Population Pharmacokinetic Analysis of Plasma, Cerebrospinal Fluid, and Brain ELND005 in Patients with Mild to Moderate Alzheimer's Disease

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ABSTRACT

Objectives: ELND005 (scyllo-inositol) is being investigated as an orally administered agent to treat Alzheimer's Disease (AD). The objective of this analysis was to develop a population pharmacokinetic (PK) model to describe plasma, cerebrospinal fluid (CSF), and brain ELND005 concentration profiles following multiple oral doses.

Methods: ELND005 or placebo was administered twice daily for 78 weeks to 351 mild to moderate AD patients randomized to placebo (n=83), 250 mg (n=88), 1000 mg (n=89) or 2000 mg (n=91). Sparse plasma samples were collected from all patients (n=351) and cerebrospinal fluid (CSF) samples were collected via lumbar puncture from a subset of subjects (N=20-26/dose), both of which were analyzed for ELND005 via validated liquid chromatography-tandem mass spectrometry. Brain ELND005 levels from a subset of subjects (N=25-26/dose), estimated by Magnetic Resonance Spectroscopy, were considered for brain PK modeling. Population PK and statistical methods were conducted following the FDA Guidance for Industry Population Pharmacokinetics and the EMA Guideline on Reporting the Results of Population Pharmacokinetic Analyses. To help inform the PK model structure, plasma and CSF ELND005 PK data from two Phase 1 studies in healthy subjects were pooled with the Phase 2 AD patient data. The structure of the model for the human brain PK compartment was also informed by prior analyses of preclinical brain ELND005 PK data obtained from mice and rat studies.

Results: Plasma concentrations of ELND005 were adequately characterized by a 2-compartment population PK model with zero-order input and first order elimination from the central (plasma) compartment. Apparent ELND005 plasma clearance was inversely related to estimated creatinine clearance. CSF ELND005 levels were well described as a function of the concentration of ELND005 in a third compartment (CSF), in series with the plasma compartment. Brain ELND005 levels were well described by a fourth compartment (brain), in series with the plasma compartment and in which transfer from plasma to the brain compartment occurred via a saturable transport process.

Conclusions: The final population PK model can be properly constructed and characterized as moderate absorption, rapid distribution into peripheral compartments, slow redistribution into central compartment, slow apparent clearance, and long apparent terminal half-life. CSF and brain levels of ELND005 were dependent on plasma ELND005 concentration with relatively slow clearance from the brain compartment.

STUDY AD201 PATIENT DATA

- Exploratory data analysis in study AD201 (**Figure 1**) suggested:
  - Plasma concentrations reached apparent steady state in no later than 12 weeks,
  - Exposure in plasma was dose proportional (250-2000 mg),
  - Moderate accumulation in plasma (2-4 fold),
  - CSF/Brain concentrations approached apparent steady state at first time of 24 weeks,
  - Exposures in CSF/brain increased from 250 to 1000 mg BID, and reached apparent saturation above 1000mg BID, and
  - After early termination of 1000 and 2000 mg groups at Week 48, CSF levels started to decrease while brain levels remained constant.
- Study AD201 patient-level plasma PK profiles by dose group are shown in **Figure 2A**. Plasma PK samples obtained outside predefined AD201 visit time windows and/or following dosing termination ("Off Visit") were included in the PK analysis.
- **Figure 2B** shows corresponding patient-level CSF PK profiles by dose group for patients. "Off Visit" CSF PK samples were included in the PK analysis.
- **Figure 2C** shows corresponding patient-level brain PK profiles by dose group for patients undergoing MRS scans. "Off Visit" brain scan results were included in the PK analysis.

Figure 1: Concentration-Time Profiles of ELND005 in Plasma (left), CSF (middle), and Brain (right) in Study AD201

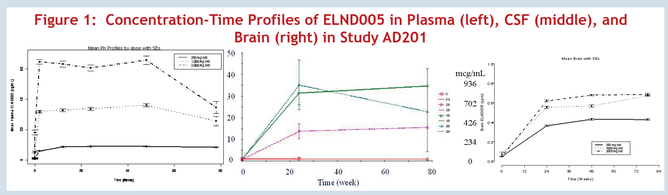
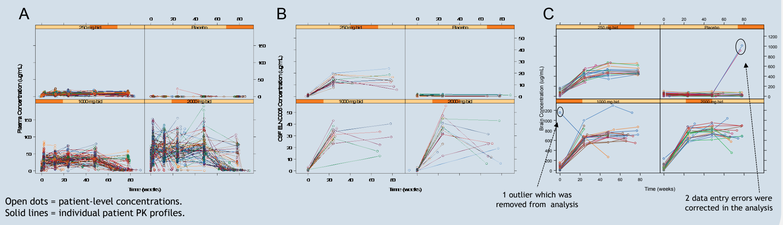


Figure 2: AD Patient Plasma, CSF and Brain PK Data



METHODS

- PK data from two Phase 1 oral, twice daily (BID) studies (HS105 and HS106) and one Phase 2 oral BID study (AD201) were used for this population PK analysis:
  - HS105 with 200, 700, 1500, and 3000 mg intensive plasma PK sampling for 7 days in healthy elderly subjects.
  - HS106 with 2000 mg intensive plasma and CSF PK sampling for 10 days in healthy young subjects.
  - AD201 with 250, 1000, and 2000 mg sparse plasma (all patients), CSF (92 patients), and brain PK (101 patients) sampling over 78 weeks in mild-moderate AD patients.
- PK analyses were implemented in NONMEM VI or 7.1.0 with Intel® Visual Fortran.
- A plasma population PK model was developed based on plasma data from studies AD201 and HS105. Various compartmental models (1, 2, and 3) and combinations of inter-individual and residual error models were evaluated.
- Once the final plasma PK model was established, CSF data from studies HS106 and AD201 were added with fixed plasma PK model parameters at the previously estimated values to develop the CSF PK model by addition of an empirical effect compartment to the central compartment of the plasma PK model.
- Upon establishment of the final plasma and CSF PK model, estimated brain concentration data from study AD201 were added with the plasma and CSF PK model parameters fixed at their previously estimated values to develop the Brain PK model via a saturable, active uptake and first order clearance mechanism.
- Plasma and CSF levels of ELND005 were measured by a validated LC-MS/MS method with a lower limit of quantitation at 0.4 µg/mL.
- Estimates of brain ELND005 concentrations were based on the ratio of the observed peak height at the scyllo-inositol location to the corresponding peak height of creatine via MRS, multiplied by 6.5 into mM, and further multiplied by 180 into µg/mL.
- For the assessment of covariate effects on plasma, CSF, and brain levels, a statistically significant change in the objective function was used to determine whether an effect existed.

OVERVIEW OF THE FINAL MODEL

- The final PK model was well established (**Figure 3**) and consistent with known ELND005 physiology.
- The model describes the observed plasma, CSF, and brain concentrations of ELND005 in Alzheimer's patients following multiple oral doses.
- Plasma ELND005 concentrations were described by a two-compartment model with zero-order input and first order elimination.
- CSF ELND005 concentrations were described by a function of ELND005 concentrations in an effect compartment in series with the central plasma compartment.
- Brain ELND005 concentrations were described by a brain compartment in series with the plasma compartment and independent of the CSF compartment:
- Transfer from plasma to brain compartment was assumed to occur via an irreversible, saturable transport process with relatively slow clearance directly from the brain compartment.

PLASMA PHARMACOKINETICS OF ELND005

- A visual predictive check of the plasma PK model is shown in **Figure 4** and final plasma estimated parameters are listed in **Table 1**.
- Apparent central plasma compartment volume (V2/F), oral absorption rate constant (KA), and apparent clearance (CL/F) were affected by a number of covariates.

$V2/F_{typical}$ = 13.5L• (WT/71.3kg)$^{1.68}$

$KA_{typical}$ = (0.0569•ln(DOS) + 0.116) •I_{HV} + (0.0099•DOS^2 - 0.0086•DOS + 0.0532)•I_{PATS}

$CL/F_{typical}$ = (2.2L/h + 2.52L/h•I_{HV}) × (ECCR/69.5)$^{0.606}$ + 0.387•I_{female}

where WT denotes weight in kilograms, DOS is the administered dose in grams, I_{HV} is an indicator for healthy subjects (coded 1 for healthy subjects and 0 for others), I_{PATS} is an indicator for AD patients (coded 1 for AD patients and 0 for others), ECCR denotes estimated creatinine clearance and I_{female} is an indicator for sex (female coded 1 and male 0).

- Based on these covariate effects, it is predicted that:
  - For every 10% increase in weight, V2/F is expected to increase by approximately 17%.
  - The effect of dose on absorption was relatively modest in AD patients, while it was more pronounced in healthy subjects.
  - Clearance is increased in healthy subjects over patients (e.g., 4.7 L/h vs. 2.2 L/h, respectively, for a male subject with median ECCR).
  - For every 10% drop in ECCR, CL/F was expected to decrease by approximately 6%.
- The basis of the observed differences in ELND005 plasma PK parameters between healthy volunteers and Alzheimer's patients remains unclear.

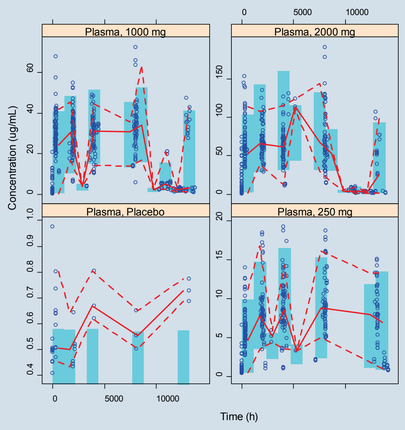


Figure 4:

Visual Predictive Check of Final PK Model: Plasma Data

Blue circles represent observations.

The red lines represent the 50th percentile (solid) and 5th and 95th percentiles (dashed) of the observed data.

The shaded area denotes the 5th to 95th percentiles (90% prediction interval) for simulated data from the final model (n=1000).

Table 1: Parameter Estimates for the Final Plasma ELND005 Population PK Model

Parameter	Estimate	%SE
CL/F (L/h, θ2)	2.2	2.8%
V2/F (L, θ3)	13.5	9.6%
K23 (1/h, θ4)	0.0737	14.7%
K32 (1/h, θ5)	0.00144	14.9%
ALAG1 (h, θ6)*	0	
Baseline (ug/mL, θ7)	0.4	fixed
HV.int effect on KA (θ8)	0.116	fixed
HV.slope effect on KA (θ9)	0.0569	fixed
PT intcpt effect on KA (θ1)	0.0532	fixed
PT.b effect on KA (θ10)	-0.0086	fixed
PT.b2 effect on KA (θ11)	0.0099	fixed
ECCR effect on CL (θ12)	0.606	11.2%
SEX effect on CL (θ13)	0.387	25.6%
WT effect on V2 (θ14)	1.68	19.6%
HV effect on CL (θ15)	2.52	12.4%
CL/F ω^2	0.0814	12%
V2/F ω^2	0.605	25.5%
K23 ω^2	1.13	18.5%
K32 ω^2	1.01	21%
KA (1/h)	0.854	18.3%
Residual error (proportional)	0.0711	10.3%

CONCLUSIONS

- The final population PK model of ELND005 in plasma, CSF, and brain has been properly constructed and indicates the following characteristics:
  - Moderate absorption,
  - Rapid distribution from vascular to deep tissue peripheral compartments with slow egress back (rate limiting step),
  - Rapid, active, saturable uptake into brain with slow clearance from the brain compartment,
  - Slow apparent total clearance, and short effective but long apparent terminal half-life.
- Apparent total clearance were affected by a number of covariates:
  - Disease state (slower in AD patients),
  - Gender (slower in males),
  - Renal function (slower with lower estimated creatinine clearance)
- The final PK model has been incorporated into exposure-response analysis of corresponding efficacy and safety outcomes in study AD201, and supported choice of clinical outcomes and dose justification for future Phase 3 studies.

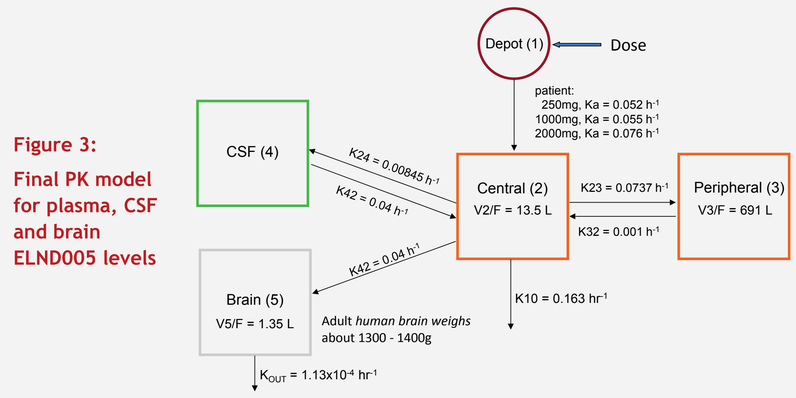


Figure 3:

Final PK model for plasma, CSF and brain ELND005 levels

CSF PHARMACOKINETICS OF ELND005

- Final estimated CSF parameters are listed in **Table 2**.
- Observed CSF ELND005 concentrations (CCSF) were found to be reasonably well described by a simple function of an "effect compartment" concentration (Ce) as follows:

  CCSF = K + C_e^{γ}

  where K denotes a baseline CSF concentration and γ is a simple exponent, estimated to be 2.4 and 0.942 in AD patients, and 0.7 and 0.722 in healthy subjects.
- The difference in CSF PK between healthy volunteers and AD patients appears to be predominantly driven by the higher baseline value in patients

Table 2: Parameter Estimates for the Final CSF ELND005 Population PK Model

Parameter	Estimate	%SE
CE0 (ug/mL, θ1)	2.40	23.9%
K24 (1/h, θ2)	0.00845	18.1%
K42 == Ke0 (1/h, θ3)	0.0406	19.6%
PATS effect on GAM (θ4)	0.942	4.52%
HV effect on GAM (θ5)	0.722	2.42%
HV effect on CE0 (θ6)	-1.7	32.2%
CE0 ω^2	0.833	30.5%
GAM ω^2	0.031	47.1%
CE0-GAM ω (covariance)	-0.0682	57.9%
Residual error (additive)	11.5	44.8%

BRAIN PHARMACOKINETICS OF ELND005

- A visual predictive check of the brain PK model is shown in **Figure 5** and final estimated brain parameters are listed in **Table 3**.
- The amount of ELND005 in the brain compartment was modeled under the assumption of time dependent saturable (transporter-mediated) kinetics as follows:

$$\frac{dA_{Brain}}{dt} = K_{IN} \cdot A_{Plasma} \cdot [Bt_{max} - A_{Brain}] - K_{OUT} \cdot A_{Brain}$$

  where K_{IN} denotes the transfer rate constant across the blood-brain barrier, K_{OUT} denotes the rate constant for clearance of brain ELND005, Bt_{max} denotes the maximum (saturable) amount of ELND005 that can be taken into the brain compartment and AB_{rain} denotes the amount of ELND005 in the brain compartment.
- There was a covariate effect of gender on Bt_{max} which was described where I_{male} is an indicator for sex (male coded 1 and female 0) as follows:

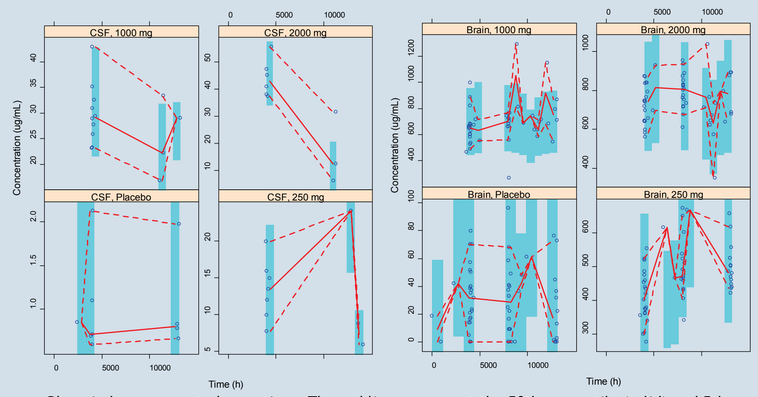
$$Bt_{max} = tvBt_{max} \cdot [1 + 0.159 \cdot I_{male}]$$

- Brain ELND005 PK data for healthy volunteers was not utilized in the present PK analysis and as a result it remains unclear whether there are apparent differences in the brain PK of healthy volunteers versus that of Alzheimer's patients.

Table 3: Parameter Estimates for the Final Brain ELND005 Population PK Model

Parameter	Estimate	%SE
K_{IN} (1/µg×h)	0.00000187	14.87%
$tvBt_{max}$ (µg)	917	5.09%
Sex effect on Bt_{max}	0.159	35.03%
K_{OUT} (1/h)	0.000113	17.70%
V5 (L)	1.35	Fixed
ω^2_{Btmax}	0.0325	26.65%
Residual error (Additive)	0.0146	29.32%
Residual error (Proportional)	863	30.24%

Figure 5: Visual Predictive Check of Final PK Model: CSF and Brain Data



Blue circles represent observations. The red lines represent the 50th percentile (solid) and 5th and 95th percentiles (dashed) of the observed data. The shaded area denotes the 5th to 95th percentiles (90% prediction interval) for simulated data from the final model (n=1000).

PATIENT DEMOGRAPHICS

- Healthy elderly subjects including 11 males and 13 females from study HS105 averaged 65 years of age, 71 kg of body weight. All subjects but 1 were Caucasian.
- Healthy young subjects including 8 males from study HS106 averaged 33 years of age, 77 kg of body weight. All subjects but 1 were Caucasian.
- Mild to moderate AD patients of Study AD201 including
  - 83-88 subjects (36-37 males and 47-51 females) who received either placebo or 250 mg for a median time of 71 weeks averaged 73 years of age, 72 kg of body weight, and were mostly Caucasian (>80%)
  - 89-91 subjects (40-41 males and 48-51 females) who received either 1000 or 2000 mg for a median time of 66 weeks averaged 72-73 years of age, 73 kg of body weight, and were mostly Caucasian (>80%).

The results in this abstract (with slight revision) have been previously presented in part at International Conference on Alzheimer's Disease (ICAD), July 2011, Paris, France and published in the conference proceedings as abstract P2-509.