ORIGINAL RESEARCH

Management of antipsychotic treatment discontinuation and interruptions using model-based simulations

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Background: Medication nonadherence is a well described and prevalent clinical occurrence in schizophrenia. These pharmacokinetic model-based simulations analyze predicted antipsychotic plasma concentrations in nonadherence and treatment interruption scenarios and with treatment reinitiation.

Methods: Starting from steady state, pharmacokinetic model-based simulations of active moiety plasma concentrations of oral, immediate-release risperidone 3 mg/day, risperidone long-acting injection 37.5 mg/14 days, oral paliperidone extended-release 6 mg/day, and paliperidone palmitate 117 mg (75 mg equivalents)/28 days were assessed under three treatment discontinuation/interruption scenarios, ie, complete discontinuation, one week of interruption, and four weeks of interruption. In the treatment interruption scenarios, pharmacokinetic simulations were performed using medication-specific reinitiation strategies.

Results: Following complete treatment discontinuation, plasma concentrations persisted longest with paliperidone palmitate, followed by risperidone long-acting injection, while oral formulations exhibited the most rapid decrease. One week of oral paliperidone or risperidone interruption resulted in near complete elimination from the systemic circulation within that timeframe, reflecting the rapid elimination rate of the active moiety. After 1 and 4 weeks of interruption, minimum plasma concentrations were higher with paliperidone palmitate than risperidone long-acting injection over the simulated period. Four weeks of treatment interruption followed by reinitiation resulted in plasma levels returning to predicted therapeutic levels within 1 week.

Conclusion: Due to the long half-life of paliperidone palmitate (25–49 days), putative therapeutic plasma concentrations persisted longest in simulated cases of complete discontinuation or treatment interruption. These simulations may help clinicians better conceptualize the impact of antipsychotic nonadherence on plasma concentrations, and the impact of medication-specific reinitiation strategies after intermittent nonadherence.

Keywords: paliperidone palmitate, risperidone, long-acting injection, pharmacokinetics, nonadherence, plasma concentrations

Introduction

The standard of care for patients with schizophrenia includes prompt initiation of antipsychotic treatment.[1–3] However, a major barrier to the effective treatment of patients with schizophrenia is nonadherence to the medication regimen, with estimated one-year rates of treatment discontinuation or interruption ranging from 40% to 75%.[4–6] Individual patients discontinue or interrupt treatment due to a variety of factors, including a lack of insight into their illness, forgetfulness, lack of social support, tolerability issues, conscious choice, and refractory or nonresponsive symptomatology.[7]

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Complete discontinuation or interruption of treatment can have severe ramifications, including relapse and the need for hospitalization.[8–10] Even short periods (ie, ≤2 weeks) of nonadherence with oral antipsychotic therapy increased the risk of a psychotic exacerbation, with hazard ratios ranging from 3.7 to 28.5, depending on the severity of medication nonadherence,[11] and the risk of hospitalization increased nearly twofold.[12]

Although patients can achieve improvement in psychotic symptoms with daily oral medication, poor adherence is a significant hurdle to achieving favorable outcomes.[13] In patients with a history of nonadherence, the American Psychiatric Association practice guidelines recommend the use of long-acting injectable antipsychotics.[1] In addition, the guidelines state that for patients who are prone to forget doses or who are intermittently nonadherent with treatment, drugs with slower rates of metabolism may be used preferentially.[1] After professional administration of a long-acting injectable formulation, patients do not need to remember to take their daily oral antipsychotic medication during the dosing period. Importantly, in the event of symptom recurrence, the clinician and caregiver will know the patient's adherence status and can correctly attribute the symptoms to medication failure or nonadherence. Long-acting injectable agents provide more stable drug exposure than daily formulations. Moreover, the long apparent half-lives for these products potentially allow more time to follow-up if a dose is delayed or missed, reducing the consequences of treatment interruption, such as risk of relapse and rehospitalization.[7,8,14–16] Data from recurrence prevention trials suggest that the median time to relapse with long-acting agents is longer than with oral extended-release formulations, and median times to relapse of 62 days have been reported following a switch from oral paliperidone extended-release to placebo[17] and of 163 days following a switch from paliperidone palmitate long-acting injectable suspension to placebo.[18,19] This increased time to relapse among patients switched from paliperidone palmitate to placebo may have resulted from persistent drug exposure, and a residual therapeutic effect, for weeks after the switch from a long-acting injectable to placebo.

Limited experimental data usually restrict the ability to visualize pharmacokinetic profiles following treatment discontinuation, or interruption and treatment reinitiation that may occur clinically in a patient receiving orally administered or long-acting injectable antipsychotic agents. However, pharmacokinetic models have been used to simulate a wide variety of situations that could be encountered clinically to inform prescriber judgment.[20] To help address these situations

encountered in every day practice, we simulated three scenarios using paliperidone and risperidone. We selected these scenarios and four formulations of paliperidone and risperidone because of: the availability of pharmacokinetic models that permit simulation of treatment discontinuation/interruption scenarios; the pharmacodynamic relationship between the atypical antipsychotics, risperidone and paliperidone (ie, paliperidone, also known as 9-hydroxy-risperidone, is the metabolite of risperidone, with both risperidone and 9-hydroxyrisperidone being active moieties), and the availability of both agents as oral and long-acting injectable formulations. Selecting two long-acting injectable formulations with substantially different release characteristics permits comparison with oral drugs and between formulations. These pharmacokinetic model-based discontinuation, interruption, and reinitiation simulations provide clinicians with a visual depiction of the plasma concentration profiles that may be anticipated with the four formulations of these two agents that have substantially different half-lives and formulation release properties.

Additional objectives of this analysis were to understand the comparative pharmacokinetics of the four paliperidone and risperidone formulations. Therefore, we also provide a brief review of the pharmacokinetic properties of these four formulations. The two oral formulations that were assessed differ in their release profiles in that risperidone displays an immediate-release profile (usually within one hour) whereas paliperidone is an extended-release tablet that uses the OROS delivery technology and displays an ascending release profile that lasts approximately 24 hours.[21,22] The extended-release profile of oral paliperidone enables initiation of treatment with an effective dose without the need for initial dose titration.[23] With multiple dosing, the oral risperidone immediate-release formulation exhibits daily peak-trough fluctuations whereas the extended-release formulation of oral paliperidone exhibits less fluctuation in steady-state plasma concentrations.[21,22,24,25]

The long-acting injectable formulations of risperidone and paliperidone differ considerably from their respective oral formulations as well as between each other. The long-acting injectable formulation of risperidone (Risperdal® Consta™; Janssen Pharmaceuticals, Inc; Titusville, NJ) uses biodegradable microspheres that are loaded with risperidone and suspended in aqueous diluent.[26,27] This formulation is characterized by no substantial release of risperidone immediately following the injection. After a single intramuscular injection of risperidone long-acting injection, there is a small initial release of the drug (<1% of the dose) followed by a lag time of 3 weeks.[26,27] The main release of the drug starts from 3 weeks onwards, is maintained for 4–6 weeks, and subsides

by 7 weeks following intramuscular injection.[26,27] Therefore, oral antipsychotic supplementation must be given during the first 3 weeks of treatment with risperidone long-acting injection to maintain therapeutic plasma concentrations until the main release of risperidone from the injection site has begun.[26,27] Steady-state plasma concentrations are reached after four injections of risperidone long-acting injection and are maintained for 4–6 weeks after the last injection.

Paliperidone palmitate long-acting injection (Invega® Sustenna™ Janssen Pharmaceuticals, Inc) is formulated as an aqueous suspension with a precisely milled particle size distribution that has sustained-release properties and permits once monthly (every 4 weeks) administration. Based on its extremely low solubility in water, paliperidone palmitate dissolves slowly at the injection site after intramuscular injection, is then hydrolyzed to paliperidone, and displays relatively constant plasma concentrations of paliperidone.[28] Following administration of the first injection of paliperidone palmitate long-acting injectable suspension, drug release begins as early as day 1 and lasts for as long as 126 days.[29] The median half-life is in the range of 25–49 days over the dose range of 39–234 mg (doses may also be expressed in mg equivalents [mg eq] of pharmacologically active paliperidone, with 39, 78, 117, 156, and 234 mg of paliperidone palmitate corresponding to 25, 50, 75, 100, and 150 mg eq of paliperidone).[30] A paliperidone palmitate initiation regimen with two intramuscular deltoid injections of 234 mg on day 1 and 156 mg on day 8 is recommended to attain therapeutic concentrations quickly.[29,31] No oral supplementation is required to initiate paliperidone palmitate treatment.

Materials and methods
Risperidone, paliperidone, and paliperidone palmitate dose selection

Pharmacokinetic model-based simulations were performed using oral risperidone, risperidone long-acting injection, oral paliperidone extended-release, and paliperidone palmitate long-acting injection. The dose of oral risperidone (3 mg/day) used for the simulations results in active moiety (risperidone plus paliperidone) exposure similar to that of risperidone long-acting injection 37.5 mg/2 weeks.[32] Risperidone long-acting injection 37.5 mg/2 weeks potentially attains an active moiety steady-state exposure similar to that of paliperidone palmitate 117 mg/4 weeks.[33] The 117 mg dose of injectable paliperidone palmitate and the 6 mg oral paliperidone extended-release dose represent the recommended maintenance doses listed in the product package inserts and provide similar exposures for paliperidone.[29,33]

It is important to note that the doses used in these pharmacokinetic model-based simulations do not represent dose equivalency across formulations because multistep comparisons of the above approximations can result in compounded deviation, and specific pharmacokinetic parameters (eg, peak-to-trough fluctuation) vary by formulation.

Scenarios addressed in pharmacokinetic model-based simulations

Pharmacokinetic simulations were performed under three scenarios (Table 1). The three simulated treatment discontinuation and interruption scenarios assumed that subjects were at steady state and received their last dose of orally administered risperidone or paliperidone on the previous day (day -1), their last injection of risperidone long-acting injection 2 weeks prior, and their last injection of paliperidone palmitate 4 weeks prior to the day of discontinuation/interruption, thus assuming discontinuation at the subsequent next administration time point of each individual formulation. In the treatment interruption scenarios, pharmacokinetic simulations were performed using medication-specific reinitiation strategies (Table 1).

Models for pharmacokinetic simulations

The pharmacokinetics of the active moiety after oral risperidone administration has been described using a two-compartment disposition model with linear elimination from the central compartment.[25] Oral absorption was modeled

Table 1 Scenarios analyzed in pharmacokinetic model-based simulations

Scenario 1	Complete treatment discontinuation without reinitiation of medication
Scenario 2	One week of treatment interruption, followed by treatment reinitiation at the following doses: • Oral risperidone 3 mg once daily • Risperidone LAI 37.5 mg every 2 weeks • Oral paliperidone ER 6 mg once daily • Paliperidone palmitate 117 mg (75 mg eq) every 4 weeks
Scenario 3	Four weeks of treatment interruption, followed by treatment reinitiation at the following doses: • Oral risperidone 3 mg once daily • Risperidone LAI 37.5 mg every 2 weeks AND oral risperidone 3 mg once daily supplementation administered from days 28 to 49 (ie, weeks 4–7 from time of interruption) • Oral paliperidone ER 6 mg once daily • Paliperidone palmitate 117 mg (75 mg eq) administered on days 28 and 35 (ie, weeks 4 and 5 from time of interruption) and every 4 weeks thereafter

Abbreviations: eq, equivalent; ER, extended-release; LAI, long-acting injection.

using a first-order process with a lag time from the gut to the central compartment.

The pharmacokinetics of the extended-release oral formulation of paliperidone have been described using a two-compartment disposition model with linear elimination from the central compartment.[24] Oral absorption was modeled with a sequential zero order input into a depot compartment and first-order absorption, with a lag time from the depot to the central compartment. The relatively faster absorption of paliperidone from the oral route allowed identification of the distributive peripheral compartment, which is not discernible in the flip-flopped paliperidone palmitate pharmacokinetic model (see below).

A compartmental model has also been developed for intramuscular risperidone long-acting injection which includes a one-compartment disposition submodel characterized by clearance and volume of distribution.[34] The plasma profile of the active moiety after intramuscular administration of risperidone long-acting injection is extremely complex because of the immediate release of a small amount of non-encapsulated risperidone followed by two sustained-release processes differing in their rate of release along with variable delay in initiation of release. Therefore, the model has three parallel absorption pathways with five absorption compartments which describe the immediate pathway and a fast and a slow sustained-release pathway.

Finally, a one-compartment model with first-order elimination has been used to describe the pharmacokinetics of paliperidone after intramuscular administration of its palmitate ester.[28] The absorption component of the model allows a fraction of the dose to enter the central compartment relatively quickly via a zero-order process. After a certain lag time, the remaining fraction of the dose enters the systemic circulation via a first-order process that determines the shape of the plasma concentration-time curve following intramuscular injection.

For all the models described above, the final parameters from the published models,[24,25,28,34] including all significant subject covariates, were used for simulating the pharmacokinetic exposure for a typical subject. Drug-drug interactions were not considered as part of this simulation exercise. The implementation of these simulations in Nonmem® software, along with the respective parameter estimates, is illustrated through control streams (codes) in Appendix 1.

Model-based simulations

Previously published pharmacokinetic models for paliperidone palmitate, oral paliperidone extended-release, risperidone long-acting injection, and oral risperidone were utilized as the simulation machinery for this analysis.[24,25,28,34] Nonmem version VI (GloboMax, Icon Development Solutions, Ellicott City, MD) with an Intel Fortran 10 compiler was used to conduct all pharmacokinetic simulations. Visualization of results was performed using S-Plus® 6.0 professional release 2 software (Insightful Corporation, Seattle, WA).

Pharmacokinetic simulations were used to predict the plasma concentrations over an 8–9-week period following treatment discontinuation (scenario 1) or interruption (scenarios 2 and 3). The simulations performed in this exercise are deterministic in nature (ie, between-subject variability and residual variability were not included in the simulations because the objective of this analysis was to visualize the typical pharmacokinetic profiles under various noncompliance situations). In the case of complete treatment discontinuation for each formulation (scenario 1), the number of days until the active moiety plasma concentrations fell below 2 ng/mL was calculated. Simulated profiles for the four formulations were also used to determine the lowest concentrations due to noncompliance ($C_{min,discontinuation}$) as a percentage of the steady-state minimum concentrations ($C_{min,steady state}$) for each treatment in scenario 2 (one week of treatment interruption with reinitiation at day 7) and scenario 3 (4 weeks of treatment interruption with reinitiation at day 28).

Results
Scenario 1: complete treatment discontinuation

Following discontinuation of oral risperidone or oral paliperidone extended-release on day-1, the active-moiety concentrations decreased substantially within a few days (Figure 1). Two weeks following the last injection of risperidone long-acting injection, the concentration of the active moiety continued to approximate the steady-state concentration for about 3–5 weeks due to the delay in release (3-week lag time between last injection and last release phase). After this lag phase, there was a subsequent and rapid decline of the concentration of the active moiety , with near zero concentrations reached by week 5 (Figure 1). The slowest decline of active moiety concentration was observed with paliperidone palmitate (Figure 1).

The mean number of days needed for the active moiety plasma concentrations of each formulation to approach 2 ng/mL is depicted in Figure 2. Complete discontinuation of paliperidone palmitate resulted in a steady and slow decline of the concentration of the active moiety over the simulation period
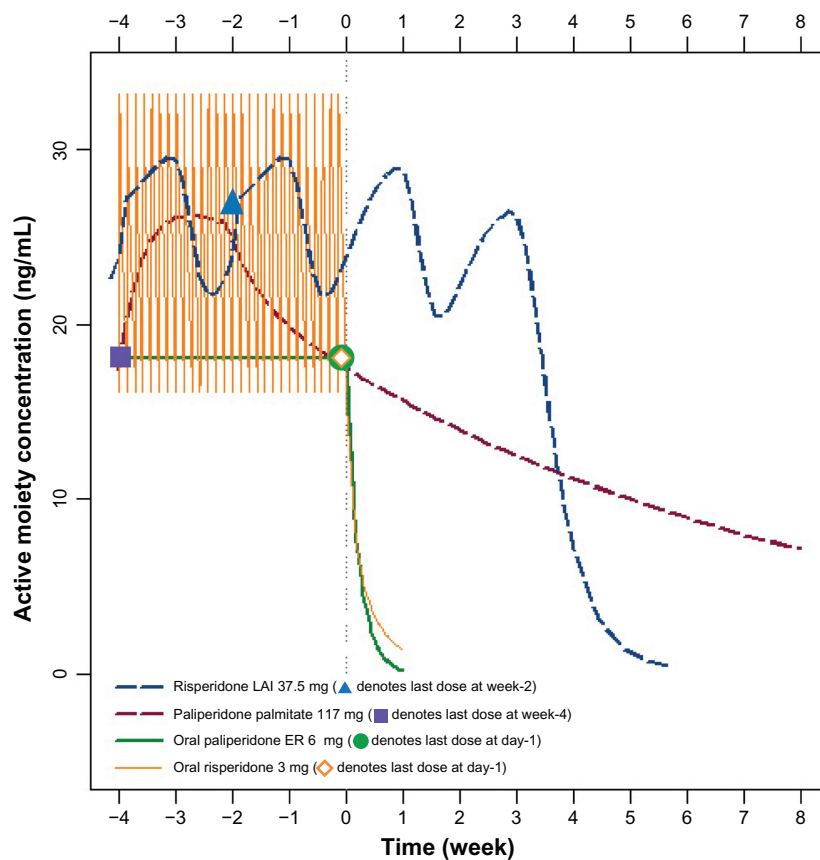
Figure 1 Active moiety concentrations following complete treatment discontinuation (week 0 denotes administration time of next scheduled dose, which was missed).
Notes: Within a few days of oral risperidone or oral paliperidone ER discontinuation, there was a substantial decrease in the concentration of the active moiety. Two weeks following the last injection of risperidone LAI, the concentration of the active moiety continued to approximate the steady-state concentration for approximately 3–4 weeks due to the delay in release (3-week lag time between last injection and last release phase). After this lag phase, there was a subsequent and rapid decline of the concentration of the active moiety, with near zero concentrations reached by week 5. As compared with the other formulations, discontinuation of paliperidone palmitate exhibited the slowest decline of the concentration of the active moiety with levels of approximately 7 ng/mL at week 8.
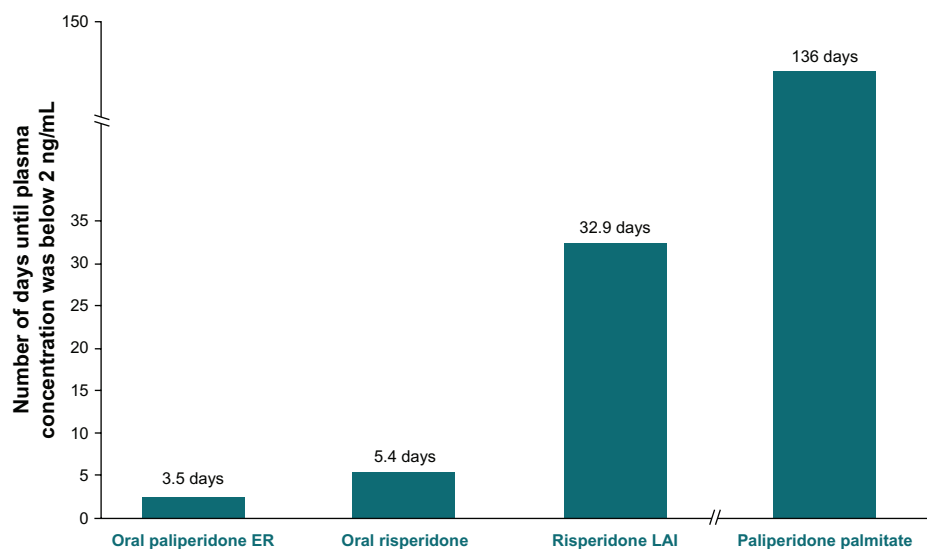**Abbreviations:** ER, extended-release; LAI, long-acting injection.

Figure 2 Number of days until active moiety plasma concentrations approach 2 ng/mL, by agent.
Notes: Following treatment discontinuation, paliperidone palmitate long-acting injectable suspension required more than 4 months (136 days) for the plasma concentrations of the active moiety to approach 2 ng/mL, with attainment of this threshold met less than one week after discontinuation of oral paliperidone ER (3.5 days) and oral risperidone (5.4 days), respectively, and approximately one month after discontinuation of risperidone LAI (32.9 days).
Abbreviations: ER, extended-release; LAI, long-acting injection.

to a concentration of 7.2 ng/mL at week 8, with this level not falling to below 2 ng/mL until day 136 (week 19.4).

Scenario 2: one week of treatment interruption

Interruption of treatment with either oral risperidone or oral paliperidone extended-release for one week resulted in concentrations of the active moiety that approached zero (Figure 3), with concentrations of the active moiety decreasing to 2%–11% of the steady-state concentration (Figure 4). Reinitiation of oral risperidone or oral paliperidone required a few days for the reattainment of steady-state concentrations of the active moiety (Figure 3).

Administration of risperidone long-acting injection at week −2 followed by a one-week interruption in the next scheduled dose affected the pharmacokinetic profile after a time delay, with concentrations of the active moiety being lower between weeks 4 and 5 despite treatment reinitiation after the one-week interruption (Figure 3). One week of interruption in risperidone long-acting injection administration was associated with a concentration of the active moiety decrease to 35% of the $C_{min,steady\ state}$ (Figure 4).

A one-week interruption in paliperidone palmitate treatment was associated with a slight decrease in concentration of the active moiety (Figure 3), with the $C_{min,discontinuation}$ reaching 90% of the $C_{min,steady\ state}$ (Figure 4).

Scenario 3: four weeks of treatment interruption

As seen with one week of treatment interruption, 4 weeks of interruption of either oral antipsychotic agent was associated with a near zero concentration of the active moiety occurring
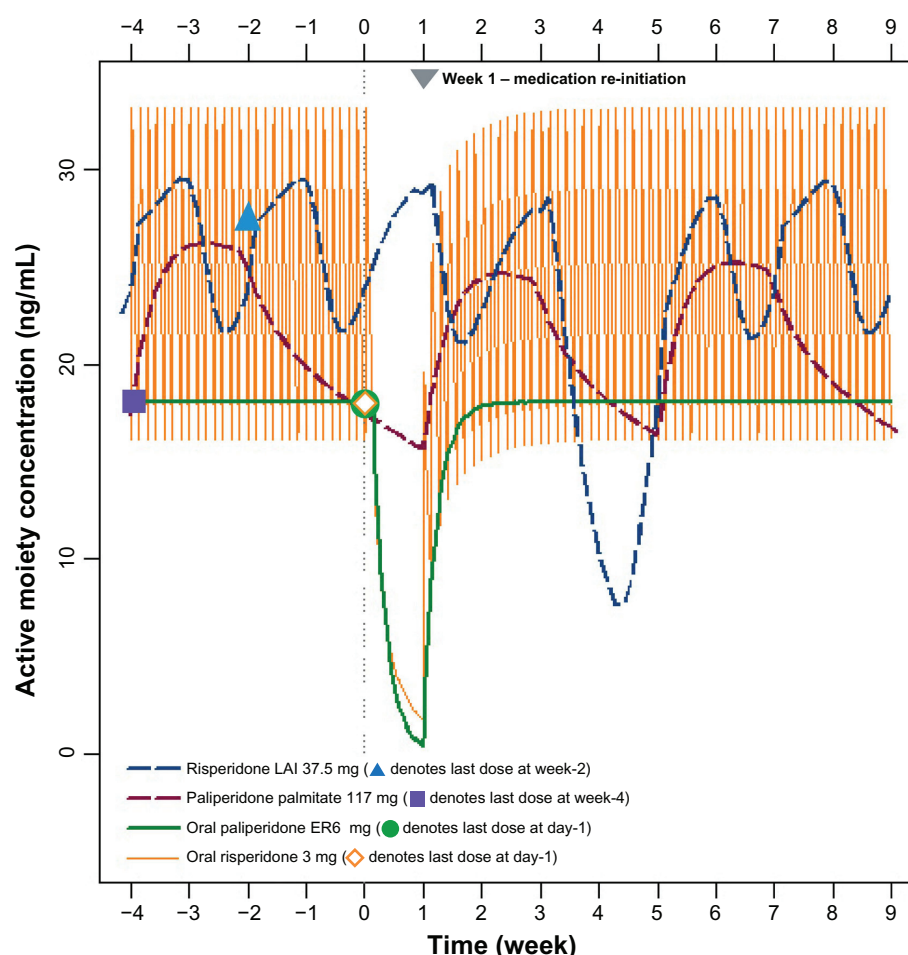

Figure 3 Active moiety concentrations following one week of treatment discontinuation (week 0 denotes administration time of next scheduled dose, which was missed).
Notes: One week of interruption of either oral risperidone or oral paliperidone ER resulted in concentrations of the active moiety that approached zero. Reinitiation of oral risperidone or oral paliperidone ER required a few days for reattainment of steady-state concentrations of the active moiety. Administration of risperidone LAI at week -2 followed by a one-week interruption in the next scheduled dose resulted in active moiety concentrations being lower between weeks 4 and 5 despite treatment reinitiation at week 1. A one-week interruption in paliperidone palmitate administration was associated with a slight decrease in active-moiety concentration, with one reinitiation dose producing a re-establishment of a near steady-state concentration.
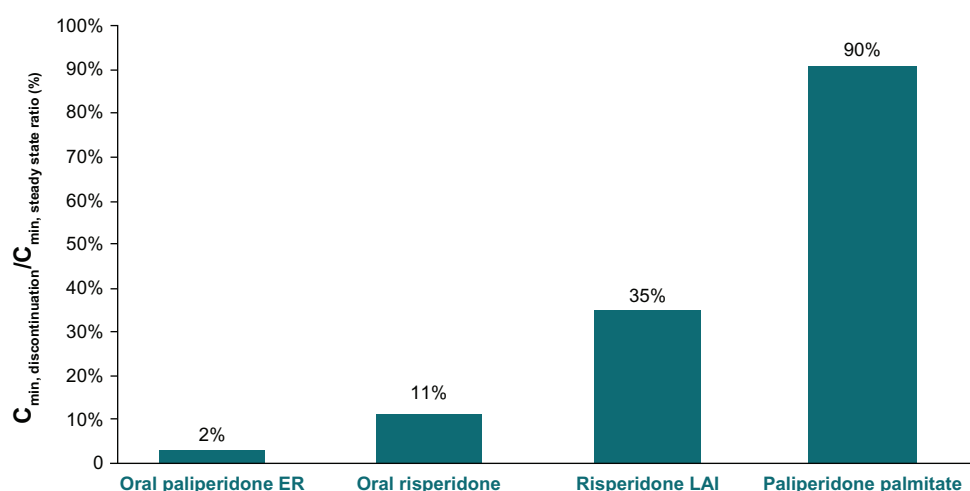**Abbreviations:** ER, extended-release; LAI, long-acting injection.

Figure 4 Lowest plasma concentration after one week of treatment discontinuation versus steady-state minimum concentration.
Notes: One week of interruption of either oral risperidone or oral paliperidone ER resulted in the concentrations of the active moiety decreasing to 2%–11% of the steady-state concentration. One week of interruption in risperidone LAI administration was associated with an active moiety concentration decrease to 35% of the steady-state minimum concentration. A one-week interruption in paliperidone palmitate treatment resulted in the plasma concentration being maintained at approximately 90% of the steady-state minimum concentration.
Abbreviations: ER, extended-release; LAI, long-acting injection.

within a few days of treatment interruption (Figures 5 and 6). Following reinitiation, steady-state concentrations of the active moiety were re-established in approximately one week (Figure 5).

Four weeks of interruption in risperidone long-acting injection administration resulted in the active moiety plasma concentration decreasing to approximately 7.2 ng/mL at the end of week 4 (Figure 5). The active moiety plasma concentration in the risperidone long-acting injection group decreased to approximately 33% of the $C_{min,steady\ state}$ concentration (Figure 6). Reinitiation of risperidone long-acting injection 37.5 mg at weeks 4 and 6, with oral risperidone 3 mg once daily supplementation during weeks 4–7, resulted in a re-establishment of concentrations of the active moiety within a few days. However, as depicted in Figure 5, the concentration of the active moiety exhibits another decline between weeks 7 and 8 because the delayed release of risperidone long-acting injection does not begin until week 7, while the risperidone from the oral supplementation rapidly washes out of the systemic circulation (ie, washout of risperidone from oral supplementation is much faster than the rise in concentrations from the reinitiation doses of risperidone long-acting injection).

Four weeks after the last administered dose of paliperidone palmitate, the concentrations of the active moiety continued a slow, steady decline (Figure 5), with the minimum concentration during this discontinuation period decreasing to 64% of the steady-state minimum concentration (Figure 6). Reinitiation of paliperidone palmitate (117 mg [75 mg eq]

on days 28 and 35), without oral supplementation, produced a rapid reattainment of active moiety plasma concentrations (Figure 5).

Discussion

The three scenarios depicted in these pharmacokinetic model-based simulations approximate those that may be seen in clinical practice (ie, patients forgetting to take their oral dose[s] of antipsychotic medication or failing to return for their next injection of long-acting injection antipsychotic). The model-based simulations visually depict what would be anticipated to occur following complete treatment discontinuation or periods of treatment interruption. The long half-lives of the long-acting injectable agents may offer a longer time to subtherapeutic active moiety plasma concentrations and pharmacodynamically related symptom recurrence in those who fail to return for their next scheduled injection. As anticipated, paliperidone palmitate, a long-acting injectable antipsychotic with one of the longest half-lives, demonstrated the slowest decline in plasma concentrations.[28,34,35]

Antipsychotic pharmacokinetic profiles are generally reported from carefully controlled single-dose and multiple-dose studies. Clinical situations of nonadherence are difficult to study in clinical trials for ethical reasons, but the resulting plasma levels can be simulated using model-based tools. This analysis provides mathematically predicted profiles of antipsychotic plasma levels in clinical situations with the objective of aiding caregivers and patients by helping them make informed decisions regarding treatment nonadherence.
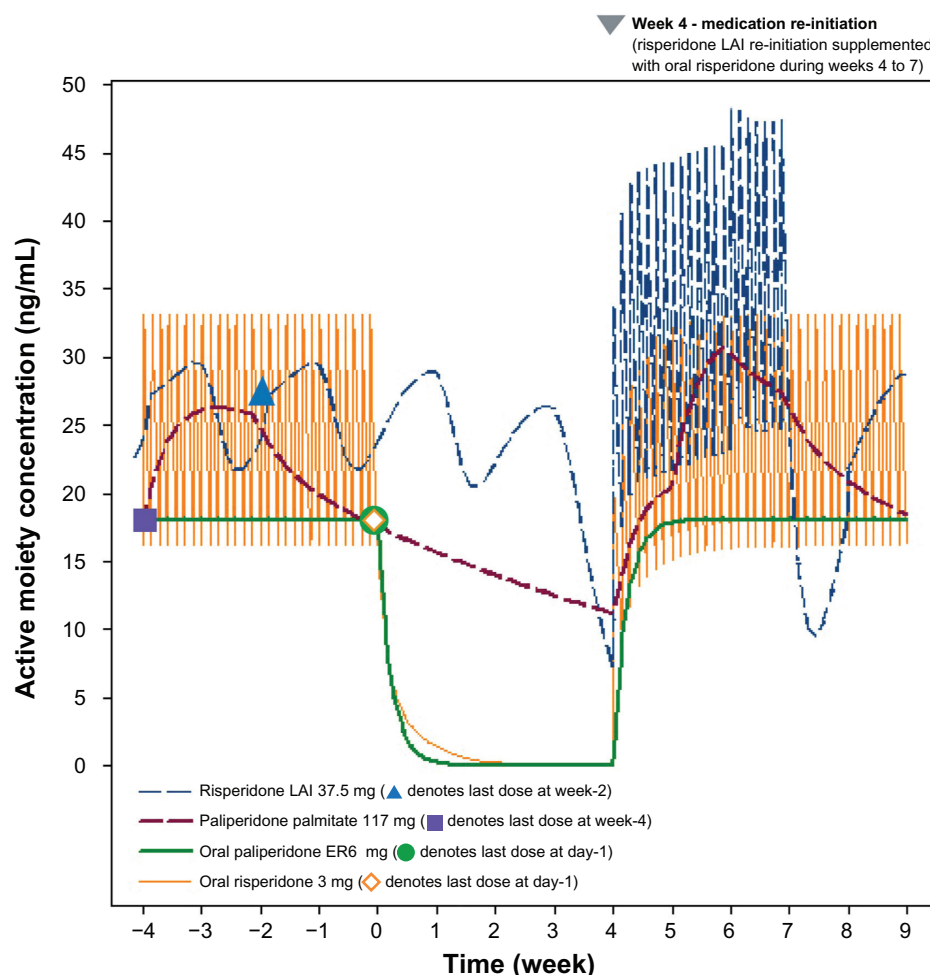
Figure 5 Active moiety concentrations following a 4-week treatment interruption and reinitiation (week 0 denotes administration time of next scheduled dose, which was missed).

Notes: Four weeks of interruption of either oral antipsychotic agent, risperidone or paliperidone, was associated with a near zero active moiety concentration, with these near zero levels occurring within a few days of treatment interruption. Following reinitiation, steady-state concentrations of the active moiety were re-established in approximately one week. Four weeks of interruption in risperidone LAI administration (ie, 6 weeks following the last administered dose) resulted in the plasma concentration of the active moiety decreasing to approximately 7.2 ng/mL at week 4. Reinitiation of risperidone LAI 37.5 mg at weeks 4 and 6, with oral risperidone 3 mg once-daily supplementation during weeks 4–7 resulted in a re-establishment of concentrations of the active moiety within a few days. However, due to the delayed-release characteristics of risperidone LAI, the active moiety concentration exhibits another decline between weeks 7 and 8. Four weeks after the last administered dose of paliperidone palmitate, the concentrations of the active moiety continued a slow, steady decline. Reinitiation of paliperidone palmitate (117 mg [75 mg eq] on days 28 and 35), without oral supplementation, produced a rapid reattainment of active moiety plasma concentrations.

Abbreviations: ER, extended-release; LAI, long-acting injection.

This is particularly important for the new long-acting injections because their mode of delivery and pharmacokinetics are designed to be different from the oral drugs and older intramuscular depot formulations. The three main scenarios assessed were complete discontinuation, short-term interruption, and longer-term interruption. Each scenario provides useful insight about consequences of nonadherence, ie, the treatment discontinuation scenarios help with the assessment of the magnitude of time that patients can go without a dose, until their concentrations reach a critical threshold at which response could be compromised (ie, the drug's "forgiveness"). The discontinuation assessments indicate that following treatment discontinuation, paliperidone palmitate

long-acting injection requires more than 4 months to approach a critical threshold of 2 ng/mL, while this threshold was reached in less than one week after discontinuation of oral paliperidone extended-release and oral risperidone, and approximately one month after discontinuation of risperidone long-acting injection (Figure 2). The short-term and longer-term interruption scenarios suggest that managing the possible clinical effects of nonadherence with risperidone long-acting injection may not be easy, because the effect of even a single delayed dose may not be evident for 4–5 weeks due to its complex absorption kinetics. Because these delayed changes in drug levels may affect drug efficacy, caregivers need to be aware of the 3-week lag time between injection
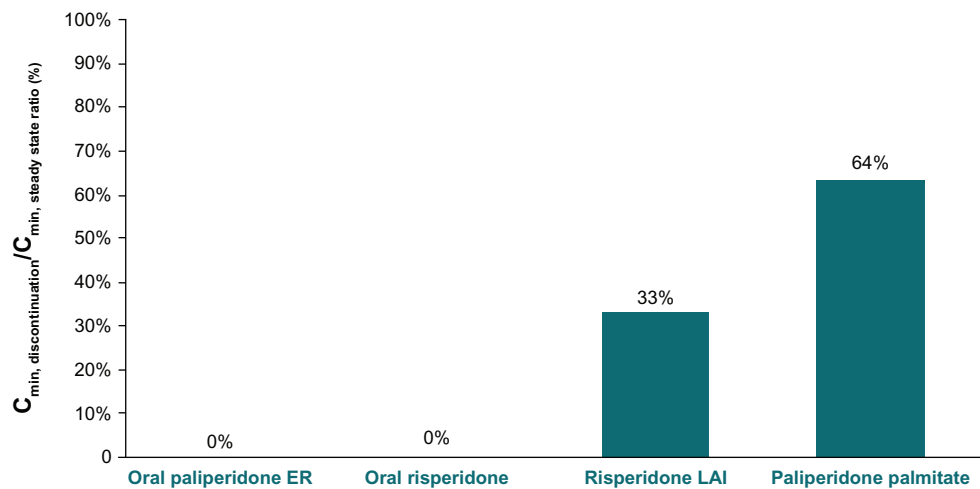
Figure 6 Lowest plasma concentration after 4 weeks of treatment discontinuation versus steady-state minimum concentration (%).
Notes: Four weeks of interruption of either oral antipsychotic agent, risperidone or paliperidone, was associated with zero concentration of the active moiety. The plasma concentration of the active moiety in the risperidone LAI group decreased to approximately 33% of the steady-state minimum concentration following 4 weeks of treatment discontinuation. Four weeks after the last administered dose of paliperidone palmitate the minimum active moiety concentration decreased to 64% of the steady-state minimum concentration.
Abbreviations: ER, extended-release; LAI, long-acting injection.

and drug release for risperidone long-acting injection. This lag time makes it difficult to anticipate the pharmacokinetic profile for risperidone long-acting injection during situations of nonadherence and the graphical representations provided in the current analysis can serve as a useful visual aid. Finally, longer-term interruptions require reinitiation methods that are specific to each drug, and paliperidone palmitate long-acting injection allows a simple two-dose reinitiation strategy without the need for oral supplementation.

The reinitiation of antipsychotic treatment in the scenarios that simulated a one-week or 4-week lapse in treatment adherence, especially in cases of long-acting injection treatment, poses challenges. Reinitiation of oral agents is straightforward because it resembles de novo treatment but attainment of therapeutic levels takes up to one week. In the case of long-acting injectable agents, it is desirable to attain therapeutic plasma levels quickly; however, reinitiation scenarios, such as with risperidone long-acting injection, which require oral supplementation for the first 3 weeks, are to some extent more complex. Discontinuation or interruption of risperidone long-acting injection is associated with a delay in the time for plasma concentrations to decrease, with the effect of these scenarios being depicted graphically. These delays may represent a time window for clinicians to intervene in the event of nonadherence to manage the delayed decreases in plasma concentration with oral supplementation. It is worth noting that oral supplementation during reinitiation has not been tested in clinical trials. The sustained concentrations of paliperidone in the 4-week interruption simulation using

paliperidone palmitate resulted in $C_{min,discontinuation}$ of 64% of $C_{min,steady state}$ 4 weeks after the missed injection. The clinical effect of these concentrations is uncertain. However, as noted by some, the long time to symptom recurrence among patients administered paliperidone palmitate who were then switched to placebo in relapse prevention studies suggests that the long half-life for paliperidone palmitate may allow more time to follow-up if a dose is delayed.[19] Furthermore, steady-state paliperidone concentrations can be rapidly re-established in this scenario using the recommended reinitiation strategy (administration of two paliperidone palmitate injections, each at the last administered dose and given one week apart, at weeks 4 and 5).[29]

Limitations of the simulations for these potential clinical scenarios are that they are model-based and that changes in active moiety plasma concentrations do not necessarily correlate strongly with pharmacodynamic changes in the efficacy or safety of an antipsychotic. However, these pharmacokinetic model-based simulations suggest that long-acting injectable formulations of antipsychotic agents offer at least a pharmacokinetic benefit in patients who are suspected of or have demonstrated incomplete medication adherence behavior. The more sustained plasma concentrations of long-acting injections may provide a wider window of opportunity to re-establish treatment without symptom recurrence or relapse compared with oral antipsychotics. Among long-acting injections, paliperidone palmitate has one of the longest apparent half-lives, and therefore may provide a longer dosing window for follow-up if a dose is delayed.

Reinitiation of paliperidone palmitate is relatively easy, with steady-state plasma concentrations rapidly reattained following administration of one dose in cases of one week of treatment interruption or two doses given one week apart in cases of 4 weeks of treatment interruption.

Disclosures

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Appendix 1
NONMEM® control streams (codes) with parameter estimates used for simulations
NONMEM® control stream for oral risperidone

```
$PROBLEM ORAL RISPERIDONE CODE
; REFERENCE: AUTHORS. THYSSEN A, VERMEULEN A, FUSEAU E, ET AL.
; REFERENCE: JOURNAL. CLIN PHARMACOKINET 2010;49:465-478

$INPUT ID TIME AMT DV CMT
$DATA a1-oral-ris.csv IGNORE = #
$SUBROUTINES ADVAN4 TRANS4

$PK
CALLFL = -2
;TYPICAL SUBJECT HAS CRCL OF 110.6 ML/MIN; WEIGHT OF 79.5 KG; and 42 YRs OF AGE

TRM1 = 0.00831*110.6                    ; CRCL ON ELIMINATION CLEARANCE
TRM2 = 4.66*((79.5/70)**0.75)           ; WGT ON ELIMINATION CLEARANCE
TVCL = (TRM1+TRM2)*((42/18.1)**(-0.172))  ; AGE ON ELIMINATION CLEARANCE
CL = TVCL                               ; ELIMINATION CLEARANCE L/HR

Q = 1.35           ; INTERCOMPARTMENTAL CLEARANCE, L/HR
V2 = 137*(79.5/70) ; CENTRAL VOLUME(L). VOLUME INFLUENCED BY BODY WEIGHT
V3 = 86.8*(79.5/70) ; PERIPHERAL VOLUME (L). VOLUME INFLUENCED BY WEIGHT
ALAG1 = 0.235      ; ABSORPTION LAG TIME IN HOURS
KA = THETA(1)      ; ABSORPTION RATE CONSTANT
S2 = V2/1000       ; SCALING FACTOR CONVERT DOSE(MG) and VOLUME(L) TO NG/ML

$ERROR
CALLFL = 0
IPRE = -5
IF (F.GT.0) IPRE = LOG(F)
Y = IPRE + ERR(1)

$THETA 2.39 ; KA (1/HR). NONMEM REQUIRES AT LEAST 1 THETA
$OMEGA 0.27 ; RESIDUAL ERROR VARIANCE. SINGLE SUBJECT SIMULATION

$SIMULATION (9215693) ONLYSIM

$TABLE ID TIME AMT IPRE
ONEHEADER NOPRINT NOAPPEND FILE = TABLE-ORAL-RIS.TXT
```

NONMEM® control stream for extended release oral paliperidone

```
$PROBLEM EXTENDED RELEASE ORAL PALIPERIDONE
; REFERENCE: AUTHORS. CIRINCIONE B, REDMAN M, FIEDLER-KELLEY J, ET AL.
; REFERENCE: JOURNAL. CLIN PHARMACOL THER 2007;81:S19.
```

```
$INPUT ID TIME DV AMT RATE CMT

$DATA a2-oral-pali.csv IGNORE = #
$SUBROUTINE ADVAN4 TRANS4

$PK
CALLFL = -2
; COVARIATES FOR A TYPICAL MALE SUBJECT
CRCL = 110.6 ; CREATININE CLEARANCE (ML/MIN)
WGT = 79.5   ; WEIGHT IN KG
HGT = 172    ; HEIGHT IN CM


LBM = (1.10*WGT)-(128*((WGT**2)/(HGT**2))) ; COMPUTE LEAN BODY MASS
CLBM = LBM/58.4
TVCL = THETA(1)*CLBM**THETA(9)+THETA(8)*CRCL
CL = TVCL


V2 = THETA(2)
Q = THETA(3)
V3 = THETA(4)
KA = THETA(5)
D1 = THETA(6)      ; MODEL DURATION, RATE = -2 IN THE DATASET A2-ORAL-PALI.CSV
ALAG1 = THETA(7)
S2 = V2/1000       ; SCALING FACTOR. CONVERT DOSE (MG) AND VOLUME (L) TO NG/ML

$ERROR
CALLFL = 0
IPRE = -5
IF (F.GT.0) IPRE = LOG(F)
Y = IPRE + ERR(1)


$THETA
8.02   ; THETA 1: CL (L/HR) ELIMINATION CLEARANCE
260    ; THETA 2: V2 (L) VOLUME OF DISTRIBUTION CENTRAL COMPARTMENT
34.5   ; THETA 3: Q (L/HR) CENTRAL TO THE 1ST PERIPHERAL COMPARTMENT
227    ; THETA 4: V3 (L) VOLUME OF DISTRIBUTION FOR PERIPHERAL COMPARTMENT
0.565  ; THETA 5: KA (1/HR) ABSORPTION RATE CONSTANT
23.9   ; THETA 6: D1 (HR) DURATION OF THE ZERO-ORDER PROCESS
0.668  ; THETA 7: ALAG1 (HR) ABSORPTION LAG TIME
0.0512 ; THETA 8: THETA(8)*CRCLA. CRCL IMPACT ON CL (LINEAR RELATIONSHIP)
0.636  ; THETA 9: CLBM^THETA(9). LEAN BODY MASS EFFECT ON CL (POWER FUNCTION)

$OMEGA 0.0466 ; RESIDUAL ERROR VARIANCE. SINGLE SUBJECT SIMULATION

$SIMULATION (9215693) ONLYSIM

$TABLE ID TIME AMT IPRE
ONEHEADER NOPRINT NOAPPEND FILE = TABLE-ORAL-PALI.TXT
```

NONMEM® control stream for risperidone LAI

```
$PROBLEM RISPERIDONE LAI
; REFERENCE: AUTHORS. SAMTANI MN, GOPAL S, SLIWA JK, ET AL.
; REFERENCE: POSTER PRESENTED AT PAGE; BERLIN, GERMANY, JUNE 8-10, 2010.
; REFERENCE: PAGE 19 (2010) Abstr 1839 [http://www.page-meeting.org/?abstract=1839]
Samtani et al. CNS Drugs. 2011;25(10):829-45.

$INPUT ID TIME AMT CMT RATE DV
$DATA a4-ris-consta.csv IGNORE = #
$SUB ADVAN5

$MODEL
COMP = (DOSE1)
COMP = (DOSE2)
COMP = (DOSE3)
COMP = (INTER1)
COMP = (INTER2)
COMP = (CENTRAL DEFOBS)

$PK
CALLFL = -2

CL = 4.25              ; ELIMINATION CLEARANCE (L/HR)
V6 = 244.66            ; CENTRAL VOLUME (L)
KA1 = 10.775           ; ABSORPTION RATE CONSTANTS (1/HR) 1ST PROCESS
KA2 = 0.005            ; ABSORPTION RATE CONSTANTS (1/HR) 2 ND PROCESS
KA3 = 0.023            ; ABSORPTION RATE CONSTANTS (1/HR) 3RD PROCESS
F1 = 0.0215            ; FRACTION OF DOSE ABSORBED VIA 1ST PROCESS
F3 = 0.78             ; FRACTION OF DOSE ABSORBED VIA 3RD PROCESS
F2 = THETA(1)-F1-F3   ; FRACTION OF DOSE ABSORBED VIA 2 ND PROCESS
ALAG2 = 8.465         ; LAG TIME (HR) SECOND PROCESS
ALAG3 = 543.19        ; LAG TIME (HR) THIRD PROCESS
D2 = 416.695          ; DURATION (HR) OF ZERO ORDER INPUT, 2 ND PROCESS
D3 = 271.535          ; DURATION (HR) OF ZERO ORDER INPUT, 3RD PROCESS
S6 = V6/1000          ; CONVERT DOSE (MG) and VOLUME (L) TO NG/ML

K16 = KA1
K24 = KA2
K46 = KA2
K35 = KA3
K56 = KA3
K60 = CL/V6

$ERROR
CALLFL = 0
IPRE = -5
IF (F.GT.0) IPRE = LOG(F)
Y = IPRE+ERR(1)
```

```
$THETA 1    ; SUM OF F1+F2+F3. NONMEM REQUIRES AT LEAST 1 THETA
$OMEGA 0.04 ; RESIDUAL ERROR VARIANCE. SINGLE SUBJECT SIMULATION


$SIMULATION (9215693) ONLYSIM
$TABLE ID TIME AMT IPRE
ONEHEADER NOPRINT NOAPPEND FILE = TABLE-RIS-CONSTA.TXT
```

NONMEM® control stream for paliperidone palmitate

```
$PROBLEM PALI PALMITATE SIMULATION
; REFERENCE: Samtani A, Vermeulen A, Stuyckens K. Clin PK 2009;48:585-600.
$INPUT ID TIME DV AMT CMT RATE
$DATA a3-PALI-PALMITATE.csv IGNORE = #
$SUBROUTINE ADVAN2 TRANS2


$PK
CALLFL = -2
AGE = 42     ; AGE (YR) FOR A TYPICAL MALE SUBJECT
BMI = 26.787 ; BODY MASS INDEX (KG/M²) FOR A TYPICAL MALE SUBJECT
CRCL = 110.6 ; CREATININE CLEARANCE (ML/MIN) FOR A TYPICAL MALE SUBJECT
IVOL = 0.75  ; INJECTION VOLUME FOR 75 MG EQ. DOSE
CL = THETA(1)*((CRCL/110.6)**THETA(2))
V = THETA(3)*((BMI/26.787)**THETA(4))
TR1 = THETA(5)
TR2 = (THETA(6)/1000)*((AGE/42)**THETA(7))
TR3 = IVOL**(-THETA(8))
KA = TR1*TR2*TR3
DUR = THETA(9)
D2 = DUR
D1 = 0.00001
ALAG1 = DUR
TER1 = THETA(10)
TER2 = THETA(11)*((BMI/26.787)**(-THETA(12)))
TER3 = IVOL**(-THETA(13))
F2 = TER1*TER2*TER3
F1 = 1-F2
S2 = V/1000 ; SCALING FACTOR. CONVERT DOSE (MG) AND VOLUME (L) TO NG/ML


$ERROR
CALLFL = 0
IPRE = -5
IF (F.GT.0) IPRE = LOG(F)
Y = IPRE + ERR(1)


$THETA
4.95  ; THETA 1 : CL, CLEARANCE (L/HR)
0.376 ; THETA 2 : CRCL EFFECT ON CL (POWER FUNCTION)
391   ; THETA 3 : V, VOLUME OF DISTRIBUTION (L)
0.889 ; THETA 4 : BMI EFFECT ON V (POWER FUNCTION)
```

```
1.23  ; THETA 5 : DELTOID INJECTION EFFECT ON KA (SHIFT FACTOR)
0.488 ; THETA 6 : KA X 10^3, ABSORPTION RATE CONSTANT (1/HR)
0.311 ; THETA 7 : AGE EFFECT ON KA (POWER FUNCTION)
0.359 ; THETA 8 : INJECTION VOLUME EFFECT ON KA (EXPONENT)
319   ; THETA 9 : ALAG1 and D2, ABSORPTION LAG and ZERO ORDER INPUT DURATION (HR)
1.37  ; THETA 10: DELTOID INJECTION EFFECT ON F2 (SHIFT FACTOR)
0.168 ; THETA 11: F2, FRACTION ABSORBED BY ZERO ORDER PROCESS
0.642 ; THETA 12: BMI EFFECT ON F2 (POWER FUNCTION)
0.288 ; THETA 13: INJECTION VOLUME EFFECT ON F2 (EXPONENT)
$OMEGA 0.0494   ; RESIDUAL ERROR VARIANCE. SINGLE SUBJECT SIMULATION

$SIMULATION (9215693) ONLYSIM
$TABLE ID TIME AMT IPRE
ONEHEADER NOPRINT NOAPPEND FILE = TABLE-PALI-PALMITATE.TXT
```