# Population Pharmacokinetic Modeling of Paliperidone Palmitate 3-Month Formulation

**Mats O. Magnusson[1*], Mahesh N. Samtani[2*], Elodie L. Plan[1], E. Niclas Jonsson[1], Stefaan Rossenu[3], An Vermeulen[3]**

[1]Pharmetheus, Uppsala, Sweden; [2]Janssen Research & Development, LLC., NJ, USA;
[3]Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium

*equal contribution

## OBJECTIVES

The overall aim of this population pharmacokinetic (PK) analysis was to characterize the dose-concentration relationship of paliperidone following administration of paliperidone palmitate 3-month formulation (PP3M). Additional aims included estimating the importance of selected covariates.

## BACKGROUND

Paliperidone is the major active metabolite of risperidone and is used in the treatment of schizophrenia. Two formulations of paliperidone are currently available: an extended-release (ER) paliperidone formulation for oral administration on a once-daily basis, and a long-acting injectable paliperidone palmitate 1-month formulation (PP1M) for monthly intramuscular administration. A modified paliperidone palmitate 3-month formulation is currently under development, which potentially can be administered every 3 months with retained efficacy.

## DATA & METHODS

Paliperidone plasma concentration data were obtained from 1 single-dose Phase 1 study (R092670-PSY-1005) and 1 repeated-dose Phase 3 study (R092670-PSY-3012). The PK data were analyzed using non-linear mixed-effects PK modeling implemented in NONMEM 7.3.0. A previously developed PK model for PP1M was used to describe the PK of paliperidone after PP1M administration [1] for patients in Study R092670-PSY-3012 who were treated with PP1M for 4 months before PP3M treatment commenced. The final model for PP3M was based on 8990 paliperidone PK samples from 651 subjects.

## CONCLUSION

The PK characteristics of paliperidone when administered as a single and multiple injections of PP3M were well captured by the developed population PK model for PP3M.

## RESULTS

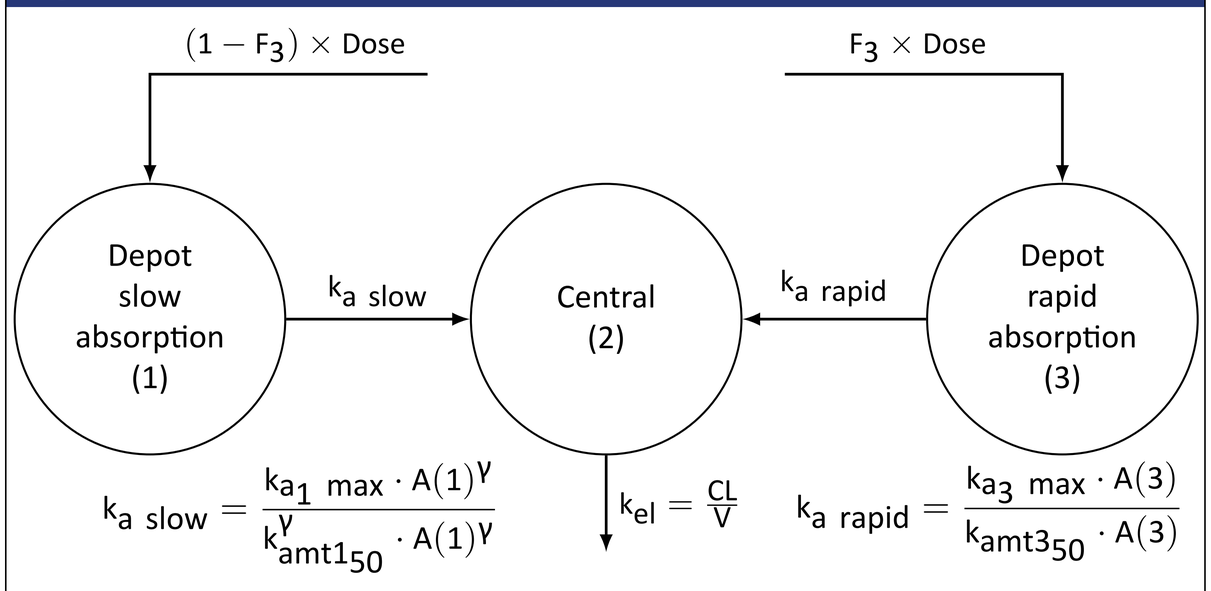
The final population PK model, which is a one-compartment disposition model with first-order elimination, is depicted in Figure 1. The absorption component of the model allowed a fraction of the dose ($F_3$) to enter into the depot compartment 3 (rapid absorption process) and the remaining fraction entered depot compartment 1 (slower absorption process). The absorption from the depot compartments was saturable, as described by the equations in Figure 1.

In addition to the structural covariates (creatinine clearance [CRCL] on clearance [CL]; body mass index [BMI] on volume of distribution [V]; injection volume [IVOL] on both the absorption rates), injection site (INJS) and sex were identified as covariates on $k_{a1\ max}$ of the slow absorption process. The parameter estimates of the final population PK model for PP3M are presented in Table 1. The relationships between covariates and the typical values (TV) of PK parameters in subject j are presented in Equation 1.

The final population PK model provided a good description of the data, as illustrated by the visual predictive check (VPC) in Figure 2.

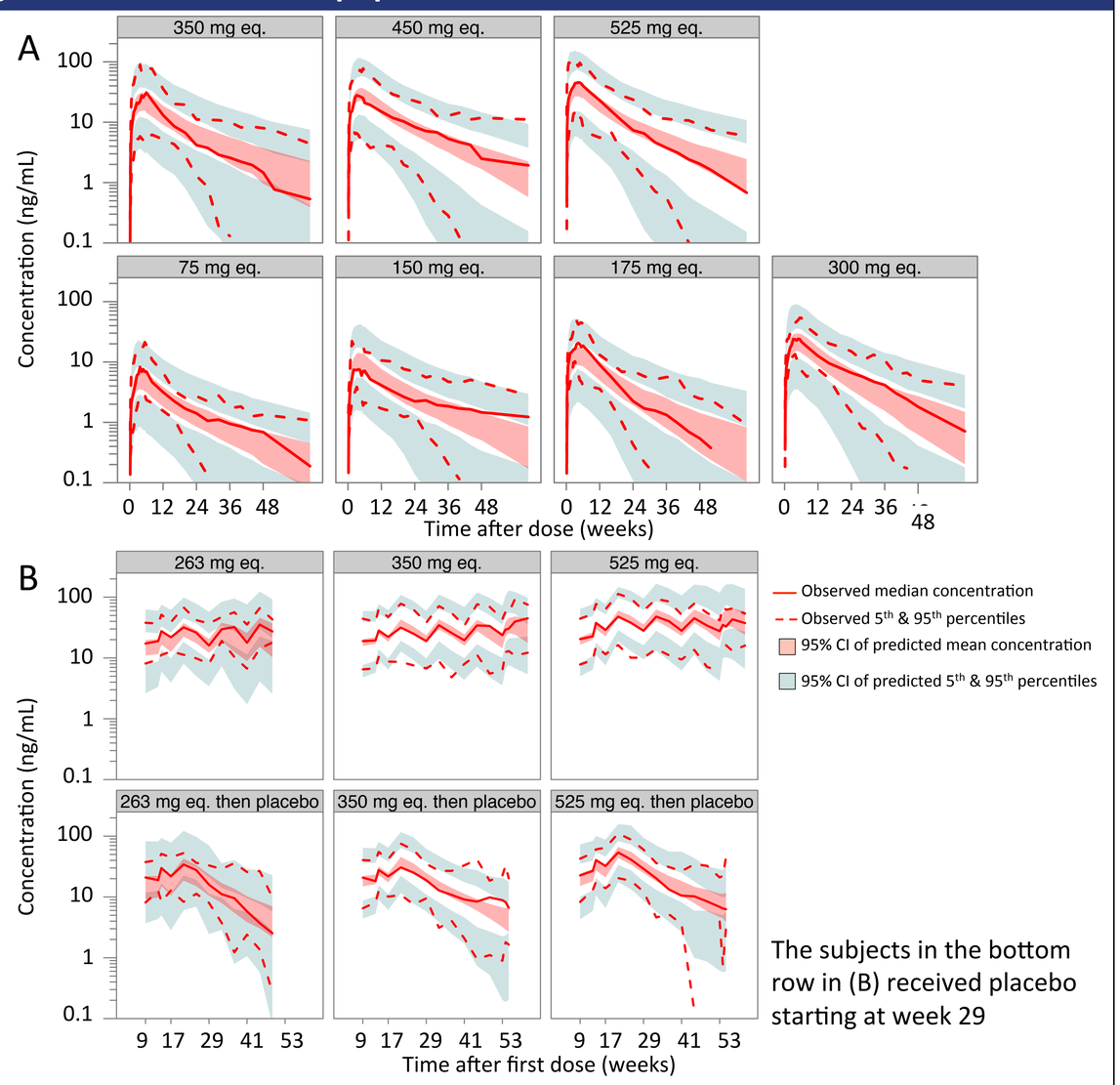
Like PP1M, paliperidone exhibits flip-flop kinetics when administered as PP3M, ie, the apparent half-life is driven by the absorption process.

### Figure 1. Illustration of the final population PK model for PP3M




A dual input model captured the absorption of PP3M, allowing a fraction of the dose ($F_3$) to enter into compartment 3, which entered the systemic circulation via a relatively rapid saturable absorption process. The remaining fraction entered the systemic circulation via a slower saturable absorption process.

### Figure 2. VPC of the final population PK model for PP3M




The subjects in the bottom row in (B) received placebo starting at week 29

The final model provided a good description of the data in study R092670-PSY-1005 (A), and in study R092670-PSY-3012 (B).

### Equation 1. Relationships between covariates and PK parameters

$$TVCL_j = 3.84 \cdot \left(\frac{CRCL_j}{115}\right)^{0.316}$$

$$TVV_j = 1960 \cdot \left(\frac{BMI_j}{26.15}\right)^{1.18}$$

$$TVka_{rapid\ j} = 164 \cdot 10^{-3} \cdot \left(\frac{IVOL_j}{1.75}\right)^{0.808} \cdot \frac{A(3)}{A(3) + 21.4 \cdot \left(\frac{IVOL_j}{1.75}\right)^{0.808}}$$

$$TVka_{slow\ j} = INJS_{ka\ slow} \cdot SEX_{ka\ slow} \cdot 90.4 \cdot 10^{-3} \cdot \left(\frac{IVOL_j}{1.75}\right)^{0.808} \cdot \frac{A(1)^{1.44}}{A(1)^{1.44} + 120^{1.44} \cdot \left(\frac{IVOL_j}{1.75}\right)^{0.808}}$$

$INJS_{ka\ slow}$: shift factor of 1 for deltoid injections and 0.746 for gluteal injections
$SEX_{ka\ slow}$: shift factor of 1 for men and 0.794 for women
No significant covariates were identified on the $F_3$ parameter

### Table 1. Parameter estimates of the final population PK model for PP3M

| Parameter | Unit | Value | RSE (%) | Parameter | Value | RSE (%) | SHR (%) |
|---|---|---|---|---|---|---|---|
| CL | L/h | 3.84 | 2.16 | IIV CL | 0.357 | 3.17 | 31.6 |
| V* | L | 1960 | | IIV V* | 0.628 | | 35.6 |
| $ka_{1\ max}$ | µg/h | 90.4 | 6.96 | IIV $ka_{1\ max}$ | 0.827 | 5.01 | 31.3 |
| $k_{amt1_{50}}$ | mg | 120 | 3.83 | IIV $k_{amt1_{50}}$ | 0.500 | 10.1 | 51.9 |
| γ | | 1.44 | 1.65 | IIV $F_3$* | 1.08 | | 29.5 |
| $V_{palmitate\ in\ plasma}$*,** | L | 156 | | IIV $k_{amt3_{50}}$ | 0.867 | 14.2 | 63.7 |
| $F_3$* | | 0.209 | | Residual error | 0.306 | 0.321 | 12.2 |
| $ka_{3\ max}$ | µg/h | 164 | 4.65 | | | | |
| $k_{amt3_{50}}$ | mg | 21.4 | 9.52 | | | | |
| CRCL on CL | | 0.316 | 21.5 | | | | |
| BMI on V* | | 1.18 | | | | | |
| IVOL on absorption rate | | 0.808 | 7.41 | | | | |
| INJS on $ka_{1\ max}$ | | -0.254 | 14.8 | | | | |
| Sex on $ka_{1\ max}$ | | -0.206 | 16.8 | | | | |

*Parameter fixed to estimate from PK model based on study R092670-PSY-1005 data only.
** Subjects with paliperidone palmitate in plasma had a lower V

*Funded by Janssen Research & Development, LLC, New Jersey, USA*

[1] Samtani MN, Vermeulen A, Stuyckens K. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: a novel once-monthly, long-acting formulation of an atypical antipsychotic. Clin Pharmacokinet. 2009;48(9):585-600.