synthetic Aß into oligomers or fibrils. The neuroprotective effects of the lead compound on excitatory synapses were investigated in 18 day in vitro (DIV) primary hippocampal neuronal cultures. The pharmacokinetic profile, including bioavailability and BBB penetration, were established in mice following oral and intravenous administration using a combined liquid chromatography-mass spectrometry (LC-MS) approach. **Results:** Our screen has identified the lead compound dubbed ARN 4261, [(E)-2-(pyridin-2-ylmethyleneamino) phenol; MW=198.2Da], which is not toxic and at low micromolar concentration shows strong effects against both oligomerization and fibrillization of synthetic Aß peptide. Treatment of primary hippocampal neurons exposed to Aß with ARN4261 restored loss of synaptic proteins expression caused by Aß oligomers. We have subsequently modified the structure of ARN 4261 producing ARN 2966 (2-[(pyridine-2-ylmethyl)-amino]-phenol) which shows comparable anti-aggregation potency to ARN 4261, but it is more stable in acidic environment, hence it is suitable for oral administration. Pharmacokinetic experiments in mice showed that $t_{1/2}$ of ARN 2966 is 6.13hr and 64.2% of orally administered dose is absorbed from the alimentary tract and passes the portal circulation. Preliminary studies show that ARN 2966 penetrates the BBB after oral and intravenous administration. **Conclusions:** Pyridin-2-ylmethylamine derivatives are a class of novel promising AD therapeutics. They are non toxic, have strong anti-Aß aggregation and neuroprotective properties and can be easily modified chemically for enhanced oral bioavailability and BBB penetration. Experiments in AD transgenic mice characterizing their effect on AD pathology in vivo are currently ongoing.

P2-499 SAFETY AND EFFICACY RESULTS OF A PHASE II RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RANGING STUDY OF ELND005 (SCYLLO-INOSITOL) IN MILD-TO-MODERATE ALZHEIMER'S DISEASE

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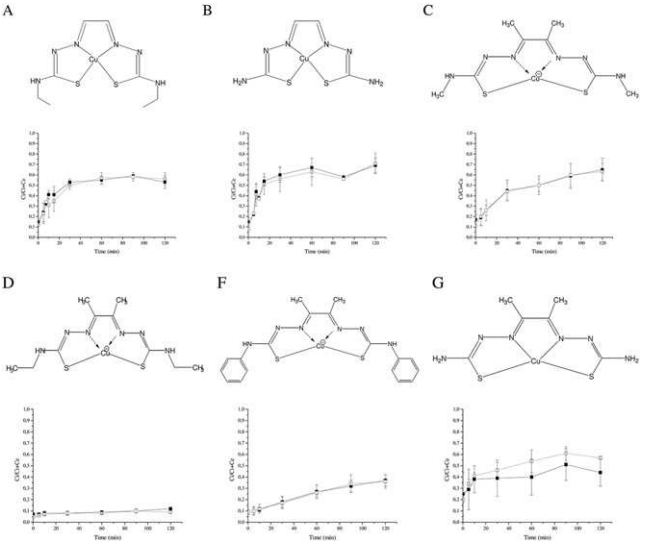
Background: ELND005(scyllo-inositol), an orally-administered small molecule, has been shown to inhibit aggregation and the toxic effects of beta-amyloid (Abeta) in animal models of AD. This study explored safety, efficacy, and biomarker effects of ELND005 in mild/moderate AD. **Methods:** Of 353 patients randomized to ELND005 (250, 1000, or 2000 mg) or placebo twice daily for 78 weeks, 351 received study drug. Co-primary endpoints were the Neuropsychological Test Battery (NTB) and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale. The study was powered based on the average effect in the 3 active dose groups. After an imbalance of infections and deaths led to early discontinuation of the 2 high-dose groups, the primary analysis was based on the comparison of 250 mg to placebo at 78 weeks, using a mixed-effects model repeated measures analysis. **Results:** There were no significant between group differences on the NTB or ADCS-ADL (n = 84/82 for 250mg/placebo). In protocol-specified subgroup analyses, mild patients on 250mg had higher NTB scores at Week 78 compared to placebo (mITT, $p = 0.110$), which were significant in the Per Protocol Set (PPS, $p = 0.007$). In mild patients, treatment differences on the ADCS-ADL, although numerically favorable, were not significant in mITT or PPS. The moderate group showed no significant differences on either primary endpoint. The adverse event (AE) incidence in mild/moderate patients was similar across the groups: placebo 91.6% versus 87.5, 90.1, and 88.4% of patients in the 250, 1000, and 2000 mg groups, respectively. The serious AE incidence was higher in the 3 ELND005 groups compared to placebo, and included 10 deaths (0 in placebo, 1 in 250mg, 5 in 1000mg, and 4 in the 2000mg); leading to discontinuation of the 2 high doses. The most common AEs in 250mg group with incidence of >5% (and double the placebo) were falls, depression, and confusional state. The safety and tolerability profile of ELND005 was similar in APOE ϵ4 carriers compared with non-carriers. **Conclusions:** Primary efficacy outcomes were not significant in the mild/moderate AD population. Positive clinical trends on the NTB in mild patients, and the acceptable safety and tolerability of ELND005 at 250mg twice daily, support further investigation of ELND005 as a potential disease modifying treatment in mild AD.



P2-500 METAL COMPLEXES FOR TREATMENT OF ALZHEIMER'S DISEASE. MECHANISM OF THEIR TRANSPORT THROUGH BLOOD BRAIN BARRIER

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Background: Dysregulation of brain metal ions homeostasis, particularly Cu and Zn, may be closely involved in the pathogenesis of Alzheimer's disease (AD) and its characteristic beta-amyloid neuropathology. Copper complexes of bis(thiosemicarbazones) have been proposed to be used for the treatment of AD as they can modulate the production of beta-amyloid peptide at neuron level. These drugs should cross the blood brain barrier (BBB). The main goal of this study is the transport of these complexes through BBB and particularly the role of P-glycoprotein (P-gp), a plasma membrane transporter commonly found in the BBB. **Methods:** Short-term accumulation and transport of the CuII(btsc) complexes (BH22, HB23, HB26, HB28, HB30 and HB32) (Fig. 1) was studied in Hepes/Na+ buffer with glucose at 37° C. For copper accumulation assays, the cells were treated with 30μM of the copper complexes. After specified time intervals, aliquots containing 106 cells were taken and washed two times. The pellets obtained after centrifugation were digested with nitric acid (65%), and the copper concentration was measured using atomic absorption spectrometer (Ci, intracellular concentration). The extracellular concentration of copper (Ce), was measured in the supernatant after the first centrifugation. For energy depletion, cells were incubated for 30 minutes in Hepes/Na+ buffer in the presence of 2-deoxyglucose and 10mM sodium azide prior to addition of copper complexes. To check the ability of the complexes to accumulate inside mitochondria of K562 cells, strictly analogous experiments were performed in the presence of 1 μM FCCP. **Results:** Fig. 1 shows the plots of Ci/Ci+Ce ratio as a function of time. The incorporation of HB23,