Tau-C. The IP products were analyzed by Western blot as well as with SDS-PAGE by using silver staining. The bands from the SDS-PAGE analysis were excised, in-gel digested with trypsin and identified by LC-MS/MS. The measured Tau-C levels by our in-house ELISA assay were 35.87 ng/mL for the AD patients and 14.7 ng/mL for the healthy controls. **Results:** The Western blot analysis detected bands at 52-64 kDa for IP products from AD patients when using our in-house antibody. No bands were detected for the IP products from the healthy controls. The SDS-PAGE analysis showed bands in the range 31-64 kDa for the IP products from AD patients. For the healthy controls bands were only detected at 64 kDa but the intensity of these was much lower when compared to the AD patients. The LC-MS/MS results of the IP products from AD patients identified the 64 kDa band from the SDS-PAGE gel as Tau-C. No significant LC-MS/MS results were obtained for the IP products from the healthy controls. **Conclusions:** Immunoprecipitation in combination with LC-MS/MS showed the presence of Tau-C in the serum of Alzheimer's patients. This shows a potential for the developed ELISA assay to be used for the diagnosis and/or prognosis of Alzheimer's disease but further analyses are needed.

WEDNESDAY, JULY 16, 2014
ORAL SESSIONS
O4-11
CLINICAL TRIALS II: ANTI-AMYLOID AND INFLAMMATION

O4-11-01 RELATIONSHIP BETWEEN CEREBROSPINAL FLUID (CSF) BIOMARKERS AND COGNITIVE PERFORMANCE OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT (MCI) AFTER LONG-TERM TREATMENT WITH CHF5074

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Background: CHF5074 is a newly identified microglial modulator previously shown to lower CSF levels of sCD40L and TNF-alpha in a 14-week, double-blind, placebo-controlled study in 96 MCI subjects. We measured CSF biomarkers, verbal memory and executive function in a subgroup of these individuals after prolonged treatment with CHF5074. **Methods:** Subjects were given the option to enter a 26-week followed by another 50-week open label extension study. Individuals received CHF5074 at the dose equal to that of their originally assigned in the double-blind study (200, 400 or 600 mg/day). Cognition was measured at Screening (Week -2), Baseline (Day -1), and at 12, 14, 26, 38, 52, 64, 76, 88 and 90 weeks. CSF biomarkers (Aβ42, tau, phospho-tau, sCD40L, TNF-alpha) were measured at Weeks 12 and 38. **Results:** Cognitive tests evaluated at Week 90 (n=42) showed statistically significant improvements compared to Baseline on Digit Symbol Substitution (+6.4±1.3 matches, $p<0.001$), Trail Making A (median -9 sec, $p<0.01$) and B (median -12 sec, $p<0.01$), Immediate Word Recall (+4.1±0.7 words, $p<0.01$) and Delayed Word Recall (+1.5±0.3 words, $p<0.01$). CSF tau levels measured at Week 38 (n=37) showed significant ($p=0.021$) dose-dependent linear trends (68.0±7.4, 57.4±5.7 and 42.7±8.0 pg/mL in the 200 mg/day, 400 mg/day and 600 mg/day groups, respectively). The mean tau values in the 600 mg/day group was significantly lower than those measured in the 200 mg/day group (-37%). Similar dose-related trends were found for phospho-tau. The other CSF biomarkers at Week 38 did not show significant difference between treatment groups. At Week 12, CSF tau levels correlated linearly with Trail Making B ($r=0.599, p<0.001$), Immediate Word Recall ($r=0.436, p=0.002$) and Delayed Word Recall ($r=0.306, p=0.035$) and predicted corresponding changes in cognitive scores at Week 90 ($r=0.523, p=0.005$, $r=0.545, p=0.003$ and $r=0.430, p=0.025$, respectively). Cognitive scores of Trail Making Test B and Delayed Word Recall at Week 90 were also predicted by tau levels measured at Week 38 ($r=0.489, p=0.009$ and $r=0.461, p=0.016$, respectively). **Conclusions:** Long-term treatment with CHF5074 (200-600 mg/day) was dose-dependently associated with a reduction in CSF tau levels in MCI subjects. CSF tau levels correlated with sustained cognitive benefit in executive function and verbal memory for up to 90 weeks.

O4-11-02 THE SAFETY AND TOLERABILITY OF ETANERCEPT IN ALZHEIMER'S DISEASE (STEADI-09): A PHASE II DOUBLE BLIND RANDOMISED PLACEBO CONTROLLED TRIAL

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Background: We have previously shown that acute and chronic systemic inflammation, associated with modest increases in peripheral levels of Tumour Necrosis Factor α (TNFα), is associated with an increased decline in cognition and an exaggeration of neuropsychiatric symptoms in subjects with Alzheimer's Disease. We hypothesised that the use of a TNF α receptor blocker (Etanercept) might, if safe and well tolerated, be worth examining for beneficial cognitive and behavioural outcomes in an AD population. **Methods:** Patients with mild to moderate AD were randomised to subcutaneous Etanercept (50mg) once weekly or to identical placebo (water) over a 6 month period with a one month wash out. Safety and tolerability of this medication was recorded with secondary exploratory outcomes of cognition (ADAS-COG; MMSE), behaviour (NPI); activities of daily living (BADLS) and clinical and carers global impressions of change measured at baseline; 3 months and 6 months. **Results:** 67 patients were screened of whom 26 failed to meet the inclusion or exclusion criteria (most exclusions were due to prior TB exposure). 41 subjects were randomised (20 Etanercept and 21 Placebo). Etanercept was well tolerated by this group with few adverse events or safety concerns. Two subjects from the Etanercept arm and six from the placebo arm failed to complete the study. Subjects in the placebo arm showed evidence of a greater rate of decline in measures of cognition, behaviour and activities of daily living compared with subjects in the Etanercept arm at 6 months who remained largely unchanged compared with baseline measures. **Conclusions:** This study shows good tolerability and safety of Etanercept in the subjects with Alzheimer's Disease. This study is also supportive of beneficial cognitive, behaviour and activities of daily living in subjects taking subcutaneous Etanercept.

O4-11-03 A PROINFLAMMATORY ENDOPHENOTYPE PREDICTS TREATMENT RESPONSE IN A MULTICENTER TRIAL OF NSAIDS IN AD

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Background: Epidemiological studies suggest that reducing inflammation through use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with decreased risk of Alzheimer 's disease (AD). However, a recent multicenter clinical trial in mild-moderate AD conducted by the Alzheimer's Disease Cooperative Study (ADCS) failed to demonstrate