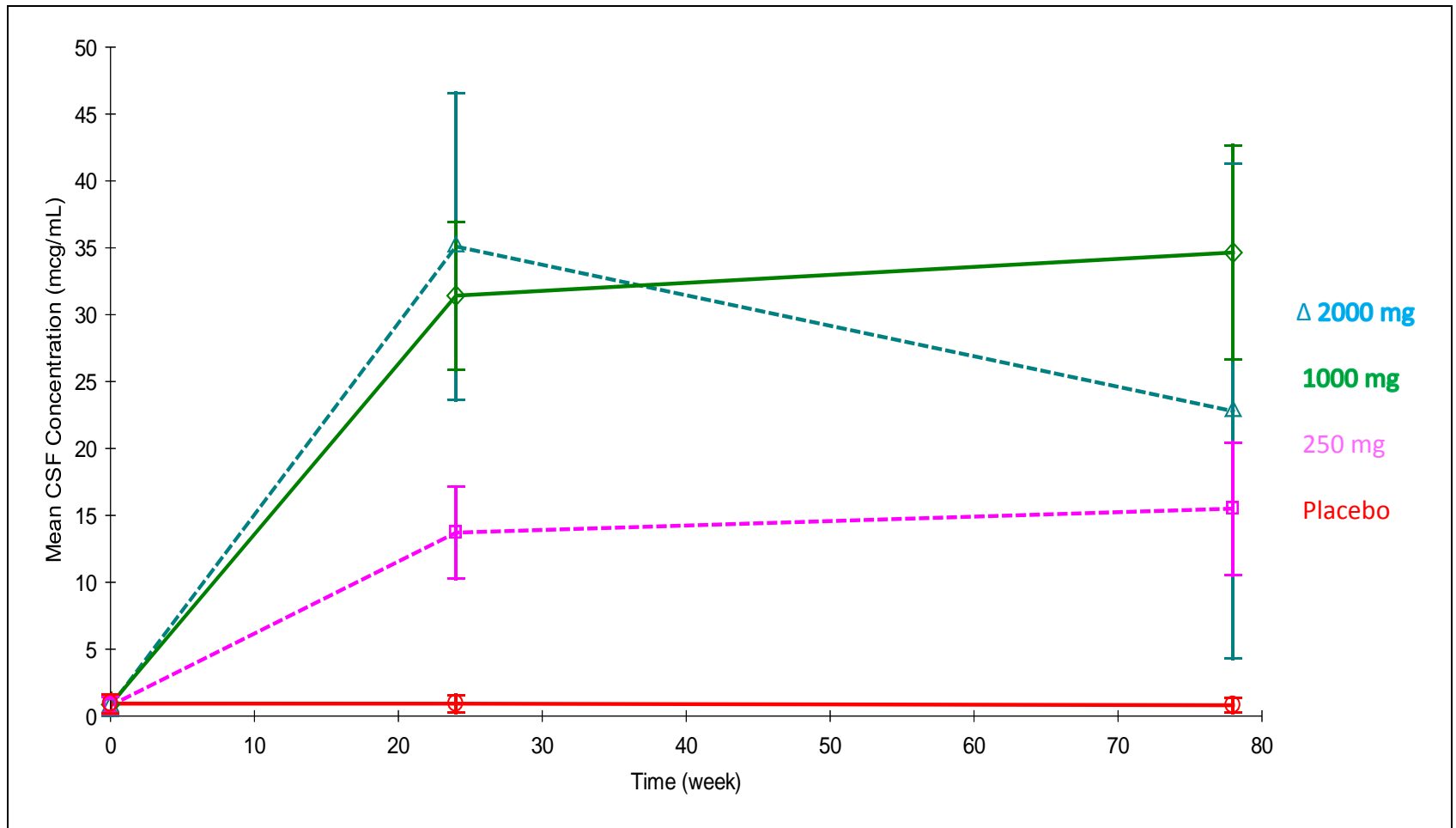
All Dose Groups: CSF Aβ42 and Tau Changes at wk 78

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



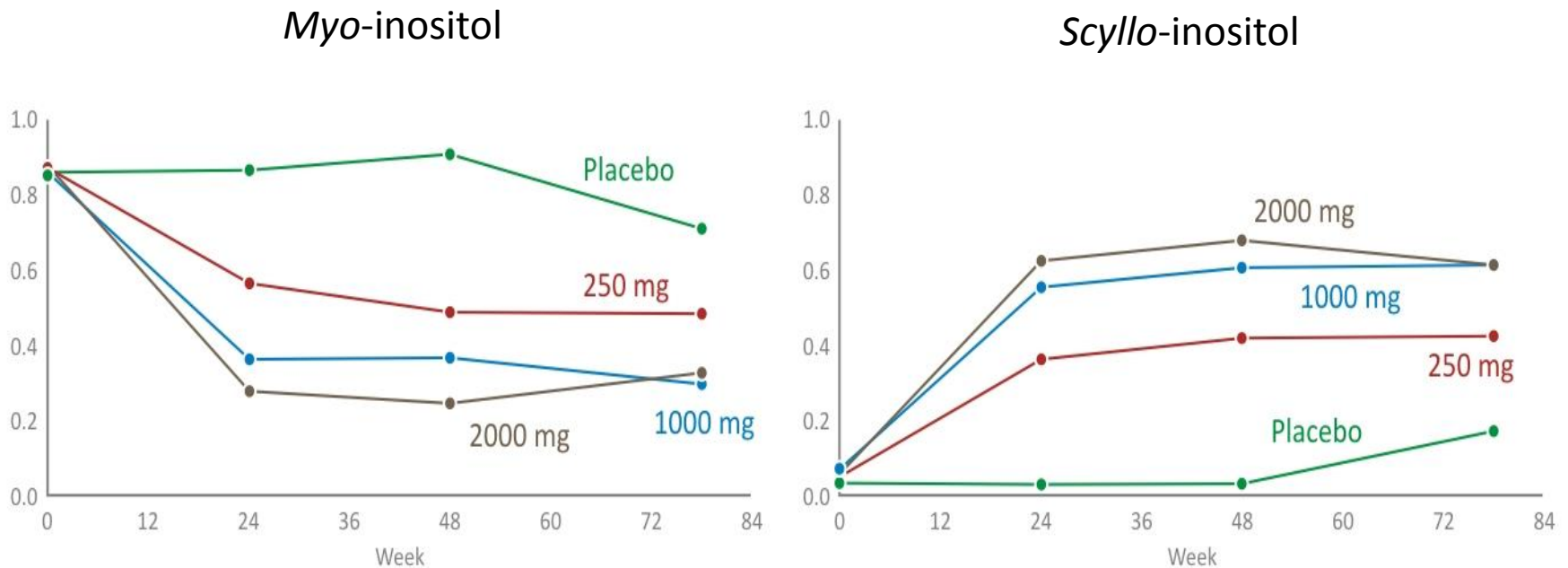
- Actual observed data, not MMRM analysis

ELND005 CSF Concentrations at 3 Dosages ($\mu\text{g}/\text{ml}$)



CSF ELND005 levels approach saturation at doses $\geq 1000\text{mg bid}$

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

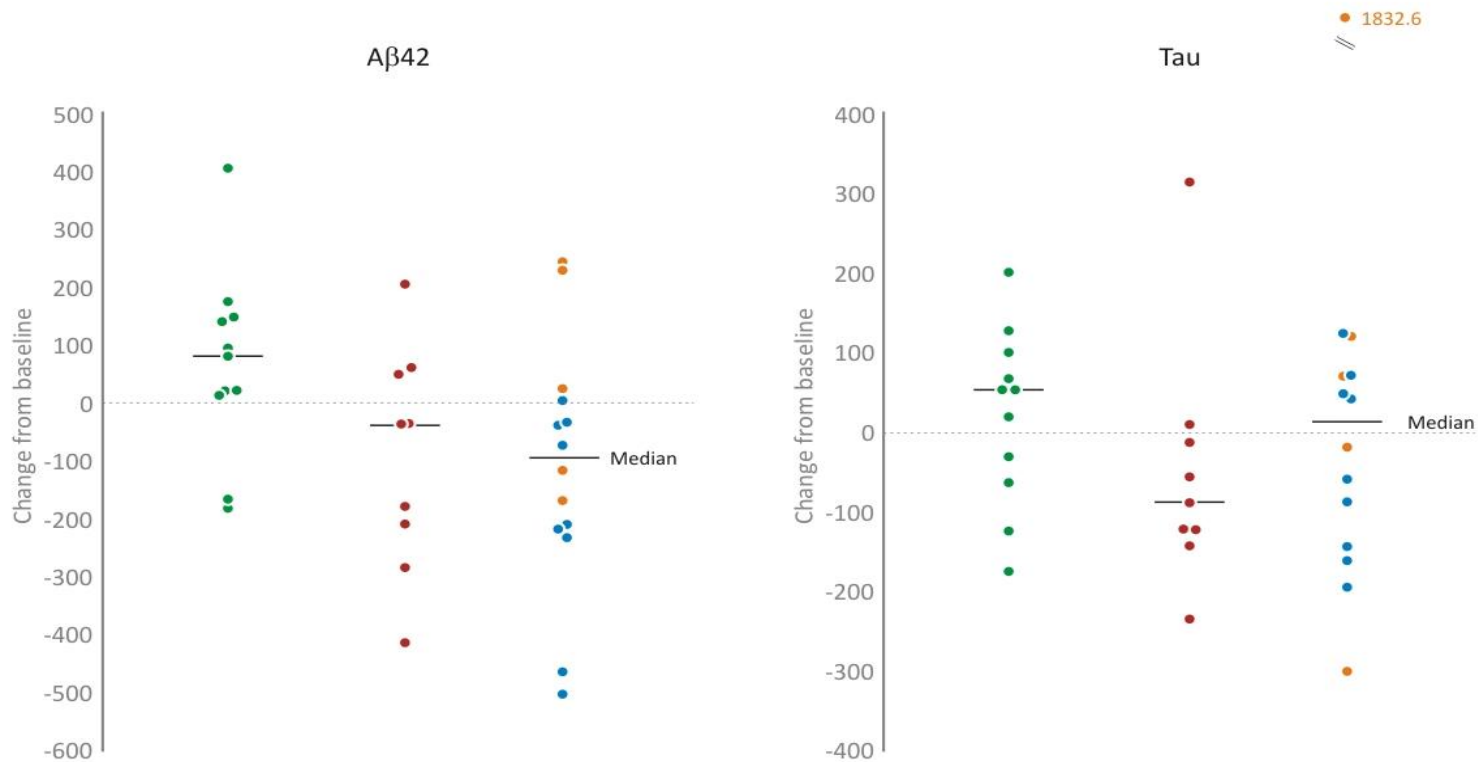


Brain levels (molar ratio to creatine) also approach saturation at doses ≥ 1000 mg bid

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

Pooled Highest Dose Groups: CSF A β 42 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 A β 42 (~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 A β 42 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