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 Aβ1-40 reduction as a marker of target engagement.
- To assess the dose- and exposure-response on CSF Aβ1-40 reduction after repeated daily dosing and to simulate Aβ reduction at different doses.

METHODS

- 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 7.1.0 [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.

RESULTS: MODELING OF PK AND CSF Aβ1-40 REDUCTION

- 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 (A_{lag}).
- CSF PK profiles were parallel to the respective plasma profiles and were described via a scaling factor (CSF-to-plasma ratio = 3.7%, Table 1).
- JNJ-54861911 resulted in a potent and sustained CSF Aβ1-40 reduction (plasma equivalent IC_{50} = 21 ng/mL, Table 1). Baseline CSF Aβ1-40 was not a predictor of Aβ reduction.

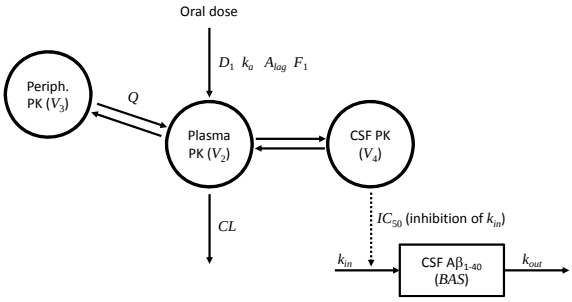

Figure 1: PK/PD model scheme linking JNJ-54861911 plasma and CSF PK to CSF Aβ1-40 synthesis. D_1: duration of zero-order absorption process. k_a: first-order absorption rate constant. A_{lag}: absorption delay. F_1: relative bioavailability. CL, Q: apparent plasma and intercompartmental clearances. V_2, V_3, V_4: apparent plasma, peripheral, and CSF volumes of distribution. BAS: baseline CSF Aβ1-40. k_{in}: zero-order Aβ1-40 synthesis rate. k_{out}: first-order Aβ1-40 elimination rate constant. IC_{50}: CSF concentration associated to 50% inhibition of Aβ1-40 synthesis.

Model	Parameter	TV (RSE%)	IIV% (RSE% *)
PK	k_a (1/h)	0.773 (10%)	33% (37%)
	D_1 (h)	0.484 (19%)	156% (25%)
	A_{lag} (for solid formulation) (h)	0.271 (5%)	135% (32%)
	F_1	100% (fixed)	IIV: 24% (24%) IOV: 15% (22%)
	CL (L/h)	10.5 (4%)	19% (30%)
	V_2 (L)	121 (7%)	-
	Q (L/h)	11.7 (13%)	-
	V_3 (L)	71.3 (8%)	17% (63%)
	V_4 (L)	194 (6%)	19% (27%)
	fu_p	6%	-
	CSF-to-free plasma ratio ($V_2/V_4 \times 100$)	62%	-
	CSF-to-plasma ratio, ρ ($fu_p \times V_2/V_4 \times 100$)	3.7%	-
	RUV plasma PK (additive in log-domain)	19% (21%)	-
	RUV CSF PK (additive in log-domain)	14% (23%)	-
PD	BAS (pg/mL)	8730 (6%)	34% (21%)
	k_{out} (1/h)	0.053 (15%)	81% (24%)
	k_{in} ($BAS \times k_{out}$) (pg/mL/h)	461	-
	Turn-over half-life (log(2)/k_{out}) (h)	13	-
	IC_{50} (ng/mL)	0.77 (4%)	-
	Plasma equivalent IC_{50} (IC_{50}/ρ) (ng/mL)	21	-
	RUV CSF Aβ1-40 (proportional)	14% (14% #)	-

Table 1: PK/PD model parameter estimates. TV: typical value. IIV: inter-individual variability. IOV: inter-occasion variability. RSE: relative standard error. RUV: residual unexplained variability. (*) relative to OMEGA parameter. (#) relative to SIGMA parameter.

RESULTS: PK/PD SIMULATIONS OF 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.

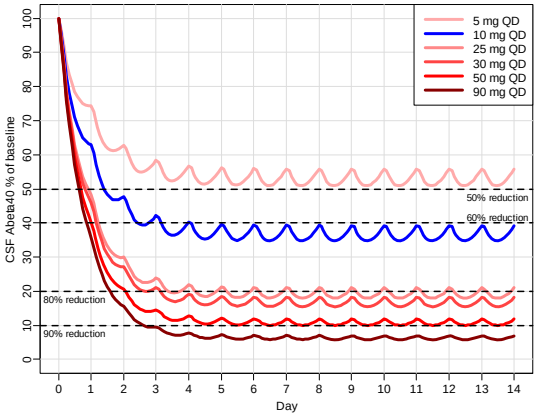

Figure 2: Simulated time course of CSF Aβ1-40 reduction over 14 days of q.d. administration, for a typical subject. The 10 mg simulation is a prediction from the PK/PD model, since 10 mg was not tested in this study.

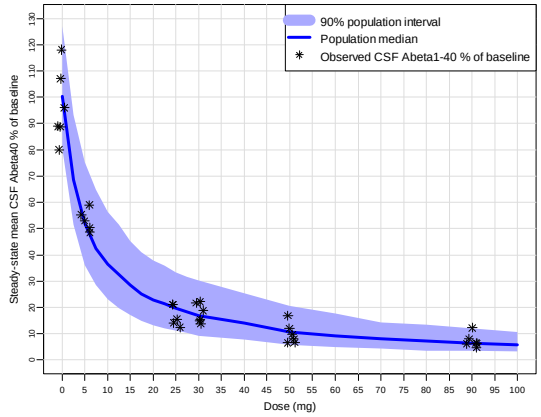

Figure 3: Dose-response relationship, i.e. steady-state mean CSF Aβ1-40 % of baseline vs dose, obtained via simulation (500 subjects/dose). Mean refers to a 24-hour average of CSF Aβ1-40 reduction. Observed values were plotted with small random scatter along x-axis for readability.

CONCLUSIONS

- 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 Aβ).
- 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.

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