significantly reduce Aβ levels in the CSF, with an acceptable safety and tolerability profile for long-term clinical studies to delay the onset of symptoms of AD in APOE4 carriers.

**O2-17-06** SAFETY AND TOLERABILITY OF CRENEZUMAB IN MILD-TO-MODERATE AD PATIENTS TREATED WITH ESCALATING DOSES FOR UP TO 25 MONTHS

Veronica Asnaghi¹, Helen Lin², Nan Hu², JillianSmith³, William Cho³, Susanne Ostrowitzki³, ¹F. Hoffmann-La Roche AG, Basel, Switzerland; ²Genentech, Inc., South San Francisco, CA, USA; ³F. Hoffmann-La Roche, Welwyn Garden City, United Kingdom; ⁴Genentech, Inc., South San Francisco, CA, USA. Contact e-mail: lin.helen@gene.com

**Background:** Crenezumab is a humanized anti-β-amyloid monoclonal antibody in development for the treatment of Alzheimer’s disease (AD). Crenezumab binds multiple forms of amyloid-beta, with high affinity for oligomers. Its IgG4 backbone with reduced effector function is hypothesized to lower the amyloid-related imaging abnormalities (ARIA) risk. In Phase II, crenezumab was generally safe and well tolerated; the highest dose tested was 15 mg/kg IV q4w. As its profile allowed for evaluation of higher doses, this study (GN29632) was designed to evaluate the safety and tolerability of crenezumab at doses up to 120 mg/kg IV q4w in preparation for Phase III studies (the latter currently ongoing at 60 mg/kg).

**Methods:** 50–90 year-old mild-to-moderate AD patients with an amyloid-positive PET scan were enrolled in 3 consecutive cohorts administering 4 infusions of 30 or 45, 60, or 120 mg/kg IV q4w crenezumab, or corresponding placebo (5:1 ratio). Upon completion of the double-blind placebo-controlled portion of the study, patients were offered to continue on active drug at the dose assigned at randomization, except for Cohort 3 patients who would receive 60 mg/kg. All patients undergo regular brain MRI to monitor for ARIA-E and ARIA-H. A secondary objective of this study is to characterize the pharmacokinetics of crenezumab at the doses investigated, and exploratory objectives include assessment of clinical efficacy and effects on imaging and plasma biomarkers.

**Results:** Twenty-six patients were enrolled in Cohort 1, 26 in Cohort 2 and 23 in Cohort 3. Safety and tolerability data collected as of May 2017 will be presented: patients receiving 30 and 45 mg/kg will have been exposed to crenezumab for up to 25 months; patients receiving 60 mg/kg will have been exposed to crenezumab for up to 21 months; and patients receiving 120 mg/kg in the double-blind portion will have been exposed to crenezumab for up to approximately 12 months.

**Conclusions:** The long-term safety and tolerability of crenezumab is evaluated in mild-to-moderate AD patients. Safety data will be presented.

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**O2-18-02** PHOSPHOLIPASE D3 CONTRIBUTES TO ALZHEIMER’S DISEASE RISK VIA DISRUPTION OF Aβ CLEARANCE THROUGH THE LYSOSOME

Celeste Karch¹, Simon Hsa², Rita Martinez³, Joanne Norton³, John R. Cirrito³, Jin-Moo Lee¹, Maria Cuervo¹, Carlos Cruchaga⁴,⁵,⁶, Alison Goate⁷, ¹Washington University School of Medicine, St Louis, MO, USA; ²Washington University in St. Louis, St. Louis, MO, USA; ³Knight Alzheimer Disease Center, Saint Louis, MO, USA; ⁴Washington University School of Medicine, Saint Louis, MO, USA; ⁵Albert Einstein College of Medicine, New York, NY, USA; ⁶Washington University in St. Louis, Saint Louis, MO, USA; ⁷Hope Center for Neurological Disorders, Saint Louis, MO, USA; ⁸Icahn School of Medicine at Mount Sinai, New York, NY, USA. Contact e-mail: karchc@wustl.edu

**Background:** Alzheimer’s disease (AD) is characterized by the accumulation of amyloid-β (Aβ) in the brain. We recently identified coding variants in the phospholipase D3 (PLD3) gene that double the risk for late onset AD. While the normal function of PLD3 is poorly understood, PLD3 is highly expressed in neurons and in brain regions most susceptible to amyloid pathology. **Methods:** We examined the impact of PLD3 risk variants on PLD3 and Aβ metabolism using CRISPR/Cas9 in induced pluripotent stem cells (iPSC). We then modeled the PLD3 expression patterns observed in AD brains in immortalized cell and AD mouse models. Lysosomal function was assessed in human brain tissue.

**Results:** PLD3...