rodent chew. Plasma and brains were collected from animals of different ages. Brains were sequentially extracted with dietylamine and formic acid to obtain the soluble and insoluble brain fractions, respectively. The levels of different Ab species and other APP processing fragments were analyzed using commercially available ELISA (Invitrogen & Innogenetics) or MSD technologies. Extensive statistical analysis was performed on all data. **Results:** We found that the levels of both endogenous mouse and transgenic human Ab rapidly increased with age, in both the soluble and insoluble brain pools, preceding the plaque deposition detected by histological analysis. However, the levels of Ab in plasma were stable over all ages studied. The obtained information on Ab levels and variability is used to perform estimations of necessary sample size for upcoming efficacy studies. **Conclusions:** This extensive biochemical characterization of the Tg2576 mouse model is used to design acute and long-term efficacy studies for pharmacological modulation of amyloid processing and clearance.

P3-012 ASSOCIATION BETWEEN NEUROPATHOLOGY AND SPATIAL LEARNING IN TRANSGENIC HAPPSL × HTAU CROSSBRED MICE

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Background: The neuropathology of Alzheimer's disease (AD) is characterized by extracellular senile plaques, which are the deposits of b-amyloid peptide and intraneuronal neurofibrillary tangles (NFTs), which are composed of aggregates of hyperphosphorylated forms of tau. A new double transgenic mouse line was established that recapitulates both main neuropathological hallmarks of AD. A cross breeding of transgenic mouse lines expressing htau and hAPP with Swedish and London mutation under the control of the murine Thy1 promoter was performed. Our aim was to investigate the association of age dependent neuropathological features with corresponding spatial learning and memory, which was tested in the Morris Water Maze (MWM). **Methods:** At 5-6 months of age, behavior of male and female $hAPP_{SL}$x htau double transgenic mice and non-transgenic littermates were evaluated in MWM. Histological analysis of brain samples was performed to determine NFTs and b-amyloid plaques. **Results:** Both double transgenic and non-transgenic littermates were able to learn the spatial navigation task as reflected by the reduction in time and length required to locate the hidden platform. However, the escape latency of double transgenic mice was higher and the swim path longer when compared to litter mates. A significant effect of the genotype was observed between the two groups especially on day 3, as double transgenic mice revealed a significantly worse performance. In the probe trial double transgenic mice showed reduced ability to remember the previous position of the platform as compared to the non-transgenic littermates. The brain histological analysis of 6 months old double transgenic $hAPP_{SL}$ xhtau crossbred mice showed both b-amyloid deposition as well as human tau positive lesioned neurons. This neuropathological feature of double transgenic $hAPP_{SL}$ × htau mice might be responsible for their impaired spatial behavior detected in the MWM. **Conclusions:** These subsets of neuropathological disturbances as well as the behavioral deficits make $hAPP_{SL}$ × htau crossbreds suitable to investigate drug candidates against AD.

P3-013 6-MONTH CHRONIC STUDY WITH PONEZUMAB (PF-04360365) CHINESE HAMSTER OVARY (CHO)-DERIVED MURINE SURROGATE IN 18-MONTH-OLD TG2576 MICE

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Background: Cerebral vasogenic edema and microhemorrhages have been raised as potential safety concerns for compounds intended to treat Alzheimer's disease by targeting amyloid ß. Here, we describe the safety of an anti-amyloid ß monoclonal antibody chronically administered to amyloid ß-bearing mice. **Methods:** 18-month-old female Tg2576 (APP K670N; M671L) mice were selected for this study because at 12 and 24 months of age they have abundant cerebral parenchymal and vascular amyloid ß and are thus a relevant animal model. Mice (N=200) were injected intraperitoneally with a murine surrogate of the humanized anti-amyloid ß monoclonal antibody ponezumab (PF-04360365) once weekly for up to 26 weeks at doses of 10, 30, or 100 mg/kg. Mortality, clinical signs, body weight, food consumption, and anatomic pathology were evaluated. Brains were examined microscopically for microhemorrhages, and other tissues were evaluated from all animals dying prior to scheduled study termination to ascertain if such deaths were compound-related. All work was approved by an Institutional Animal Care and Use Committee and, for the most part, was conducted under Good Laboratory Practice conditions. **Results:** There were no compound-related changes in clinical signs, body weight, or food consumption. The numbers of surviving animals were generally similar in all groups. No compound-related anatomic macroscopic or microscopic findings were present. The incidence of Perl's iron-positive brain microhemorrhages was low and similar across all groups, and there was no increase in severity in mice given the test antibody, even at the highest dose. As expected, drug exposure and plasma amyloid ß levels increased with increasing dose of test article, and higher plasma drug levels were correlated with higher plasma amyloid ß levels. Most spontaneous deaths were attributed to age-related neoplasms typical of mice this age. Similar to other deglycosylated murine antibodies, this antibody demonstrated reduced binding against a panel of recombinant murine Fc gamma receptors, indicating a low potential to increase immune effector function. **Conclusions:** Within the limits of this study, administration of this CHO-derived surrogate of ponezumab to 18-month-old amyloid ß-bearing Tg2576 mice for up to 26 weeks did not result in an increase in microhemorrhages or other pathologies.

P3-014 DEVELOPMENT OF PRECLINICAL MODELS OF VASOGENIC EDEMA (VE) AND MICROHEMORRHAGE (MCH) USING *IN-VIVO* BIOIMAGING AND HISTOPATHOLOGY

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Background: Cerebral VE and MCH are potential safety concerns for compounds targeting amyloid ß in Alzheimer's disease (AD). We sought animal models to explore how VE and MCH are related to cerebral amyloid angiopathy (CAA), a condition observed in ~80% of patients with AD. We also investigated whether histopathologic data for MCH alone are suitable as a surrogate risk assessment for VE and MCH in preclinical studies. **Methods:** We compared PSAPP mice that overexpress amyloid precursor protein (APP) and have a presenilin mutation (PS1), Tg2576 mice that over express APP but do not have a PS1 mutation, and wild-type (WT) mice. All were 18-21 months old. Magnetic resonance images (MRI) of 5-10 mice/strain were examined for VE and MCH. For histopathology, one longitudinal half of each brain was used. Four replicate sections were produced from each brain sample. These were stained with hematoxylin and eosin (HE) for pathologic findings, Perl's iron for MCH, 6E10 antibody for amyloid ß, and anti-albumen antibody for albumen leakage into the brain. Because MCHs were infrequent in these sections, additional sections (30-36) of each brain were cut and stained with Perl's iron. **Results:** The relative amount of parenchymal and vascular (CAA) amyloid ß was consistent with literature findings (PSAPP>Tg2576>WT). No VE was observed in HE sections or with MRI. However, immunohistochemistry for albumen revealed VE in 1 of 10 PSAPP and 1 of 5 Tg2576 mice. MCHs were detected using MRI in 9 of 10