

A Mechanism-Based PK/PD Model for Posdinemab (JNJ-63733657), a Humanized Monoclonal Antibody Targeting pTau, in healthy and Alzheimer's Disease Subjects



Neuroscience TA

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INTRODUCTION

Posdinemab (JNJ-63733657) is a humanized IgG₁ monoclonal anti-tau antibody in clinical development for the treatment of Alzheimer's Disease (AD)^{1,2}. JNJ-63733657 binds to human phosphorylated tau at threonine 217+ (pTau), which is hypothesized to prevent the spreading of tauopathy in the brain by interacting with and neutralizing pTau seeds in the interstitial fluid (ISF)³.

OBJECTIVES

To describe the time-course of JNJ-63733657 concentrations in serum and cerebrospinal fluid (CSF) after intravenous (IV) administration using the available clinical data from a Phase 1 study, and characterize the relationship between JNJ-63733657 and free and total pTau levels in CSF in healthy and AD subjects.

METHODS

A total of 69 subjects were included in the study, 53 (76.8%) subjects received IV JNJ-63733657 at dosages ranging from 1 to 60 mg/kg given as a single dose or multiple doses every 28 days (Q4W) for 13 weeks whereas the remaining 16 subjects (23.2%) were assigned to placebo. From the 69 subjects, 56 (81.2%) were healthy and the remaining 13 (18.8%) were AD subjects. A mechanism-based pharmacokinetic-pharmacodynamic (PK/PD) model was developed using NONMEM[®] VII software.

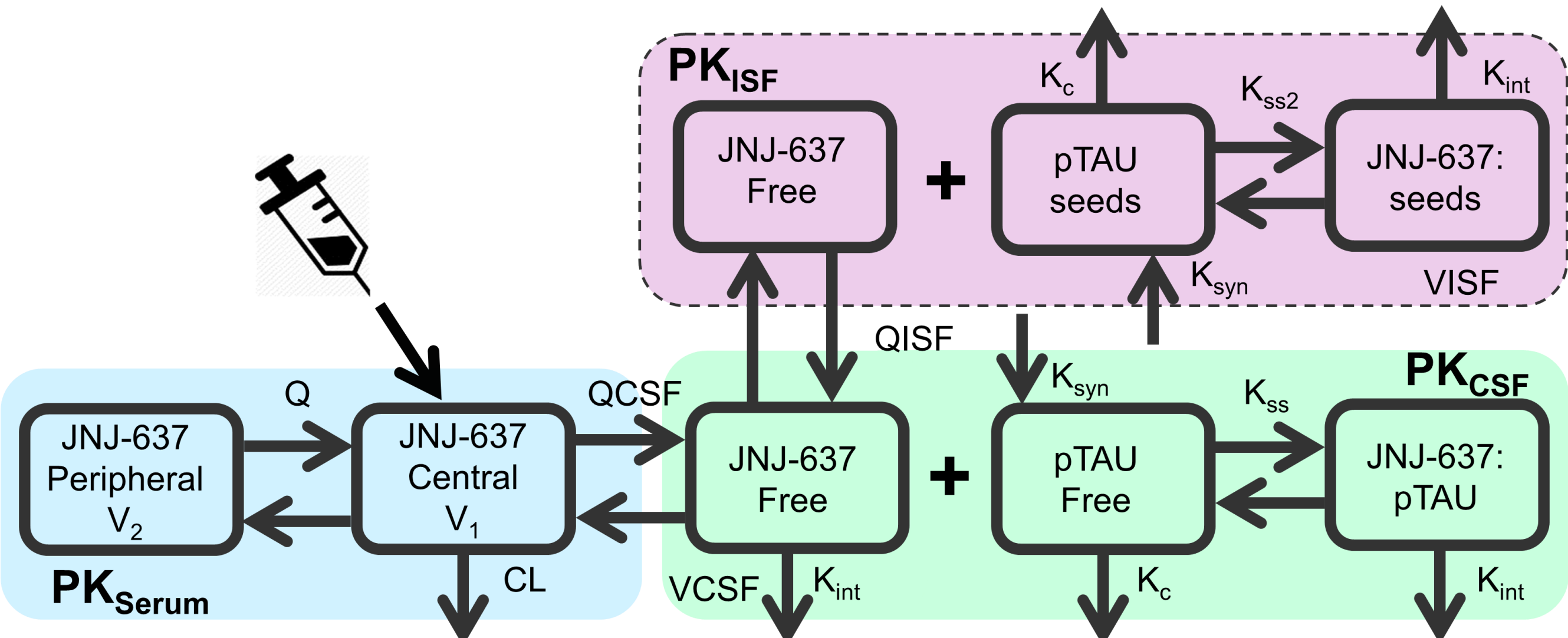


Figure 1. Schematic of the mechanism-based PK/PD model for JNJ-63733657 and pTau in CSF and ISF.

RESULTS

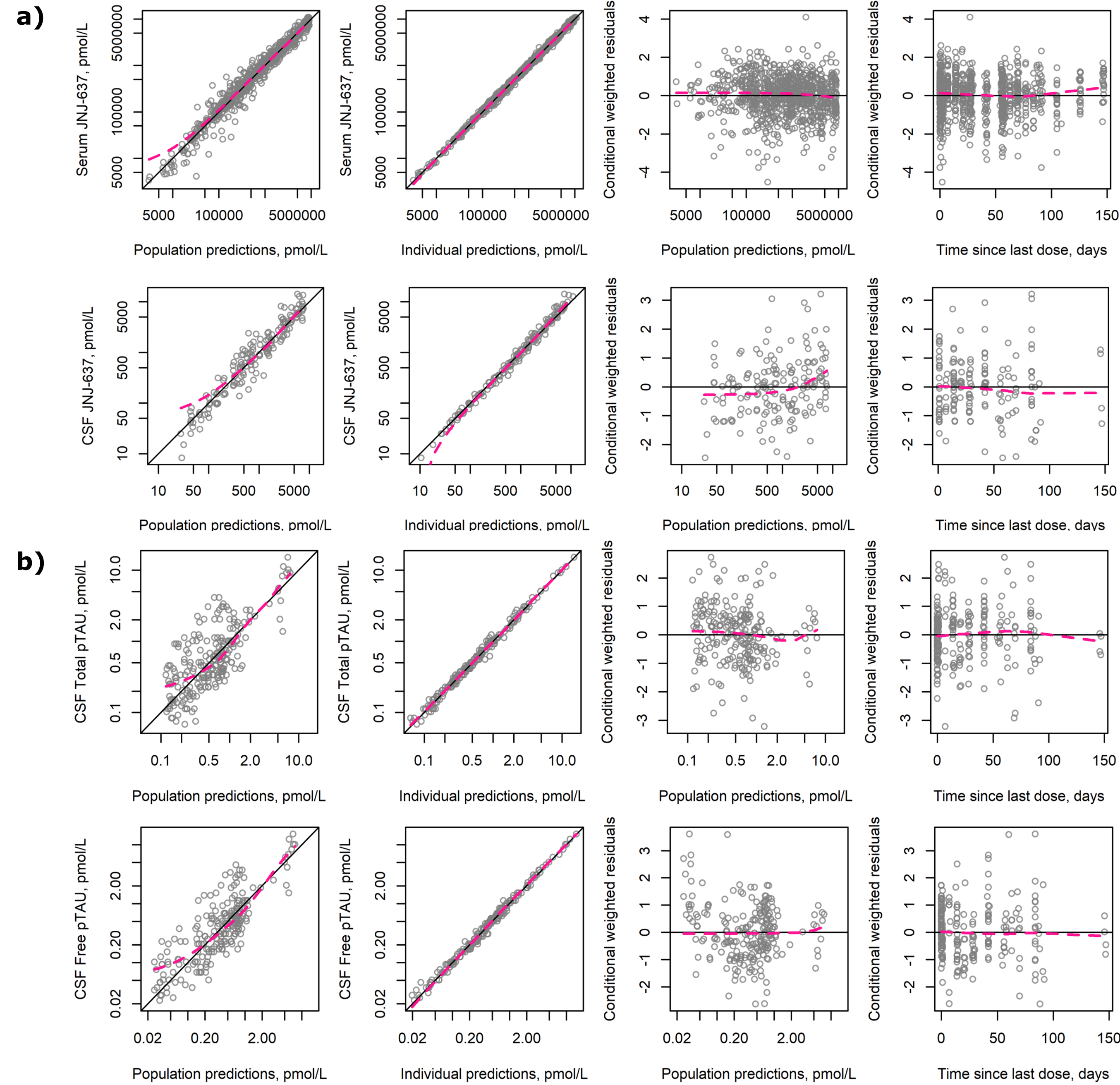


Figure 2. Goodness-of-fit plots of the mechanism-based PK/PD model developed for a) JNJ-63733657 in serum and CSF, and b) free and total pTau in CSF.

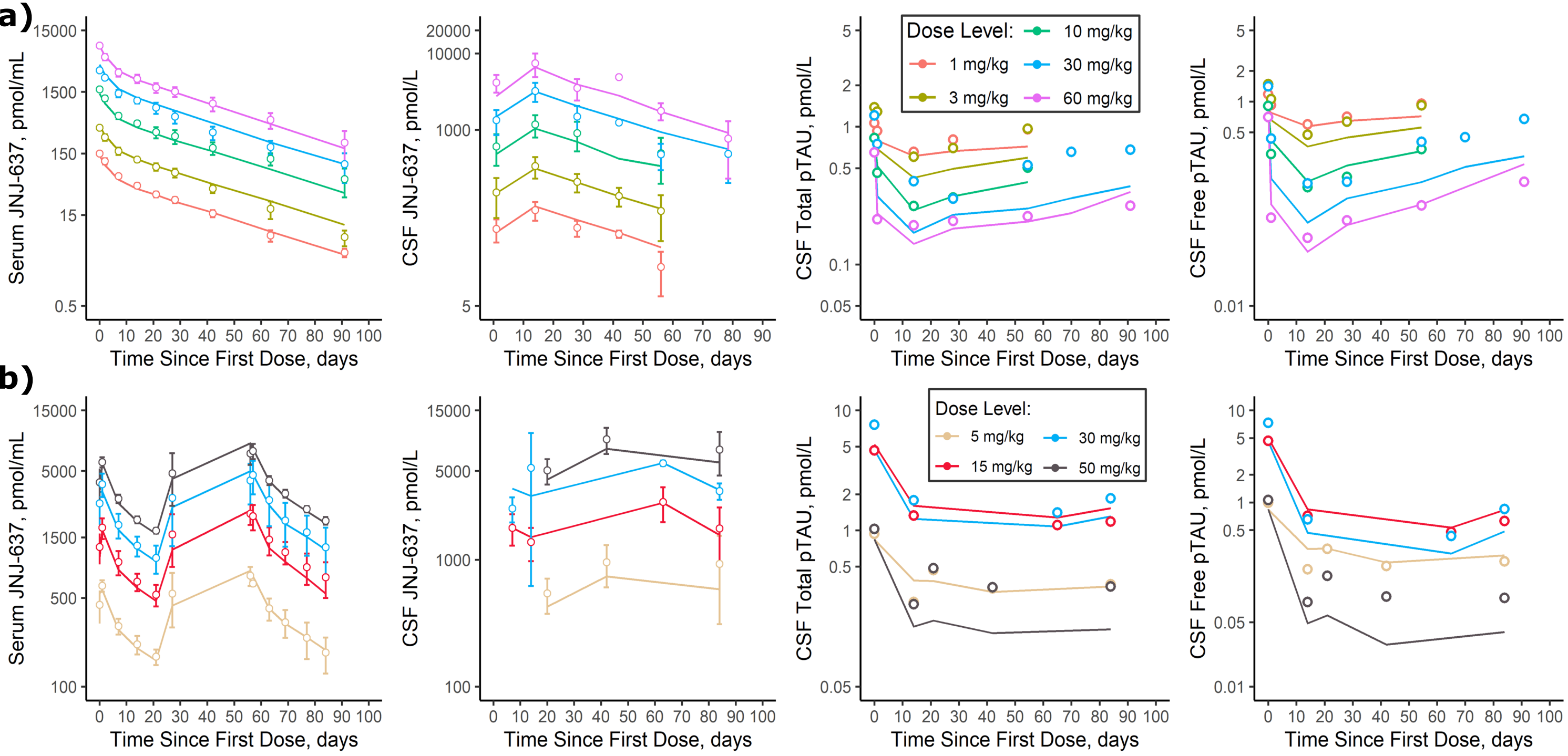


Figure 3. Mechanism-based PK/PD model predictions stratified by dose for the a) SAD and b) MAD cohorts. Healthy subjects were treated with 1, 3, 10, 30 and 60 mg/kg in SAD cohort and with 5 and 50 mg/kg in the MAD cohort. AD subjects were treated with 15 and 30 mg/kg in the MAD cohort.

RESULTS

Table 1. Parameter estimates (RSE, %) for the mechanism-based PK/PD model for JNJ-63733657 and pTau in CSF.

Structural Model Parameters		Inter-individual Variability (IIV; CV %)	
Parameters (units)	Estimate (RSE %)	Estimate (RSE %)	
PK serum	CL × 10 ⁻³ (L/h)	9.21 (6.60)	23.3 (21.3)
	V ₁ (L)	3.12 (5.84)	17.7 (44.1)
	Q × 10 ⁻³ (L/h)	24.8 (8.42)	44.5 (25.4)
	V ₂ (L)	2.87 (5.05)	22.2 (44.7)
PK CSF	QSCF × 10 ⁻⁸ (L/h)	3.42 (6.40)	27.3 (33.4)
	VSCF × 10 ⁻³ (L)	1.93 (8.59)	27.1 (92.0)
	QISF × 10 ⁻⁵ (L/h)	1.57 (6.40)	-
	VISF × 10 ⁻³ (L)	350 (8.55)	83.8 (94.0)
PD pTAU	Baseline _H (pmol/L)	0.813 (8.14)	67.6 (30.9)
	Baseline _P (pmol/L)	5.98 (17.6)	-
	K _c (h ⁻¹)	0.034 (7.84)	23.7 (113)
	K _{int} (h ⁻¹)	0.252 (9.44)	42.1 (58.2)
Residual variability (CV%)			
σ ₁	JNJ-63733657 _{serum}	8.71 (4.01)	
σ ₂	JNJ-63733657 _{CSF}	19.5 (21.3)	
σ ₃	pTau _{total}	11.6 (9.18)	
σ ₄	pTau _{free}	13.7 (20.6)	

RSE: relative standard error; CV: coefficient; objective function value: -4042.09. The binding affinity between JNJ-63733657 and Tau seeds in ISF (K_{ss2}) was fixed to be 20-fold lower than K_{ss} (in-vitro data).

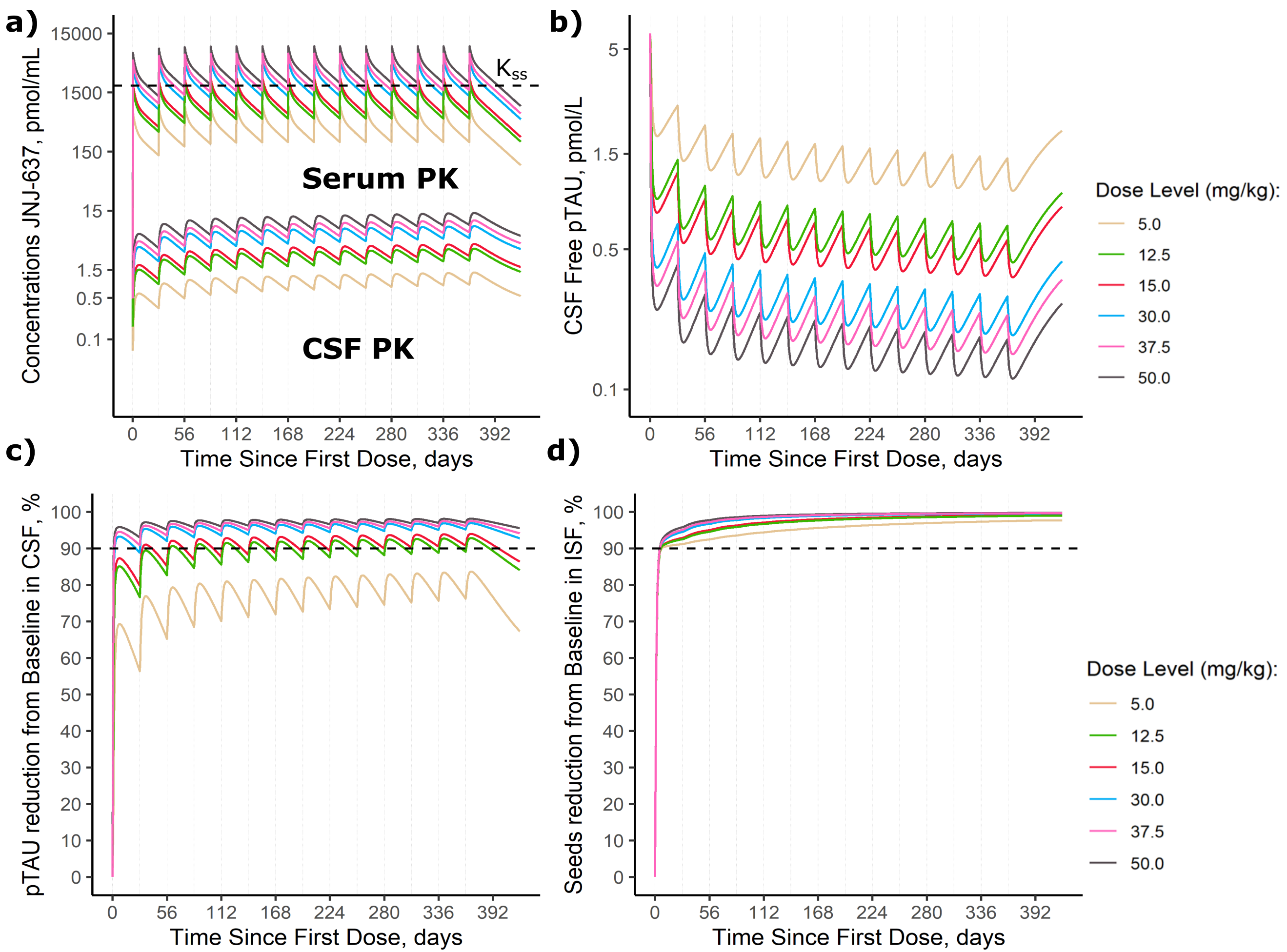


Figure 4. Deterministic simulations using the mechanistic PK/PD model to evaluate the time course of JNJ-63733657 in serum and CSF (a), free pTau in CSF (b), total reduction of pTau in CSF (c) and total reduction of Tau seeds in ISF (d) across different dosing regimens to guide the IV dose selection for Phase 2 study (AUTONOMY)².

Table 2. Model-based deterministic simulations calculating the maximum free pTau and Tau seeds reduction from baseline across the different IV dosing regimens evaluated after 1 year dosing.

Dose Level (mg/kg)	Model-predicted maximum pTau reduction from baseline in CSF (%)	Model-predicted maximum Tau seeds reduction from baseline in ISF (%)
5.0	83.4	94.2
12.5 ^a	92.7	96.5
15.0	93.8	96.9
30.0	96.8	98.2
37.5 ^b	97.5	98.5
50.0	98.1	98.8

^aA 1000 mg flat dose will provide a 96.5% Tau seeds reduction in ISF corresponding to a 12.5 mg/kg for a 80 kg subject. ^bA 3000 mg flat dose will provide a 98.5% Tau seeds reduction in ISF corresponding to a 37.5 mg/kg for a 80 kg subject.

The Tau seed reduction needed for efficacy in AD subjects is currently unknown, thus the current model does not establish any direct relationship with efficacy outcomes. Given K_{ss2} assumption, a 90% Tau seeds reduction in ISF is achieved earlier than in CSF and for all doses evaluated.

CONCLUSIONS

- The mechanistic PK/PD model successfully described the available clinical data and demonstrated JNJ-63733657 PK in serum is dose-proportional and time-independent.
- Model-based simulations informed that the dose level and dosing interval provided Tau seeds reduction in ISF (>90%) at steady-state.
- The model provides a simulation-framework which allows investigation of different PK/PD profiles under various dosing regimens.

REFERENCES

- Janssen Research & Development, LLC. A study to investigate safety and tolerability, pharmacokinetics and pharmacodynamics of JNJ-63733657 in healthy subjects and subjects with Alzheimer's disease; ClinicalTrials.gov Identifier: NCT03375697; December 18, 2017.
- Janssen Research & Development, LLC. A Study of JNJ-63733657 in Participants with early Alzheimer's disease (Autonomy); ClinicalTrials.gov Identifier: NCT04619420; November 6, 2020.
- Galpern Wendy R, Mercken Marc, Van Kolen Kristof, et al. A single and multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of the anti-phospho-tau antibody JNJ-63733657 in healthy subjects. July 2019, Alzheimer's & dementia: the journal of the Alzheimer's Association 15(7): p252-p253, 2019 doi: 10.1016/j.jalz.2019.06.077.