Population Pharmacokinetic Analysis of JNJ-37822681, a Specific and Fast-Dissociating D_2 Antagonist for the Treatment of Schizophrenia : Dose Predictions Based on Simulated D_2-Receptor Occupancy

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Introduction

JNJ-37822681 is a novel centrally active dopamine D_2 receptor antagonist characterized by a high selectivity and fast dissociation from the receptor, which has potential therapeutic value for the treatment of schizophrenia ([1]). A population pharmacokinetic (PK) model was developed with the aim to describe the PK of JNJ-37822681 in healthy volunteers and in patients with schizophrenia. The main objectives were to obtain estimates for PK parameters and associated inter- and intra-individual variability, to evaluate the effects of covariates and to provide exposure parameter estimates derived from sparse samples of subjects participating in a Phase IIb study. This study was designed to evaluate efficacy, safety and tolerability of JNJ-37822681 at fixed doses of 10, 20 and 30 mg bid. The exposure parameter estimates and former PET-study data were used to simulate D_2 occupancy and to guide dose selection for subsequent studies.

Methods

Data included

Data were obtained from 378 subjects enrolled in 3 Phase I and 2 Phase II trials, representing oral dosage regimen ranging from 10 mg single dose up to 80 mg per day, given either once daily (od) or twice daily (bid).

Structural model development

Nonlinear mixed effects modeling of pooled data was conducted using NONMEM® VI ([2,3]). Various structural models were tested to evaluate their fit to the data. Between-subject variability (IIV) for PK parameters was evaluated using an exponential error model and the residual error was described using an additive model in the log domain. The FOCE method was applied throughout the analysis.

Covariate analysis

Screening for covariate relationships was based upon clinical criteria, scientific plausibility and graphs of individual posterior estimates of random effects (ETAs) *vs.* covariates. Only effects for which a clear trend could be observed were further tested in NONMEM using forward addition and backward elimination.

Model validation

The model was validated on a subset of data from a Phase IIb study in subjects with acute exacerbations that were not used to build the model. Model diagnostics were evaluated to determine the goodness-of-fit of the model to the validation dataset. Prediction errors were computed that provide a measure of bias and precision ([4]).

Final model

Following validation of the model, including the significant covariates, the model was applied to the combined dataset and population PK parameters were re-estimated, resulting in the final model. This model was used to predict exposure parameters at steady-state for each subject in the Phase IIb study. Predictability of the final model was confirmed by visual predictive check (VPC).

D_2 receptor occupancy

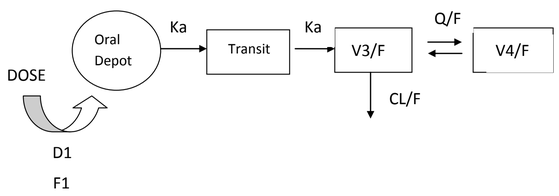
D_2 occupancy in striatum was simulated using the predicted exposure combined with parameters from a sigmoid E_{max} model established on former ^{11}C-raclopride PET data after single dose of JNJ-37822681 to healthy volunteers.

Results

Structural model development

A two-compartment disposition model with zero-order input in a depot compartment followed by first-order absorption into and first-order elimination from the central compartment combined with a transit compartment provided the best fit to the data.

Schematics of the compartmental model used to describe PK of JNJ-37822681



Covariate analysis

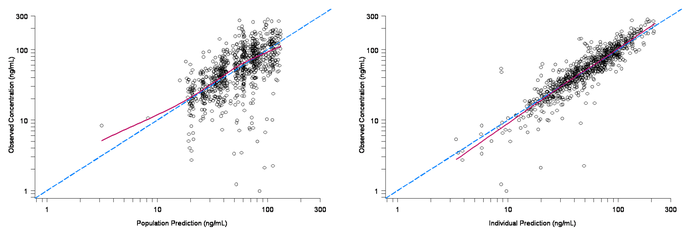
Overview of Covariate Model Development

Covariate	Model	OFV	Delta OFV
Stepwise forward addition			
Base structural model	M1	-2387	
Add food on Ka	M2	-2606	-219
Add food on D1	M3	-2565	-178
Add food on F1	M4	-2472	-85
Add sex on CL	M5	-2398	-11
Add creatinine CL on CL	M6	-2391	-4
Add body weight on CL	M7	-2389	-2
Add age on CL	M8	-2387	0
Backward elimination			
Covariate model	M9	-2703	
Remove sex on CL	M10	-2690	13
Remove food on F1	M11	-2632	71
Remove food on D1	M12	-2701	2
Remove food on Ka	M13	-2487	216
Final covariate Model	M14	-2701	

Gender was a significant covariate on oral clearance and food a significant covariate on the absorption rate constant and oral bioavailability.

Model validation

Diagnostics plots for model validation



Despite the presence of a few outliers, no substantial bias was observed, suggesting that the model is acceptable.

External validation: Distribution for PE% and |PE|%

	N	Median	median cut-off to pass validation	25th percentile	75th percentile
Prediction error percents (PE%)	816	0.24	±15	-7.98	8.65
Absolute prediction error percents (|PE|%)	816	8.3	30	3.91	14.95

The model was considered valid from an accuracy and precision point of view.

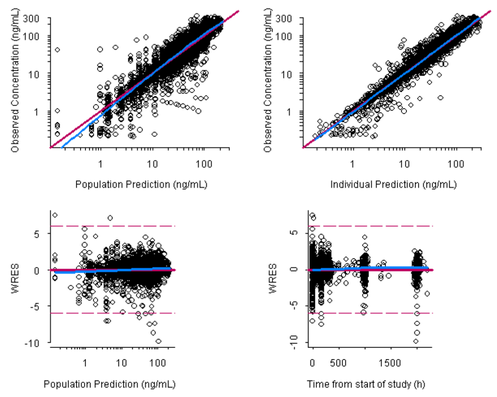
Final model

Parameter estimates from the final model

Parameter	Parameter Estimate	Parameter SEE (%CV)	IIV Estimate (%CV)	IIV SEE (%CV)
CL/F (males) (L/h)	27.1	3.84	33.2	24.5
CL/F (females) (L/h)	24.0	4.29		
Ka (fasted) (1/h)	2.85	12.6	52.7	31.2
Ka (fed) (1/h)	1.29	8.60		
V3/F (L)	280	3.61		
V4/F (L)	605	3.95	17.2	57.6
Q/F (L/h)	55.3	5.39		
D1 (h)	0.796	5.54	58.9	18.6
F1 (fasted)	1.00		15.6	24.9
F1 (fed)	0.89	3.94	31.2	39.2
Residual Error (%)	34.8	8.35		

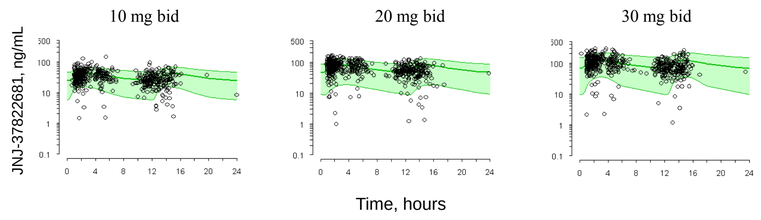
PK parameters were estimated with good precision (SEE below 15%), the random-effect parameters with somewhat lower precision. The exposure was somewhat higher (5 to 20%) in females compared to males (lower CL/F in females compared to males).

Goodness-of-fit plots for final model



The diagnostic plots demonstrated a lack of bias and a good fit of the model to the JNJ-37822681 plasma concentrations. Predictability of the final model was confirmed by VPC.

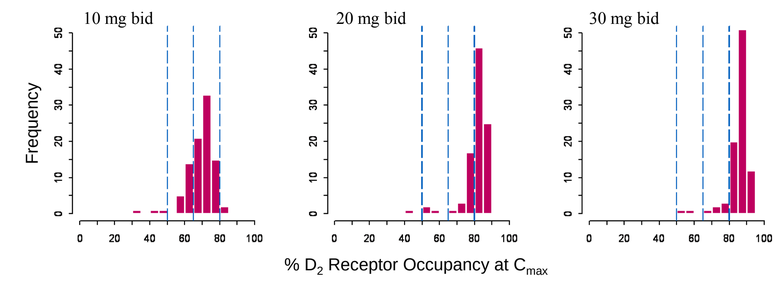
Predicted median concentration (with 95% PI)-time profiles overlaid with observed plasma concentrations

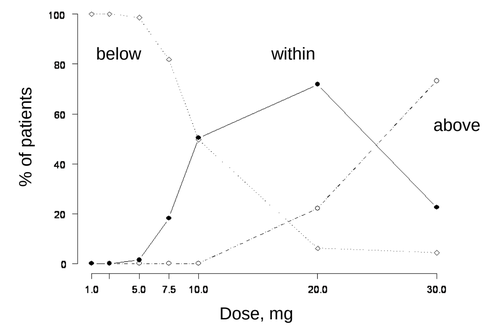


Dose predictions based on simulated D_2 occupancy

Simulation of D_2 receptor occupancy at C_{max} demonstrated that it was in the 65-80% range at 10 mg bid, and partially or almost fully above the 80% threshold at doses of 20 and 30 mg bid, respectively.

Distributions of the peak D_2-receptor occupancies





Percentage of patients below, within or above the therapeutic (65-80%) D_2-occupancy range ([5])

From these data, it was concluded that 5 or 7.5 mg bid could be a non-effective or minimal effective dose, whereas an optimal efficacy balance might be achieved at 10 mg bid.

Conclusion

A two-compartment PK model with zero-order release followed by first-order absorption and first-order elimination including a transit compartment, best described the individual PK profiles of JNJ-37822681.

Evaluation of subject covariates demonstrated that gender was a significant covariate on CL/F and food on Ka and F1.

The population PK model passed external validation, was considered valid from an accuracy and precision point of view and allowed determination of individual exposure parameters at steady-state for each subject in a Phase IIb study.

Simulated D_2 occupancy based on predicted exposure and former PET-study data guided dose selection for subsequent studies.

References

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