Background: The role of tau phosphorylation in the evolution of Alzheimer's Disease (AD) is gaining prominence offering new therapeutic targets. Casein kinase 1 delta (CK1d) is required to generate hyperphosphorylated tau through direct phosphorylation of specific pathogenic sites, by priming tau for subsequent hyperphosphorylation by GSK3 b and through the direct activation of CDK5, another tau kinase. CK1d also plays important roles in other features of AD such as cell cycle control, neuritic sprouting and sleep dysfunction, further suggesting it as an important therapeutic target. The closely related casein kinase 1 epsilon (CK1e) which has a virtually identical ATP binding site has also been shown to regulate gamma-secretase activity and thus the production of toxic amyloid. **Methods:** We have developed two selective CK1d/e inhibitors, PS110 & PS278-05, using several rounds of in silico design and in vitro testing. TMHT mice aged 8.5 months were treated once daily with vehicle or vehicle plus active compound at 30 mg/mg. Cogntive performance was tested using the Morris Water Maze on days 50-54 and animals sacrificed at day 56. Levels of tau phosphorylation at several pathogenic sites were determined using Western blot (pT231 & pS396) and mass spectrometry methods (pS46, pT50, pS113, pT181, pS199, pT231, pS262, pS396, pS404 & pS433) and levels compared between animals treated with vehicle or active compounds. **Results:** Treatment with PS110 and PS278 led to improved cognitive performance in Morris Water Maze with no overt toxicity issues. A significant loss of phosphate at several human tau sites known to be phosphorylated by GSK3 b after upstream CK1d priming, or directly by CDK5 was detected by both immunological and mass spectrometry methods in PS110 treated animals. Interestingly we also see a general loss of soluble heat stable tau in treated animals suggesting CK1d/e inhibition stops the production and accumulation of hyperphosphorylated tau in this model. **Conclusions:** The continued failure of therapies targeting single aspects of AD pathology suggests a multi-pathway approach is required. Preliminary data with selective CK1d/e inhibitors suggests we are intervening through multiple modes of action. Implications of these data for the development of PS110 and PS278-05 towards human trials will be discussed.

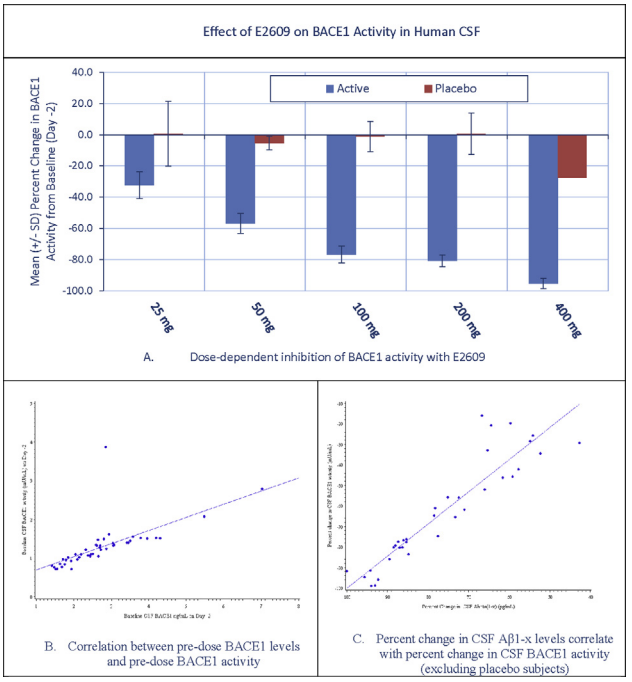

Figure 1. Effects of E2609 on BACE1 Activity in Human CSF

P4-411 **CLINICAL STUDY OF E2609, A NOVEL BACE1 INHIBITOR, DEMONSTRATES TARGET ENGAGEMENT AND INHIBITION OF BACE1 ACTIVITY IN CSF**

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Background: A multiple ascending dose Phase I clinical study of the beta-secretase inhibitor, E2609, was conducted in healthy individuals. E2609 or placebo (8:2) was administered orally once daily to 50 subjects (5 dosing cohorts: 25 mg to 400 mg) for 14 days. CSF was collected prior to dose initiation (day -2) and 12 hours after the final dose on day 14. Total BACE1 enzyme levels were measured in the CSF samples to determine if E2609 has a pharmacodynamic effect in the CNS. Target engagement of BACE1 by E2609 was assessed by measuring BACE1 activity after 14 days. **Methods:** CSF samples collected from the study were thawed and tested in batch format. Absolute amounts of BACE1 enzyme in CSF were quantified using a commercially available ELISA modified to improve sensitivity. To measure BACE1 activity, we developed and applied a specific and sensitive, fluorescence-resonance energy transfer based assay. Levels of various Aβ species in CSF were evaluated by IP/MS and ELISA. **Results:** BACE1 protein levels were detected in all CSF samples tested. Levels of BACE1 activity in CSF were reduced by 20 to 99% following 14 days of daily dosing with E2609 and correlated with increased doses (Figure 1A). Pre-dose levels of BACE1 enzyme concentration and pre-dose levels of BACE1 activity were moderately correlated ($r = 0.67$, $p < 0.0001$, $n = 46$), suggesting that BACE1 protein present in CSF is active (Figure 1B). In addition, as shown in Figure 1C, the percent change of BACE1 activity levels was very highly correlated with the percent change in levels of Aβ1-x ($r = 0.92$, $p < 0.0001$, $n = 35$) as well as other Aβ species. BACE1 protein levels were relatively unchanged from baseline in subjects receiving daily dosing of E2609, regardless of dose or extent of BACE1 inhibition. **Conclusions:** E2609 dose-dependently inhibited BACE1 activity in CSF after 14 days of daily dosing. BACE1 activity reductions were highly correlated with reduced levels of all Aβ species present in CSF. Taken together, these data suggest that E2609 crosses the blood-brain barrier and directly engages its target in the brain, confirming the amyloid-based mechanism of action of this novel BACE inhibitor.

P4-412 **EFFECT OF MEMANTINE ON THE PROGRESSION OF DRIVING IMPAIRMENT IN MILD ALZHEIMER'S DISEASE**

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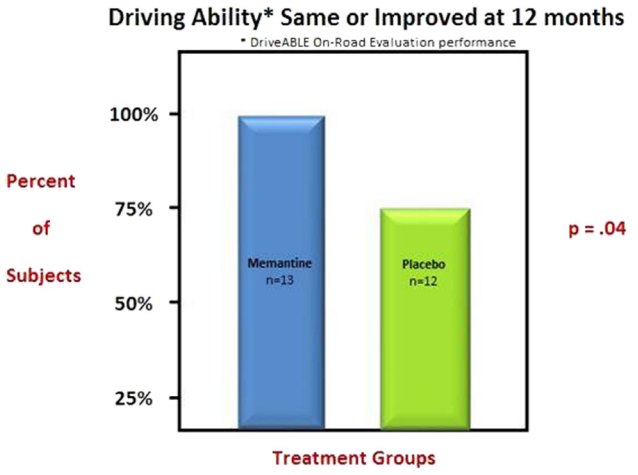
Background: It is hypothesized that treatment with memantine may delay the progression of driving impairment in patients with mild Alzheimer's disease. Driving is a hallmark of adulthood and independence. Slowing the progression of driving impairment in this population may extend the quality of life of those with Alzheimer's disease and ease the burden on their caregivers. **Methods:** Sixty otherwise healthy men and women $\geq$ 60 years with mild (MMSE $\geq$ 23) Alzheimer's disease were screened. 43 subjects met eligibility criteria and were randomized at a 1:1 ratio in a double-blind, 12 month trial of memantine 20 mg/day verses placebo. Stable doses of acetylcholinesterase inhibitors were permitted. Driving ability was measured by a standardized on-road driving test (DriveABLE). Cognitive performance was measured on a battery of driving-related neuropsychological assessments including measures of executive functioning, visuospatial ability, attention and orientation. The primary outcome measure was the number of subjects in each group able to pass the DriveABLE test at month 12 (endpoint). The secondary outcome measures were the change from baseline



Treatment Group Comparison of Characteristics at Baseline

ANOVAS	Treatment (1)	Placebo (2)	*p*
	SD	*SD*	
Age	78.13 (6.38)	80.47 (5.92)	.22
MMSE	28.12 (1.99)	27.66 (1.63)	.49
FULD	17.93 (5.84)	18.86 (4.99)	.63
REY FIGURE (copying)	27.53 (6.05)	29.30 (4.08)	.38
CDR	2.40 (1.11)	2.3 (1.30)	.80
Trails A (seconds)	39.62 (12.37)	50.33 (17.27)	.05*
Trails A (errors)	.06 (.25)	.20 (.56)	.37
Trails B (seconds)	117.75 (43.00)	195.33 (138.57)	.02*
Trials B (errors)	.87 (1.36)	1.73 (2.08)	.18

Chi Squares

			χ^2	*p*
% Male	52%	71%		.20
Ethnicity (% EA)	95%	90%		.48
White Race	95%	100%		.32
No Crashes%	77%	90%		.41
No Tickets %	100%	90%		.13
Limit % Yes	38%	61%	1.20	.27

to endpoint on the cognitive assessments. **Results:** Comparison of the treatment and placebo control groups at baseline indicates few significant differences in participant characteristics. There were no significant differences in age, gender, ethnicity or race. The groups did not differ statistically on mean MMSE, Fuld, Rey Figure or Trails A and B error rates. They did differ on Trails A and B time to complete. Placebo group participants required significantly more time to complete both Trails A and Trails B at baseline ($p = .05$ and .02 respectively). A greater percentage of treatment group participants reported having been involved in a prior crash (23% vs. 10%). This difference did not achieve statistical significance. Preliminary analysis suggests efficacy of memantine delaying progression of driving impairment. At 12 months, 100% of the treatment group either stayed the same or improved their driving ability, while only 75% of the placebo group did the same or better ($p = .04$). **Conclusions:** Addition of memantine to the drug regimen appears to have efficacy in delaying driving impairment in subjects with mild Alzheimer's disease.

P4-413 MULTIPLE DAILY COGNITIVE MEASUREMENTS IMPROVE ACCURACY AND INCREASE STATISTICAL POWER, ALLOWING SMALLER SAMPLE SIZES FOR POP TRIALS IN ALZHEIMER'S DISEASE

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Background: Current methods for proof of principal (PoP) trials of symptomatic treatments for Alzheimer's disease may be larger and costlier than necessary with sample sizes commonly ranging between 75 and 125 per arm. Previously we reported on the results of an RCT comparing donepezil to placebo in 124 Mild to Moderate AD patients that was conducted to examine whether sensitivity to drug could be enhanced by multiple daily cognitive measurements at baseline (10x in2wks) and three monthly follow ups (5x in1wk) using CogState computerized tests (Jaeger et al, 2011). Results showed a trend favoring donepezil on NTB Memory subscale but not ADAS-Cog or total NTB, and significant effects on CogState One Card Learning (OCL). There was significant heterogeneity with respect to the degree of day to day variance on this test (Zettergren, 2011), suggesting that repeated measurement, capturing daily clinical fluctuation, was responsible for the relatively greater sensitivity of OCL compared with NTB and ADAS-Cog. **Methods:** New analyses were conducted to determine the impact of number repeated measurements on power and sample size requirements. **Results:** Correlation matrices of OCL for each baseline and follow up time reveal correlations ranging from $\sim$ 0.45-0.65 in the donepezil and control groups, contrasting with correlations of .87 and .78 in healthy and schizophrenia samples respectively (Pietrzak, 2009). Correlations were constant over time (i.e. do not increase with repeated measurement) suggesting that the variance is due to random day to day fluctuation and not differing rates of learning effects. It is possible to calculate the impact of each repeated measurement on the variance estimate, and hence power and required sample size as a function of these correlations. We report on model results offering guideline for future studies. For example with 5 daily measures at baseline and follow up, the decrease in variance associated with each repeated measure asymptotes and < 30 subjects per arm would be required to detect a donepezil effect with $>80\%$ power. **Conclusions:** Dramatic efficiencies in sample size can be achieved if the statistical "noise" emanating from increased day to day variance in AD patients is reduced by repeated daily cognitive measurement.

P4-414 CAREGIVERS CAN RECOGNIZE THERAPEUTIC EFFECTS FROM IMPROVEMENTS IN DEMENTIA PATIENTS' VOLITION AND ACTIVITY

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Background: It is said that only a few caregivers recognize pharmacotherapeutic effects on dementia. Our outpatient caregivers, however, tell us that they can often see therapeutic effects based on improvements in their patients' volition and activity. Objectives: To investigate factors allowing caregivers to recognize pharmacotherapeutic effects, and to assess improvements which allow caregivers to see therapeutic effects after administration of a cholinesterase inhibitor (ChE-I). **Methods:** The subjects were 55 Alzheimer-type dementia (AD) patients aged 54-91 years with a disease duration of 1-10 years and a educational period of 6-18 years. **Methods:** Before and after administration of ChE-I, MMSE and CIBIC-J-Plus (Mental Function Impairment Scale (MENFIS) and Disability Assessment for Dementia(DAD) scores were evaluated through statistical processing employing the Student t -test in order to examine factors allowing caregivers to recognize drug effects. **Results:** After the administration of ChE-I, neither