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Population Pharmacokinetic Modeling and Simulation of TV-46000: A Long-Acting Injectable Formulation of Risperidone

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Abstract

TV-46000 is a long-acting subcutaneous antipsychotic that uses a novel copolymer drug delivery technology in combination with a well-characterized molecule, risperidone, that is in clinical development as a treatment for schizophrenia. A population pharmacokinetic (PPK) modeling and simulation approach was implemented to identify TV-46000 doses and dosing schedules for clinical development that would provide the best balance between clinical efficacy and safety. The PPK model was created by applying pharmacokinetic data from a phase 1 study of 97 patients with a diagnosis of schizophrenia or schizoaffective disorder who received either single or repeated doses of TV-46000. The PPK model was used to characterize the complex release profile of the total active moiety (TAM; the sum of the risperidone and 9-OH risperidone concentrations) concentration following subcutaneous injections of TV-46000. The PK profile was best described by a double Weibull function of the in vivo release rate and by a 2-compartment disposition and elimination model. Simulations were performed to determine TV-46000 doses and dosing schedules that maintained a median profile of TAM concentrations similar to published TAM exposure following oral risperidone doses that have been correlated to a 40% to 80% dopamine-D2 receptor occupancy therapeutic window. The simulations showed that therapeutic dose ranges for TV-46000 are 50 to 125 mg for once-monthly and 100 to 250 mg for the once every 2 months regimens. This PPK model provided a basis for prediction of patient-specific exposure and dopamine-D2 receptor occupancy estimates to support further clinical development and dose selection for the phase 3 studies.

Keywords

dose selection, LAI, long-acting injectable, modeling and simulations, population pharmacokinetics, risperidone, schizophrenia, TV-46000

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Schizophrenia is a severely debilitating psychotic disorder characterized by positive symptoms (eg, delusions, hallucinations, and grossly disorganized or catatonic behavior) and negative symptoms (eg, affective flattening, alogia, and avolition).[1] Cognitive deficits are common; they include impairment of executive functioning and attention, as well as difficulties with short- and long-term memory. The worldwide lifetime morbidity risk of the disorder is about 1% across diverse geographic, cultural, and socioeconomic regions.[2] As the disease in most patients follows a chronic course with long-lasting impairment, long-term treatment with antipsychotic agents is necessary. Second-generation antipsychotics, such as oral risperidone, are currently the standard of care and treat positive symptoms, but do not adequately reduce negative and cognitive symptoms, and nonadherence and adverse events remain challenges.[3] Nonadherence to long-term oral medication regimen is one of the most significant therapeutic issues in the treatment of schizophrenia and related disorders. Consequently, many patients do not experience the full benefit of antipsychotic drug therapy and have frequent relapses and exacerbations that often require hospitalization.[4] The use of a long-acting injectable (LAI) antipsychotic agent could increase compliance in patients with schizophrenia.[5,6] In addition, evidence supported by neuroimaging suggests that the early use of LAI risperidone may improve clinical outcomes in patients with schizophrenia.[7–10]

LAI antipsychotic treatments are underused.[11,12] Most clinical practice guidelines recommend the use of LAI antipsychotics only in patients who are noncompliant with oral therapy, have frequent recurrence of schizophrenic symptoms, or simply prefer this route of administration.[13] With each relapse of schizophrenia leading to a further decrease in a patient's level of mental and functional status, an added value of a long-acting agent includes stabilization of the disorder and prevention of further mental and functional decline.

TV-46000 was developed as a long-acting subcutaneous antipsychotic that uses a novel copolymer drug delivery technology,[14] in combination with a well-characterized molecule, risperidone. Upon subcutaneous (SC) administration of TV-46000, a solvent exchange process begins between the solvent and its aqueous SC fluid, resulting in precipitation of the copolymers with entrapment of drug within the depot that is formed under the subcutaneous milieu. The depot slowly degrades through hydrolysis of the copolymers' ester bonds, ensuring maintenance of therapeutic risperidone concentrations in the bloodstream over an extended period of 1 or 2 months dependent on the injected volume.

This population pharmacokinetic (PPK) modeling and simulation activity was conducted to identify TV-46000 dose regimens for the phase 3 clinical development program. The objective was to determine dose regimens that would enable the best balance between clinical efficacy (symptom and functional improvement) and safety (eg, minimal extrapyramidal symptoms). Current research supports a therapeutic window of dopamine-D2 receptor occupancy (D2RO) levels in the striatum following dosing by antipsychotic drugs that should lay between 40% and 80% for optimal antipsychotic effect and minimal side effects.[15–18] The lower occupancy threshold is required for clinical efficacy, whereas exceeding the higher threshold may lead to an increased risk of side effects such as extrapyramidal symptoms. The clinical effects, including safety and efficacy of TV-46000 are thought to derive from both the parent molecule, risperidone, and its primary active metabolite, 9-hydroxyrisperidone (9-OH risperidone), both of which have similar pharmacological activity. The plasma concentration of the total active moiety (TAM) is calculated as the sum of risperidone and 9-OH risperidone plasma concentrations corrected by their respective molecular weights. TAM levels in the plasma directly correlate to the D2RO.[19] The model-based approach used for TV-46000 was similar to the one recently deployed for another new, long-acting, sustained-released formulation of risperidone.[20,21]

The PPK model was developed to provide a comprehensive description of the absorption, disposition, and elimination of TAM after SC injections of multiple doses of TV-46000 and includes an assessment of the influence of key covariates on these pharmacokinetic (PK) parameters. The model applied PK data from a phase 1 study in patients with a diagnosis of schizophrenia or schizoaffective disorder who were given single or multiple doses of TV-46000. The model simulated possible dose regimens for TV-46000 that maintained the median profile of TAM concentrations within the therapeutic window for D2RO as previously described.[19,22] The final PPK model provided a basis for prediction of patient-specific exposure and D2RO estimates to support further phase 3 clinical development.

Methods

Data

The PK data collected in study TV-46000-SAD-10055 were used to build the PPK model. The study was an open-label, single- and multiple-dose, adaptive phase 1 study in sequential groups of patients with a diagnosis of schizophrenia or schizoaffective disorder to evaluate the safety, tolerability, and PK of TV-46000. The study protocols were approved by the Schuluman Associates Institutional Review Board, Inc. (Cincinnati, Ohio), and the study was conducted in accordance with the ethical principles described in the Declaration of

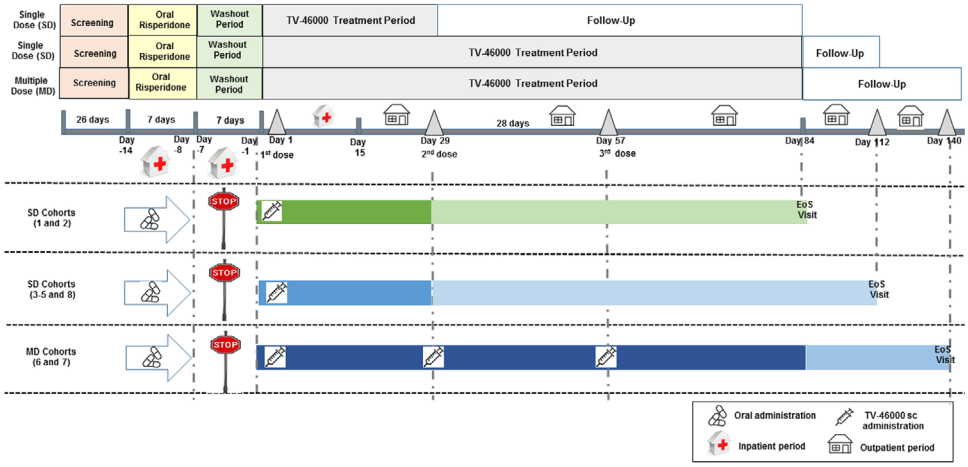

Figure 1. Single-ascending dose/multiple-ascending dose study scheme. EoS, end of study.

Helsinki, Good Clinical Practice guidelines, and any conditions required by a regulatory authority and the institutional review board. All study participants provided written informed consent. Study sites included PRA-EDS (Marlton, New Jersey; principal investigator, David Krefer, DO), Atlanta Center for Medical Research (Atlanta Georgia; principal investigator, Robert Riesenberg, MD), and California Neuropsychopharmacology Clinical Research Institute (San Diego, California; principal investigator, James Y. Chen, MD, PhD).

Study participants (N = 99) were clinically stable patients who were not currently on an antipsychotic treatment other than oral risperidone. Potential patients were screened against the inclusion and exclusion criteria, and eligible patients were randomly assigned to either a cohort with n = 12 (cohorts 1-7) or a cohort with n = 15 (cohort 8). The oral and SC injection dosing regimens for each cohort were as follows, respectively: cohort 1, 2 mg/day orally and 50 mg/month given as a single SC dose; cohort 2, 2 mg/day orally and 75 mg/month given as a single SC dose; cohort 3, 3 mg/day orally and 100 mg/month given as a single SC dose; cohort 4, 4 mg/day orally and 150 mg/month given as a single SC dose; cohort 5, 6 mg/day orally and 225 mg/month given as a single SC dose; cohort 6, 3 mg/day orally and 75 mg/month given 3 times as SC dose; cohort 7, 5 mg/day orally and 150 mg/month given 3 times as an SC dose, cohort 8, 5 mg/day orally and 225 mg/month given as a single SC dose. The SC injections were administered in the abdomen for cohorts 1 through 7 and in the upper arm for cohort 8. The study scheme as shown in Figure 1 consisted of a screening period of up to 26 days; an inpatient oral risperidone period of 7 days followed by a 7-day inpatient washout period; an inpatient and outpatient TV-46000 treatment period of up to ≈4 weeks (cohorts 1 and 2) or up to 12 weeks (cohorts 3-8); and a follow-up period of ≈8 weeks (cohorts 1, 2, 6, and 7) or 4 weeks (cohorts 3, 4, 5, and 8) that included PK blood sample collections, safety assessments, and an end-of-study visit.

Treatment

Oral risperidone (ZyGenerics, Pennington, New Jersey) was administered as a capsule (2-6 mg daily) during the oral risperidone period (study days –14 to –8). Patients on a stable dose of oral risperidone that corresponded to the intended study oral dose continued with their current oral risperidone dose during the oral risperidone period. Patients on a stable dose of oral risperidone other than their intended study oral dose were switched to oral risperidone at the intended oral dose (2-6 mg daily). Efforts were made to allocate patients to dose groups that matched their stable oral dose. The intended oral risperidone dose was selected for each cohort to match the anticipated maximum exposure upon TV-46000 dose administration.

Doses of TV-46000 and administration regimens were chosen on the basis of previous exposure results from an earlier pilot pharmacokinetic study in healthy volunteers that used subtherapeutic doses (Study RISPE1ZG15EU, Teva data on file). TV-46000 was supplied as ready-to-use white opaque injectable suspension in a refrigerated single-use 2-mL glass vial containing 30% w/w risperidone. The glass vial was closed with a rubber stopper and sealed with a seal cap. Thereafter, the appropriate volume was withdrawn into the treatment syringe. Each syringe was prepared immediately before dosing and was administered by the same medical technician at each site. The 3 administrations to each of the patients in cohorts 6 and 7 were administered in a randomized fashion on opposite sides of the abdomen (ie, left, right, left or vice versa).

During the oral risperidone washout, TV-46000 treatment, and follow-up periods, rescue medications such as lorazepam and zolpidem and oral

antipsychotics (excluding risperidone) that do not interfere with metabolism of risperidone could be added as deemed necessary by the investigator.

Pharmacokinetic Sampling and Concentration Level Determination

Blood samples for PK measures were collected at multiple predose and postdose time points as described for each of the cohorts in the Supplemental Methods. The blood samples were collected into 2-mL dipotassium ethylenediaminetetraacetic acid tubes, which were immediately stored on ice and processed within 30 minutes of collection by centrifugation at 1500 *g* for 10 minutes at 5°C. The resultant plasma was transferred into 2 appropriately labeled 2-mL screw-capped polypropylene cryovials, the primary tube contained at least 0.5 mL of plasma. Samples were frozen within 60 minutes of collection and stored at –70°C or below until they were shipped to Teva Pharmaceuticals Ltd. (Debrecen, Hungary) for the analysis of risperidone and its active metabolite, 9-OH risperidone.

Risperidone and 9-OH risperidone, were quantified in human dipotassium ethylenediaminetetraacetic acid plasma using protein precipitation with acetonitrile followed by reversed-phase high-performance liquid chromatography–tandem mass spectrometric detection using validated bioanalytical methods. The high-performance liquid chromatography column was XBridge C18, 2.1 × 100 mm, 3.5 μm (Waters Corp., Milford, Massachusetts). Solutions for mobile phase included Solution A, 5 mM of ammonium acetate in water, pH = 4; and Solution B, 500 mL of methanol and 500 mL of acetonitrile with 1000 mL of water. Qtrap4000 liquid chromatography–tandem mass spectrometry (SCIEX, Framingham, Massachusetts) in multiple reaction monitoring mode was used for monitoring the concentration levels of risperidone and 9-OH risperidone in plasma samples. The following ion transitions (Q1-Q3 m/z values) were monitored: for risperidone, 411-191; and for 9-OH risperidone, 427-207. The isotope labeled internal standards were monitored as follows: risperidone-D4, 415-195; and 9-OH risperidone-D4, 431-211. Electrospray ionization in positive mode was used with the following parameters: ion source temperature was 600°C, ion spray voltage was 3500 V, declustering potential was 96 V for risperidone and risperidone-D4 and 121 V for 9-OH risperidone and 9-OH risperidone-D4, entrance potential was 10 V, collision energy was 41 eV, and cell exit potential was 14 eV. The lower limit of quantification (LLQ) was 0.10 ng/mL for risperidone and 0.292 ng/mL for 9-OH risperidone. The within- and between-run precision (coefficient of variation [CV]) and accuracy (bias) values were the following: over the calibration range of 0.1 to 100 ng/mL for risperidone, the maximum CV for the LLQ was 5.8%, and the mean bias was between –9.1% and –5.1%; for all other concentrations the CV was not more than 3.8%, and the bias was between –9.8% and –3.6%; over the calibration range of 0.3 to 300 ng/mL for 9-OH risperidone the maximum CV for the LLQ was 2.6% and the mean bias was between –5.0% and –1.1%; for all other concentrations the CV was not more than 5.9% and the bias was between –8.7% and 0.7%. As stated above, TAM is defined as the sum of risperidone and 9-OH risperidone corrected by molecular weight, according to the following formula:

$$[TAM] = [risperidone] + [9 - OH\ risperidone] \cdot (410/426) \quad (1)$$

General Considerations for Data Management

Statistical analysis software–based programs were used to merge and convert the plasma concentration time–course and covariates data to NONMEM data sets. Two subjects from cohort 4 were excluded from the analysis as these patients admitted self-medication of oral risperidone during the treatment with TV-46000. The remaining 97 patients were included in the analysis data set. Drug concentrations below the LLQ were not imputed and were considered as missing in the analysis. Initial review of the data did not identify any outlier; therefore, all the available data of the 97 subjects were included in the analysis data set.

Population Pharmacokinetic Analysis

The PPK model used to characterize the complex release profile of TAM following the SC injections of TV-46000 was developed using a convolution-based modeling strategy with a prescribed input function.[23] The time course of TAM concentrations was characterized by two phases of drug release: a first phase associated with an initial release of a fraction of the dose administered, and a second phase associated with a second release of the remaining fraction of the dose administered. In this model, the TAM concentration (C_p), resulting from an arbitrary dose, was described by convolution as:

$$C_p(t) = f(t) * I(t) = \int_0^t f(\tau) \cdot I(t-\tau) \cdot d(\tau) \qquad f(t) = \frac{dr}{dt} \quad (2)$$

where f(t) is the in vivo TAM delivery rate, I(t) is the unitary impulse response, * is the convolution operator, and r(t) is the time-varying fraction of the dose released. The r(t) values were computed using a finite

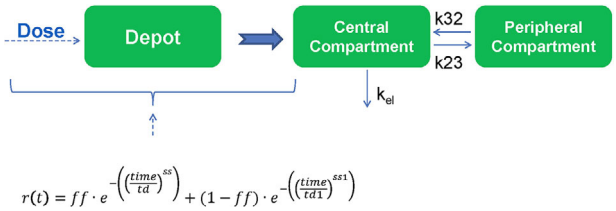

Figure 2. TV-46000 2-compartment PPK model with time varying absorption rate. kel, first-order elimination rate constant; k23 and k32, peripheral compartment distribution rate constants; ff, fraction of the dose released in the first process; ss, sigmoidicity factor for the first process; ss1, sigmoidicity factor for the second process; td, time to absorb 63.2% of the dose released in the first process; td1, time to absorb 63.2% of the dose released in the second process.

difference approach. The schematic of the TV-46000 PPK model is presented in Figure 2.

The multiphase release profile of the TAM was modeled using a double Weibull function r(t), an approach commonly used to capture complex release profiles:[23,24]

$$\mathrm{r}(\mathrm{t}) = \mathrm{ff} \cdot \mathrm{e}^{-\left(\left(\frac{\mathrm{time}}{\mathrm{td}}\right)^{\mathrm{ss}}\right)} + (1-\mathrm{ff}) \cdot \mathrm{e}^{-\left(\left(\frac{\mathrm{time}}{\mathrm{td1}}\right)^{\mathrm{ss1}}\right)} \quad (3)$$

where *ff* is the fraction of the available dose released in the first process, *td* and *td1* are the times to release 63.2% of the dose in the first and the second processes, and *ss* and *ss1* are the sigmoidicity factors for the first and second processes.

The disposition and elimination of TAM (C_p) was characterized by a 2-compartment model:

$$\begin{aligned}
\frac{\mathrm{dA1}}{\mathrm{dt}} &= -\mathrm{A1}*\mathrm{f}(\mathrm{t}) \\
\frac{\mathrm{dA2}}{\mathrm{dt}} &= \mathrm{A1}*\mathrm{f}(\mathrm{t}) - \mathrm{kel}*\mathrm{A2} - \mathrm{k23}*\mathrm{A2} + \mathrm{k32}*\mathrm{A3} \\
\frac{\mathrm{dA3}}{\mathrm{dt}} &= \mathrm{k23}*\mathrm{A2} - \mathrm{k32}*\mathrm{A3} \\
\mathrm{f}(\mathrm{t}) &= \frac{\mathrm{dr}}{\mathrm{dt}} \\
\mathrm{Cp} &= \frac{\mathrm{A2}}{\mathrm{V}}
\end{aligned} \quad (4)$$

where kel = CL/V is the elimination rate constant and V/F the volume of distribution, k23 and k32 are the first-order transfer rate constants from/to compartment 2/3, respectively.

Allometric scaling functions[25] on volume (V/F) and clearance (CL/F) were included in the base model to account for PK changes with weight.[26] Considering the relatively homogeneous population included in the trial, the allometric coefficients of 0.75 for clearance and 1 for volume were fixed in the model according to Anderson and Holford[27]:

$$\begin{aligned}
CL &= CL_t \cdot \left[\frac{WT}{70}\right]^{0.75} \\
V &= V_t \cdot \left[\frac{WT}{70}\right]^{1} \\
A &= \pi r^2
\end{aligned} \quad (5)$$

where CL_t is the typical value of the clearance in adult subjects (with WT = 70 kg), WT is the body weight, and V_t is the typical value of the volume in adult subjects.

The stochastic approximation expectation-maximization (SAEM) with interaction computational algorithm was used for estimation of PPK model parameters with NONMEM software version 7.4 (Icon Development Solutions, Ellicott City, Maryland) and Fortran compiler gfortran version 4.6.0. The maximum number of iterations in the stochastic phase (NBURN) of the SAEM method was 1000 followed by 500 iterations in the accumulation phase (NITER). Convergence was assessed visually based on SAEM convergence plots for the fixed and random effect parameters.

The estimated model parameters included the mean structural model parameters, the magnitude of interindividual variability (IIV), and the magnitude of residual variability. The structural model parameters included the fixed-effect parameters ([kel, first-order elimination rate constant; k23 and k32], peripheral compartment distribution rate constants; V, volume of distribution of the central compartment [V = V/F]; and parameters of the Weibull time varying input function [SS, TD, SS1, TD1, FF]). The IIV model described the unexplained random variability in individual values of structural model parameters (ie, IIV on kel, K23, K32, SS, TD, SS1, TD1, and ff). It was assumed that the IIV of the model parameters was log-normally distributed. The residual (unexplained) variability, which was composed of but not limited to intraindividual variability, experimental errors, process noise, and/or model misspecifications, was modeled using additive, proportional, and combined additive and proportional error structures.[20]

Covariate Analysis

The following variables: cohort, dose, injection site, age, BMI, weight, height, gender, race, ethnicity, and baseline creatinine clearance (CLCr) level were evaluated as potential covariates. The *CLCr* parameter, an estimate of the glomerular filtration rate, was calculated using the serum creatinine data (*SCr*) and the Cockcroft and

Gault formula:

$$CLCr = \{((l\ 40 - age) \cdot weight) / (72xSCr)\} \cdot 0.85\ (if\ female) \quad (6)$$

Covariate model building was a stepwise process consisting of a forward and a backward selection procedure. The likelihood-ratio test was used to evaluate the significance of incorporating or removing fixed effects into the population model based on alpha levels that were set a priori. Initially, each covariate (cohort, dose, injection site, age, BMI, weight, height, gender, race, ethnicity, and CLCr) was individually included in the base model. A covariate was retained in the model if a reduction in –2LL (log likelihood-ratio test) was ≥3.84 ($\chi^2 < 0.05$). After the full model was defined, the significance of each covariate was tested individually by removing each one at the time from the full model. A covariate was retained in the model if, upon removal, the –2LL increased by more than 6.64 points ($\chi^2 < 0.001$).

Model Evaluation

The PPK model was evaluated using goodness-of-fit (GOF) plots including (1) the observed data vs individual and model-predicted concentrations, (2) the weighed residuals vs individual predictions, and (3) the conditional weighted residual vs time. Model performance, validation, and stability were assessed using the visual predictive check (VPC) method.[28,29] Five hundred replicates of the original data set were simulated on the basis of the final model, and a 90% prediction interval was computed on the basis of the simulated data sets. Concentration means and quantile distributions were compared between the simulated and observed data. The VPC method was also used to evaluate the adequacy of the final model, including the effects of statistically significant covariates.

Pharmacokinetic/D2RO Model

The relationship between TAM concentrations and the striatal D2RO was predicted using a well-established published E_{max} model[20]:

$$RO = RO_{max} \frac{Cp}{K_d + Cp} \quad (7)$$

where RO is the D2RO, Cp is the TAM plasma concentration and K_d is the apparent equilibrium dissociation constant, 10.1 ng/mL, which is the TAM concentration at which 50% D2RO is observed.[20] E_{max} is the maximal effect at high drug concentrations when all the receptors are occupied by the drug. RO_{max} is the maximal receptor occupancy that can be achieved. As for most antipsychotics, the value of RO_{max} was fixed to 100% in the model. For the K_d parameter a value of 10.1 ng/mL was used.

Simulations

After an initial screening of TV-46000 doses 50 to 300 mg once monthly (q1m) and once every 2 months (q2m) was performed, based on the comparability of the maximum plasma concentration (C_{max}) and exposure to those following oral administration, the range of possible doses was narrowed down. The following simulations were conducted using the PPK model parameters:

- The expected TAM exposure was simulated after TV-46000 administered q1m at 50 to 150 mg or administered q2m at doses of 100 to 250 mg.
- Estimation of area under the plasma concentration–time curve (AUC), C_{max}, and minimum plasma concentration at steady state for TV-46000 administered q1m at doses of 50 to 150 mg and administered q2m at doses of 100 to 250 mg.
- Expected D2RO simulated at steady state using the final PPK model parameters jointly with the PK/D2RO model described below. The following doses and dosage regimens were considered: 50 to 150 mg administered q1m and 100 to 250 mg administered q2m.

The simulations of the expected TV-46000 TAM exposure, and D2RO values were conducted using a Monte Carlo approach as implemented in the NONMEM software. According to this methodology, individual patient data were generated by resampling the individual parameter values from the distribution defined by the fixed and random effect parameter values estimated in the PPK analysis. The PPK/pharmacodynamic (PD) analyses used the oral risperidone doses 2 to 5 mg, which represents the comparable TAM exposure for TV-46000 doses 50 to 250 mg. Thus, the simulated exposures and D2RO values were compared to published reference values for repeated administration of oral risperidone at steady state for doses 2 to 5 mg.

Results

Data

The demographic characteristics of the 99 patients with clinically stable schizophrenia who provided PK data for this study were as follows: mean (SD) age was 44.4 (8.8) years, body mass index was 28.6 (4.4) kg/m^2, and CrCL was 115.76 (21.9) mL/min. Eighty percent were men and 95.9% were Black or African American. All patients enrolled in the study were required to have a diagnosis of schizophrenia or schizoaffective disorder. Female patients were either of non–childbearing

Table 1. List of the Models Evaluated

Run	Reference Run	–2LL	Change in –2LL	Model Tested	*P* Value
1-comp		15507.12			
2-comp	1-comp	15351.05	–156.07	No allometric scaling and no covariate	<.001
Run 1[a]	2-comp	15339.78	–11.269	Allometric scaling and no covariate	<.001
Run 2	Run 1	15360.63	20.85	Allometric scaling and td (injection site)	NS
Run 3	Run 1	15350.63	10.85	Allometric scaling and V (injection site)	NS
Run 4	Run 1	15352.47	12.69	Allometric scaling and CL (age)	NS
Run 5	Run 1	15337.65	–2.132	Allometric scaling and V (age)	NS

–2LL = objective function defined as –2 times the maximum log of the likelihood of the data; CL, clearance; NS, not significant; td, time to absorb 63.2% of the dose released in the first process; V, volume of distribution.
[a] Preferred model.

potential or used contraceptive methods, per the protocol-specified criteria. There were no clinically significant findings regarding medical history of the patients. The 8 cohorts were well matched in their demographic characteristics and comparable in their use of prior and concomitant medications.

Safety

There was 1 death during the study: a completed suicide by a patient in cohort 8. In addition to the death, 1 other serious adverse event occurred during the study (exacerbation of schizophrenia). Both of these serious adverse events were considered by the investigators and sponsor to not be related to TV-46000 or oral risperidone. No patients were withdrawn from the study due to an adverse event.

The percentage of patients reporting at least 1 adverse event across the 8 cohorts ranged from 42% to 100% with the highest incidence of adverse events occurring in the 225 mg TV-46000 single dose cohorts (cohort 5, 100% of patients; and cohort 8, 93% of patients). The most frequently reported treatment-emergent adverse events were weight increase (34%), injection site reactions (23%), insomnia (9%), sedation (8%), headache (8%), increased blood creatine phosphokinase (7%), and auditory hallucinations (6%), most were mild to moderate in severity.

Population Pharmacokinetic Model Development

Model development was conducted according to a sequential approach. All tested models are listed in Table 1 in the chronological order in which they were evaluated. The first column of the table lists each model tested. The second column lists the reference run to which the test run was compared. The third and fourth columns list the –2LL for each test run and the change in –2LL from the reference run (test-reference), respectively. The fifth column describes briefly the hypothesis or objective that was tested by the model. The test outcome in the last column describes the conclusion, which was either not statistically significant or statistically significant, that can be drawn from the comparison with the reference run based on χ^2 statistics. An initial model did not include an evaluation of covariates or allometric scaling on volume (V) and clearance (CL) parameters.

The second model including allometric scaling on V and CL performed better than the model without allometric scaling (note that the mean subject weight on the study was 87 kg). Therefore, this model was considered as the reference model (run 1). The subsequent models evaluated the potential impact of the selected covariates.

The graphical inspection of the distribution of the empirical Bayesian estimates of individual model parameters (V, CL, TD, TD1, SS, SS1, FF) vs covariates (cohort, dose, injection site, age, BMI, weight, height, gender, race, ethnicity, CLCr) indicated the following: (1) the TD parameter appeared to be higher in the upper arm injection site with respect to the abdomen injection site; (2) the V/F parameter appeared to be lower in the upper-arm injection site with respect to the abdomen injection site; and (3) the CL/F parameter decreased with an increase in age, whereas the V/F parameters increased with an increase in age. Thus, formal covariate tests were conducted to verify the impact of injection site (abdomen vs upper arm) on the TD and V/F parameters and the effect of age on the CL/F and V/F parameters. None of the covariates formally tested significantly improved the objective function of the reference model (runs 2-5; Table 1). Therefore, the reference model was considered as the final model.

The estimated population parameters values of the reference model are presented in Table 2. In this table, SE represents the standard error of the parameter estimates, and RSE represents the relative standard error ([SE/Final parameter estimate]*100). Individual TAM concentrations vs time plots in log-linear scale were visually inspected, and it was determined that for each of the cohorts, the absorption of TV-46000 is

Table 2. PPK Model Parameter Estimates

	Parameter	Estimate	SE	RSE, %
Fixed effect	td (week)	2.69	0.435	16.20
	td1 (week)	3.32	0.316	9.50
	ss	0.616	0.0202	3.30
	ss1	3.66	0.292	8
	ff, %	0.511	0.0291	5.70
	CL/F, L/wk	354	13.6	3.80
	V/F, L	374	35	9.40
	k23 (week 1)	1.48	0.45	30.40
	k32 (week 1)	2.34	0.753	32.20

	Parameter	Estimate	SE, %	RSE, %	Shrinkage, %
Random effect	td	0.163	7.38	45.30	54.60
	td1	0.733	10.30	14.10	6.49
	ss	0.0247	1.48	59.90	24.70
	ss1	0.185	6	30.40	20.50
	ff	0.115	2.99	26	3.67
	CL/F	0.117	3.26	27.90	27.80
	V/F	0.147	7.07	48.10	19.00
	k23	1.41	35.20	25	29.10
	k32	1.9	136.00	71.60	23.40
Residual effect	Error prop.	0.152	0.0119	7.80	5.04
	Error_add.	1.58	0.28	18.30	

CL/F, apparent clearance; ff, fraction of the available dose released in the first process; k23 and k32, first-order transfer rate constants from/to compartment 2/3; PPK, population pharmacokinetic; RSE, relative standard error; SE, standard error of the parameter estimates; ss and ss1, sigmoidicity factors for the first and second processes; td and td1, times to release 63.2% of the dose in the first and the second processes; V/F, apparent volume of distribution.

characterized by a dual release process with 2 distinct release rates. The in vivo release model indicates that TAM was released according to a dual process characterized by the time to release the drug (td = 2.69 weeks and td1 = 3.32 weeks) and by the release rate (ss = 0.616 and ss1 = 3.66). While the fraction of the dose released in the 2 processes was similar (ff = 0.55%) and the times of drug release (td and td1) were not very different in the 2 processes, the rate of release in the 2 processes (ss and ss1) were very different.

This in vivo release function describes the multiphase continuous process of TAM release associated with a TV-46000 SC injection. Based on the model outcomes, a typical fraction of 50% is released with 2.6 weeks, and by weeks 4 to 8, typical fractions of 79% up to 93% of the total TAM concentration are released. The GOF diagnostic plots by cohort for the PPK model are presented in Figure S1. Overall, there was no apparent bias in the GOF plots, suggesting that the PPK model was adequate in describing the TAM concentration-time course.

Model performance/validation and stability was assessed using VPCs. Five hundred replicates of the original data set were simulated on the basis of the final model. The 90% prediction interval was estimated using the 5% and 95% percentiles of the distribution of the simulated exposure. The observed concentrations vs time were plotted by cohort on the prediction intervals with the medians of model predictions to visually assess the concordance between the simulated and observed data. Figure 3A and B illustrate single-dose administration of 75 mg (cohort 2) and 150 mg (cohort 4); Panels C and D illustrate 3 consecutive once-monthly doses of 75 mg (cohort 6) and 150 mg (cohort 7) respectively, the VPC figures for all cohorts 1 through 8 are shown in Figure S2 and representative individual fitted curves for cohorts 2, 4, 6, and 7 are shown in Figure S3.

In Figure 3A through D, the VPCs showed that the model developed to characterize the TAM plasma concentration–time course following the SC injections of TV-46000 performed well: The distribution of the observed data was reasonably well predicted in terms of typical profile (median curves identified by the solid blue lines) and IIV (90% prediction intervals identified by the light blue shaded areas), indicating that the PPK model properly described the observed data.

Simulations

The aim of the simulation activities was to provide TV-46000 dose recommendations for the phase 3 studies that would provide TAM exposure similar to that following oral risperidone administration in terms of

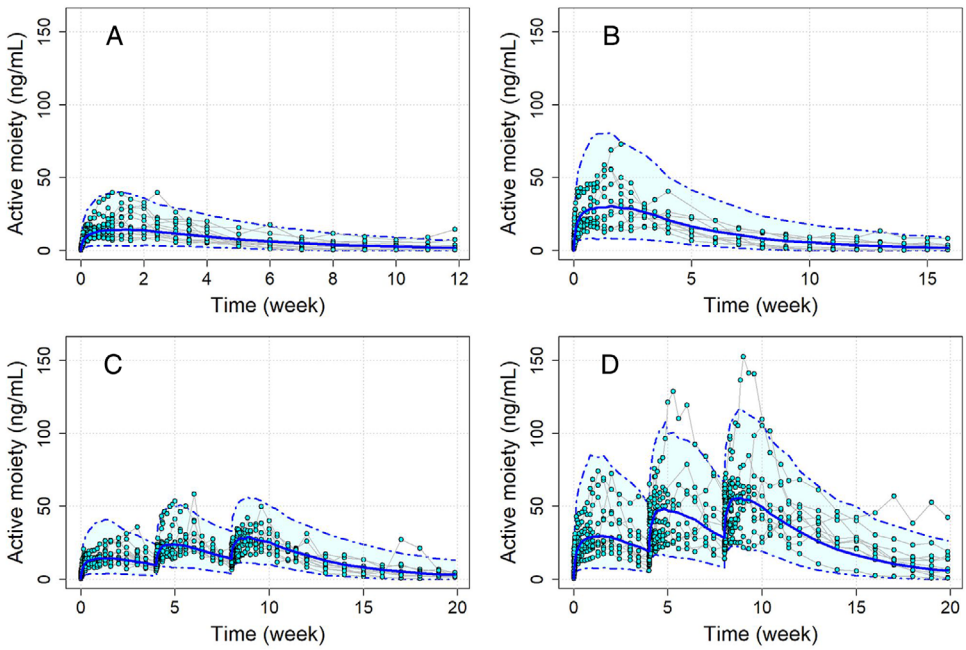

Figure 3. Visual predictive checks of the model of the total active moiety plasma concentration–time course following single and repeated administration of 75 mg and 150 mg SC injections of TV-46000; observed and model-predicted profiles following single-dose administration of 75 mg (A, cohort 2) and 150 mg (B, cohort 4); and administration of 3 once-monthly doses of 75 mg (C, cohort 6) and 150 mg (D, cohort 7). Blue circles represent observed individual plasma levels. Predicted median curve is identified by the solid blue line and interindividual variability is identified by the 5th and 95th prediction intervals (blue dashed lines) bordering the 90% prediction intervals (light blue shaded area).

overall exposure (dosing period), average daily exposure, and minimal and maximal plasma concentrations. The comparability and acceptability of TV-46000 exposure to oral risperidone was evaluated using the PPK model combined with the PK/PD model to predict D2RO.

The parameters derived from the PPK model were used to simulate the expected TAM exposure levels for different dosing regimens for TV-46000. The dose ranges evaluated were 50 mg to 300 mg administered q1m or 50 mg to 300 mg administered q2m. The desired dose regimen was one that provided comparable exposure metrics to corresponding oral risperidone dose and maintained TAM concentration above the clinically relevant concentration of 10 ng/mL throughout the dosing interval. Based on the estimated steady-state parameters including AUC, C_{max}, and minimum plasma concentration, the following dose ranges were considered for further evaluation, 50 to 125 mg q1m and 100 to 250 mg q2m. Figure S4 shows the simulated profiles for all tested dose regimens.

The estimated steady-state AUC over the dosing interval (AUC_{tau}) and daily AUC of TV-46000 (ie, AUC_{tau} at steady state divided by dosing interval) for the doses administered either q1m, q2m, the observed oral steady-state AUC_{tau} obtained in this phase 1 study, as well as corresponding exposure parameters taken from published data, are presented in Table 3. The exposures of TAM, such as the daily AUC during the dosing interval at steady state are similar when comparing any dose from the q1m regimen with double the dose from the q2m regimen (ie, 100 mg q1m vs 200 mg q2m). Furthermore, predicted TAM exposure at steadystate increased proportionally with the increasing dose for the 2 TV-46000 dosing regimens (q1m and q2m). The overall exposure per dosing interval (ie, AUC_{tau}) of q2 m was twice higher compared to q1m (Table 3). The daily exposure (AUC) of TV-46000 was comparable to the daily exposure of corresponding doses of oral risperidone.

Thus, simulated TAM plasma concentration following TV-46000 administered as a 100-mg dose q1m or 200-mg dose q2m in comparison to the published values for oral risperidone at a daily 4 mg dose is shown in Figure 4.

Prediction of D2RO

The expected D2RO values for the TV-46000 doses were simulated using the PPK model for TV-46000 jointly with a previously described PK receptor occupancy model.[20] The following dose regimens that have the potential to match oral risperidone exposure were considered: 50 to 150 mg q1m and 100 to 250 mg q2m. The simulated D2RO for TV-46000 dose regimens of

Table 3. Risperidone TAM Steady-State Daily Exposure (ng · h/mL) Following Oral Administration (Observed and Extrapolated Mean From Published References) and TV-46000 Administration (Median Model-Based Simulation)

	Oral Risperidone Administration					
	Published Findings			TV-46000 Simulations		
Oral Risperidone Daily Dose	Eerdekens et al[a] (ng · h/mL)	Gutierrez et al[b] (ng · h/mL)	Observed Oral Risperidone AUC_{tau} (ng · h/mL)	Dosing Regimen	AUC_{tau} (ng · h/mL)	Daily AUC_{ss} (ng · h/mL)
2 mg	428	358	321	50 mg q1m	14 076	503
				100 mg q2m	29 419	525
3 mg	644	537	496	75 mg q1m	21 136	755
				150 mg q2m	44 243	790
4 mg	860	717	593	100 mg q1m	28 607	1022
				200 mg q2m	58 508	1045
5 mg	1074	896	765	125 mg q1m	34 402	1229
				250 mg q2m	73 558	1314

AUC_{tau}, total area under the plasma drug concentration curve for the entire dosing interval (ie, a month or 2 months); Daily AUC_{ss}, AUC_{Tau} divided by the number of days in the dosing interval (28 or 56 days).
[a] Daily AUC_{ss} values for 2-mg and 4-mg doses are calculated from Eerdekens et al[22] Table 4 values for AUC_{14} divided by the 14 days in the dosing interval; interpolated values for 3 mg and 5 mg.
[b] Daily AUCss value is based on dose normalized data from 1-mg tablet formulation; Table 3 Gutierrez et al.[30]

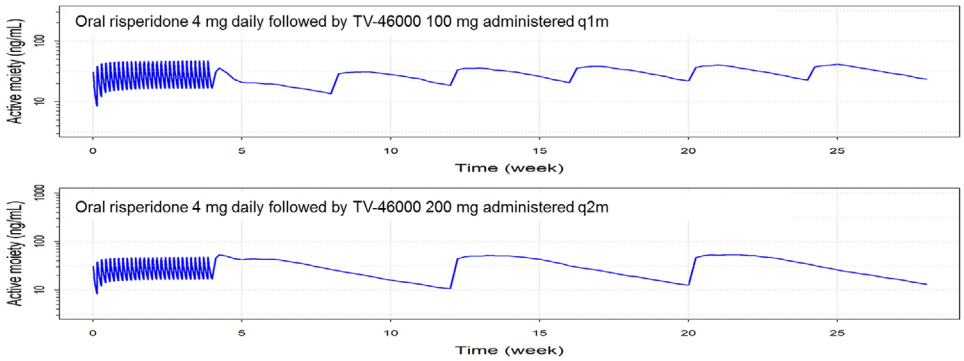

Figure 4. Simulated total active moiety plasma concentration for oral risperidone 4 mg daily followed by 100 mg TV-4600 administered q1m or 200 mg TV-46000 administered q2m. The dark blue line represents median plasma concentration from oral risperidone (weeks 0-4) from Eerdekens et al.[22] Subcutaneous injections of TV-46000 week 5 through month 6. The light blue area represents 90%CI. q1m, once monthly; q2m, once every 2 months.

75 mg q1m and 150 mg q2m are presented in the Figure 5A and B while simulated D2RO for all dose regimens are shown in Figure S5. The 90% (dark blue area) and the 95% (light blue area) prediction intervals are reported in the simulations.

Discussion

The PPK model was developed to provide a comprehensive characterization of the complex release profile of TAM following the SC injections of TV-46000. The model was further used to support doses and dosing regimen selection for phase 3 studies to aid in the clinical development of TV-46000.

Preliminary evaluation of TV-46000 PK revealed a complex and multiphase oral absorption profile, presenting double peaks and prolonged disposition/elimination process. These distinguishing features required the development of a complex PPK model that accounted for dual absorption processes: a first (faster) absorption process that may be associated with the initial release from the depot and results in reaching therapeutic plasma concentrations within 24 hours, and a second, slower absorption process that may be associated with the drug release from the in situ depot and results in a sustained release over 28 or 56 days, depending on dose. Dual absorption peak models have been used previously to describe other extended-release formulations and long-acting injectable treatments.[23,24]

PK model development was conducted in a stepwise approach: first, the model without covariates, and then, the model with allometric relationship

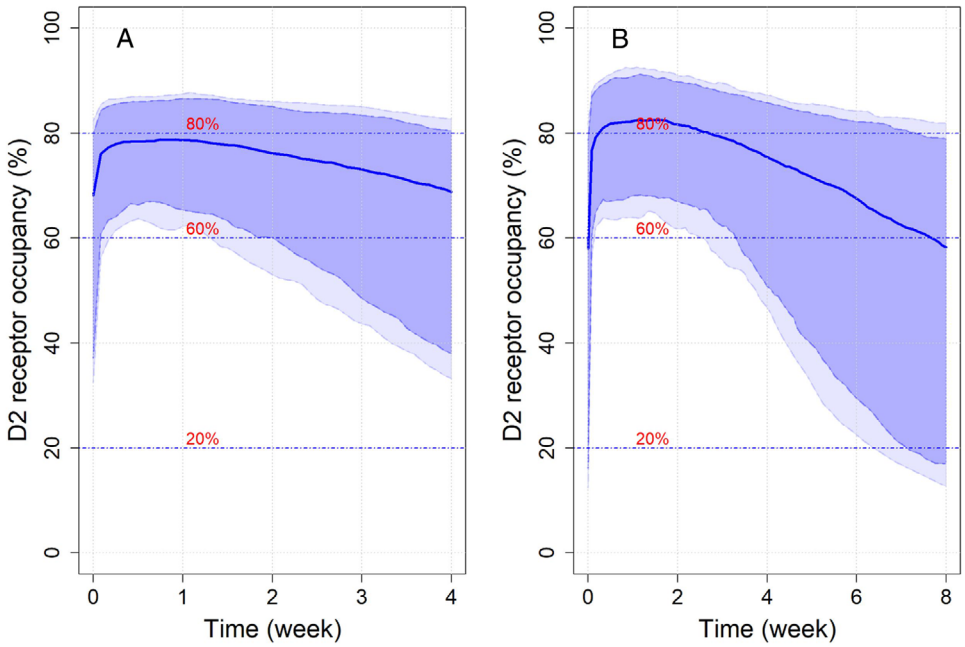

Figure 5. Estimated dopamine-D2 receptor occupancy (D2RO) profiles following 75 mg q1m (A) and 150mg q2m (B). Estimated D2RO profiles following multiple-dose administration. D2RO levels were estimated on the basis of the correlation between D2RO and simulated plasma levels (75 mg q1m [A] and 150 mg q2m [B]). The dark blue line represents median profile, and the purple and pink shaded areas represent the 90th and 95th prediction intervals, respectively. The 2 panels have different time scales. Reference lines present the estimated D2RO levels related to 20%, 60%, and 80% occupancy.

between body weight and V and CL. A model that included allometric scaling (weight) on V and CL performed better than a model without allometric scaling and was therefore used as the reference model in the analysis. The TAM concentration PK profiles following administration of TV-46000 were found to be best described by a double Weibull function of the in vivo release rate and by a 2-compartment disposition and elimination model. Exploratory analysis revealed collinearities between weight and age and weight and CLCr.

One of the limitations of the study was the skewed distribution of race and sex in the phase 1 study cohorts (96% Black or African American and 80% male). Thus, the visual examination on the effects of race and ethnicity and sex on the model parameters was not conclusive. Other potential covariates were explored. TV-46000 was administered to all cohorts except 1 as a subcutaneous injection into the abdomen. Visual examination of the distribution of the model parameters prompted covariate analyses to test the effect of injection site on the TD and V/F parameters and the effect of age on CL/F and V/F. The results of the formal testing indicated that there were no statistically significant changes in exposure due to differences in injection site location or due to age; therefore, the final model included the data collected following abdomen and upper arm combined.

The precision of the estimated parameters, the GOF plots and the VPCs indicated that the model properly described the observed TAM data. The model provided reasonable description of the time course of TAM observed following either single or repeated doses of TV-46000. The outcomes of the analysis supported a linear PK profile for TV-46000 in doses ranging from 50 mg to 250 mg. TV-46000 exposure was comparable to exposure levels previously published and observed in the current study of daily oral risperidone exposure of 2- to 5-mg daily doses. The dose strengths for both q1m (50, 75, 100, or 125 mg) or q2m (100, 150, 200, or 250 mg) regimens, provided adequate exposure over 28 and 56 days, respectively. At corresponding doses, TAM AUC following TV-46000 q2m (100, 150, 200, or 250 mg) dosing was twice the TAM AUC following the q1m (50, 75, 100, or 125 mg) dosing, while the average daily exposures (AUC and AUC during the dosing interval at steady state) were similar.

In addition to PPK modeling, a PK/PD model was applied to predict D2RO levels from the predicted TV-46000 TAM plasma concentrations using a previously published model. The relationship between D2RO and therapeutic outcome has been described on a continuous scale for many neuroleptic drugs.[30–35] D2RO ranging between 40% and 80% was previously demonstrated to be associated with risperidone therapeutic efficacy.[15] The PPK model together with the

D2RO model was used to simulate D2RO following TV-46000 dosing. In general, for both the q1m and q2m dosing regimens, the majority of the profile was within the preferable range of 40% to 80% D2RO during the intended dosing interval.

The simulated D2RO data provided, along with the PPK simulations, supported the selection of TV-46000 doses and dosing regimens for clinical development. The simulated TAM exposure results suggest that TV-46000 doses of 50 to 125 mg administered once a month and 100 to 250 mg administered once every 2 months were characterized by a median exposure within the range of the published and observed exposure of daily oral risperidone doses of 2 to 5 mg. Collectively, we have demonstrated that as the corresponding doses of q1m or q2m provide comparable mean and daily exposure over the dosing interval. This finding suggests that the dose regimens can be interchangeable, which, along with the 2 possible injection sites, allows both patients and physicians flexibility to improve compliance. Currently, the selected doses are being evaluated to confirm the long-term efficacy and safety of TV-46000.

Conflicts of Interest

I.P. and M.L. are paid consultants to Teva Pharmaceutical Industries, Ltd. A.M.W., E.H., O.S., A.K., R.T., P.L., M.L., and A.E. are current or former employees of Teva Pharmaceutical Industries, Ltd. R.G. was a paid consultant to Teva Pharmaceutical Industries Ltd and has been a consultant to Ironshore Pharmaceuticals; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Biomedical Science Institutes; Nanomi BVs; Laboratorios Liconsa; Massachusetts General Hospital; UCB; Recordati Rare Diseases; Indivior, Tris Pharma; and F. Hoffmann–La Roche.

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