Modelling pharmacokinetics and CSF Aβ1-40 reduction in humans after dosing with JNJ-54861911, a novel oral BACE inhibitor

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INTRODUCTION

- Alzheimer’s disease (AD) is characterized by progressive dementia, cognitive decline, and memory loss. Neuritic plaques, that are composed of aggregates of amyloid beta (Aβ) peptide, are a hallmark of AD [1].
- Amyloid reduction via beta-secretase cleaving enzyme (BACE) inhibition is a potential therapeutic target in AD [2].
- JNJ-54861911 is a potent BACE inhibitor tested in Phase 1 clinical trials [3].

OBJECTIVES

- To model the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of JNJ-54861911.
- To model the pharmacodynamic (PD) effect of JNJ-54861911 on CSF Aβ-40 as a marker of target engagement.
- To assess the dose- and exposure-response on CSF Aβ-40 reduction after repeated daily dosing and to simulate Aβ reduction at different doses.

METHODS

- A two-compartment PK model with sequential zero- and first-order absorption with linear disposition captured the PK of JNJ-54861911 in plasma (Figure 1).
- Steady-state was reached by approximately 5 days after repeated q.d. dosing of JNJ-54861911.
- Tablet differed from oral suspension only for an absorption lag (Δtabs), Table 1).
- JNJ-54861911 resulted in a potent and sustained CSF Aβ1-40 reduction (plasma equivalent IC₅₀ = 21 ng/mL, Table 1). Baseline CSF Aβ1-40 was not a predictor of Aβ reduction.

RESULTS: MODELING OF PK AND CSF Aβ1-40 REDUCTION

- Simulation of a 14-day treatment regimen illustrates the sustained Aβ1-40 reduction, with relatively small daily variations (about 6% at 5 mg) (Figure 2).
- A 10 mg q.d. regimen (not tested in the clinical trial) is expected to attain about 60% reduction (Figure 2).
- Simulation of steady-state average CSF Aβ1-40 reduction and associated variability (Figure 3) evidences that:
  - 10 mg q.d. attains >50% reduction in the majority of subjects;
  - 25 mg q.d. provides robust (>80%) reduction in most subjects;
  - Aβ1-40 reduction approaches 90% at a dose of 50 mg q.d. and improves only marginally for higher doses.

RESULTS: PK/PD SIMULATIONS OF CSF Aβ1-40 REDUCTION

- The integrated, semi-mechanistic population PK/PD model captured the time course of JNJ-54861911 PK and allowed to link plasma concentrations to CSF concentrations, which are possibly reflective of brain penetration [6].
- Modeling and simulation of CSF Aβ1-40 time course helped to quantify the dose-and exposure-response of JNJ-54861911, as well as the associated variability (due to inter- and intra-individual variability of PK and PD).
- The PK/PD model of Aβ1-40 reduction allowed to compare different doses and infer a potential range of therapeutic doses for long-term treatment.

CONCLUSIONS

- Plasma and CSF concentrations of JNJ-54861911, dosed as an oral suspension or a tablet, were obtained from healthy elderly volunteers in a Phase 1 multiple ascending dose trial. Serial CSF samples to assess JNJ-54861911 PK and the time course of amyloid markers were obtained via 36-hour catheterization [3].
- JNJ-54861911 PK and treatment effect on CSF Aβ1-40 were analyzed via population PK/PD modeling with NONMEM 7.10 [4].
- Drug effect was modeled by linking JNJ-54861911 CSF concentrations to CSF Aβ1-40 reduction via a semi-mechanistic indirect response PK/PD model (see e.g. [5]).
- The PK/PD model was used to simulate the expected Aβ1-40 reduction for a wide range of doses, including those not tested in the Phase 1 study. Inter- and intra-individual variability of PK and Aβ was incorporated in the simulations.

REFERENCES


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