for pharmacokinetic and Abeta (x-40, x-42 and total) biomarker analysis. Results: No clinical abnormalities were identified and no significant changes on safety ECG, telemetry, vital signs, or labs were observed up to 360 mg single dose. Doses were escalated up to the pre-defined exposure limit and maximum tolerated dose has not been established. Following single doses under fasted condition, PF-06648671 was absorbed rapidly with median t\textsubscript{max} of 1 to 1.5 hours. The mean terminal t\textsubscript{1/2} was 13.9 to 23.1 hours. The C\textsubscript{max} and AUC\textsubscript{inf} increased by approximately 88- and 140-fold over the dose range of 2 to 360 mg. With high-fat meal, a delayed median t\textsubscript{max} of 4 hours was observed. AUC\textsubscript{inf} slightly increased by 23% while C\textsubscript{max} decreased by 24% compared to the fasted state. Significant, dose-dependent reductions in plasma Abeta42, 40 and total were observed. The placebo-adjusted maximal change from baseline was -56.9% and -68.8% for plasma Abeta42 and 40, respectively, after a single dose of 360 mg. As expected, the reduction in Abeta total was substantially less than in Abeta40 and 42. Conclusions: PF-06648671 was generally safe and well tolerated in healthy subjects after single oral doses up to 360 mg. Robust and dose-dependent reductions in plasma Aβ40 and Aβ42 were observed following single dose administrations. A multiple ascending dose study in healthy adult and elderly is ongoing with CSF Aβ effect evaluated at steady state.

P2-010 PHARMACOKINETIC AND PHARMACODYNAMIC STUDY (54861911ALZ1006) WITH A BACE INHIBITOR, JNJ-54861911, IN HEALTHY ELDERLY JAPANESE SUBJECTS
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Background: Reduction of Aβ production by inhibition of BACE1 is a highly conserved process in many species and should thus be similar across genetically different human populations. Still demonstration of this similarity for new compounds or concepts is warranted, before applying in larger studies. We report the results from the first clinical trial of the BACE inhibitor, JNJ-54861911, in healthy elderly Japanese subjects, to investigate safety, tolerability and pharmacokinetics, as well as to explore the effect of JNJ-54861911 on amyloid-beta (Aβ) levels in cerebrospinal fluid (CSF) and plasma following single dose administration. Methods: Three sequential cohorts of healthy elderly Japanese (aged 55 to 75) male subjects received a single oral dose (25, 50 or 100mg) of JNJ-54861911 or placebo as tablet(s) under fasted conditions. CSF was collected at baseline and 24h after dosing. Each cohort included 8 subjects, 6 on active drug, 2 on placebo, to assess safety, tolerability, plasma and CSF exposure and pharmacodynamics (PD) including Aβ (Aβ1-37, 1-38, 1-40 and 1-42), sAPPα and sAPPβ. To account for inter-subject variability of baseline Aβ and sAPP levels, reductions were expressed as % of predose. Results: Exposure to JNJ-54861911 in plasma appeared to increase generally dose proportional. Median t\textsubscript{max} and t\textsubscript{1/2} of JNJ-54861911 in plasma was comparable between the 3 dose groups. Concentrations in CSF increased linearly with increasing plasma concentrations of JNJ-54861911. The mean of the maximal Aβ1-40 concentration decrease in plasma was 78%, 85% and 88% for the 25-, 50- and 100-mg cohorts, respectively. The Mean reduction for Aβ1-40 in CSF was 54%, 66% and 65% after 24 hours for the 25-, 50- and 100 mg cohorts, respectively. All other Aβ species, as well as sAPPβ, had parallel reductions. Conclusions: JNJ-54861911 confirmed to be a potent, brain-penetrant BACE inhibitor, achieving strong Aβ reductions after single dose. The tested dosed of JNJ-54861911 were safe and well tolerated in an elderly Japanese subjects.

P2-011 PHARMACOKINETIC/PHARMACODYNAMIC MODELING OF CSF Aβ1-40 REDUCTION IN AN EARLY ALZHEIMER’S DISEASE STUDY OF JNJ-54861911, AN ORAL BACE1 INHIBITOR
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Background: Data from a Phase 1b study in Early Alzheimer’s disease (AD) patients (prodromal and asymptomatic at risk for AD) treated with JNJ-54861911, an oral BACE1 inhibitor, were analyzed via population pharmacokinetic/pharmacodynamic (PK/PD) modeling with the objective to (i) characterize the plasma PK of JNJ-54861911 following multiple once-daily doses of 10 or 50 mg, (ii) assess drug penetration into the central nervous system (CNS), and (iii) quantify the impact of JNJ-54861911 exposure on cerebrospinal fluid (CSF) amyloid beta 1-40 (Abeta1-40) reduction. Methods: Population PK modeling of individual plasma concentrations, obtained via sparse sampling over 28 treatment days, was applied to characterize the JNJ-54861911 plasma PK. CNS penetration was evaluated as the ratio between CSF concentration (obtained on Day 28 via lumbar puncture, LP) and unbound plasma concentration at the same time point. The relationship between JNJ-54861911 exposure and CSF Abeta1-40 reduction was assessed via PK/PD modeling of individual Abeta1-40 reductions, which were calculated as the percent change between baseline Abeta1-40 (obtained via LP) and Day 28 Abeta1-40 for each patient. The modeling findings were compared with results from a previously published JNJ-54861911 multiple-dose study in healthy subjects (HS’s). Results: JNJ-54861911 was characterized by linear PK and an oral clearance of 8.3 L/h, which is similar to the HS estimate (10.5 L/h). Total exposure was dose-proportional and similar to HS values. The ratio between unbound plasma concentration and CSF concentration on Day 28 was estimated as 84%. The PK/PD model of CSF Abeta1-40 reduction in HS’s described Early AD data satisfactorily. The potency parameter (i.e. the plasma concentration associated to 50% inhibition of Abeta1-40 synthesis, IC50), estimated as 21 ng/mL on HS’s, did not require re-estimation. Baseline Abeta1-40 and subject population (i.e. prodromal or asymptomatic at risk for AD) were non-significant covariates of IC50 (p=0.05). Conclusions: JNJ-54861911 is characterized by linear PK and high CNS penetration. Results from the Early AD study confirmed the potent and dose-dependent CSF Abeta1-40 reduction observed in HS’s. Model simulations confirmed that once-daily 10 mg and 50 mg JNJ-54861911 can attain 60-70% and 90% Abeta1-40 reduction respectively, while 25 mg, not tested in this study, is predicted to attain about 80% Abeta1-40 reduction.