Neurol Ther (2025) 14:829–848
https://doi.org/10.1007/s40120-025-00723-z

ORIGINAL RESEARCH

Population Pharmacokinetic Modeling of TV-46000, a Risperidone Long-Acting Subcutaneous Antipsychotic for the Treatment of Patients with Schizophrenia

Itay Perlstein · Avia Merenlender Wagner · Anna Elgart · Anthe S. Zandvliet · Farina Hellmann · YuWei Lin · Eline van Maanen · Nele Plock · Floris Fauchet · Rajendra Singh

Received: September 18, 2024 / Accepted: February 24, 2025 / Published online: March 23, 2025

ABSTRACT

***Introduction*:** TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) agent that combines risperidone and an innovative, copolymer-based drug delivery technology in a suspension suitable for subcutaneous administration from a prefilled syringe. The objective of the current analysis was to characterize the pharmacokinetics (PK) of TV-46000 based on pooled data from phase 1 and phase 3 studies, and to further support clinical use aspects of TV-46000.

***Methods*:** A population PK (popPK) model was developed using TV-46000 PK data obtained from three phase 1 studies ($n=267$) and two phase 3 trials ($n=425$). A sequential parent–metabolite model structure was used, and the total active moiety (TAM) concentration–time profiles were simulated for TV-46000 once monthly (q1m) and once every 2 months (q2m) across the range of available doses and different administration sites.

***Results*:** The popPK model adequately characterized the PK of risperidone and its active metabolite. TV-46000 reaches therapeutic plasma TAM concentrations (≥10 ng/mL) within 24 h following first dose administration. Three months after initiation of TV-46000, 86% and 88% of steady-state TAM exposure were achieved for q1m and q2m, respectively, and steady state was fully attained by 6 months (i.e., >90% of steady-state TAM exposure). In addition,

Prior Presentation: Part of this work was presented at the 36th Annual European College of Neuropsychopharmacology Congress in Barcelona, Spain, on October 7–10, 2023 (Perlstein et al. 2023) and the 5th Annual Schizophrenia International Research Society Conference in Toronto, Ontario, Canada, on May 11–15, 2023 (Perlstein et al. 2023).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-025-00723-z.

I. Perlstein
Magic Wand Research LLC, Philadelphia, PA, USA

A. Merenlender Wagner
Teva Pharmaceutical Industries Ltd., Quantitative Pharmacology and Biosimilar Sciences, Netanya, Israel

A. Elgart
Teva Pharmaceutical Industries Ltd., Innovative Medicines, Global Clinical Development, Netanya, Israel

A. S. Zandvliet · F. Hellmann · Y. Lin · E. van Maanen · N. Plock · F. Fauchet
Certara, Radnor, PA, USA

R. Singh (✉)
Teva Branded Pharmaceuticals LLC, Quantitative Pharmacology and Biosimilar Sciences, West Chester, PA, USA
e-mail: Rajendra.singh@tevapharm.com

simulated D2 receptor occupancy for TV-46000 was generally within the therapeutic window of 60–80% during both dosing intervals.
Conclusions: The developed popPK model, together with corresponding simulations, supports TV-46000 as a LASCA that offers flexible dosing intervals (q1m or q2m) and administration sites (abdomen or upper arm) and does not require oral supplementation or loading dose(s).

PLAIN LANGUAGE SUMMARY

TV-46000 is a long-acting injectable that is prescribed to patients with schizophrenia. The aim of this analysis was to characterize the amount of the drug in the blood over time (pharmacokinetics) and associated variability after subcutaneous injection, using modeling and simulations. The model showed that TV-46000 had similar exposure to that of other orally administered risperidone medications taken for schizophrenia. The exposure was similar whether patients were administered the injection of TV-46000 once monthly or once every 2 months. There were no differences in exposure whether the drug injection was administered in the arm or abdomen. Administering TV-46000 1 week earlier or later than the dosing instructions did not significantly affect the concentration of the drug in the blood over time. The simulations also suggested that TV-46000 bound to the receptors in the brain at levels needed to treat schizophrenia when it was given either once monthly or once every 2 months.

Keywords: TV-46000; Schizophrenia; Population pharmacokinetic modeling; Risperidone; Long-acting subcutaneous antipsychotic

Key Summary Points

Why carry out the study?

TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) agent that combines risperidone and an innovative, copolymer-based drug delivery technology in a suspension suitable for subcutaneous administration from a prefilled syringe.

The objective of the current analysis was to characterize the pharmacokinetics of TV-46000 based on pooled data from phase 1 and phase 3 studies, and to further support clinical use aspects of TV-46000.

What was learned from the study?

The pharmacokinetic modeling performed here demonstrated that TV-46000 reaches therapeutic plasma total active moiety (TAM) concentrations (≥ 10 ng/mL) within 24 h following first dose administration, with sustained release of risperidone over time.

The model also demonstrated that TV-46000 provides similar TAM exposure for both sites of administration (arm and abdomen), with pharmacokinetic parameters comparable to orally administered risperidone.

The developed model, together with corresponding simulations, supports TV-46000 as a LASCA that offers flexible dosing intervals (once monthly or once every 2 months) and administration sites (abdomen or upper arm) and does not require oral supplementation or loading dose(s).

INTRODUCTION

TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) agent that combines risperidone and an innovative, copolymer-based drug delivery technology in a suspension suitable for subcutaneous (sc) administration from a prefilled syringe (PFS) [1, 2]. Other risperidone formulations include R064766 [3] and LY03004 [4], which are intramuscular formulations administered once every 2 weeks, and RBP-7000, an sc

formulation administered once monthly (q1m) [5]. Patient acceptance of intramuscular long-acting injectable antipsychotics (LAIs) is limited by pain or discomfort [6], contributing to the stigma and poor perceptions of LAIs. The subcutaneous administration of an LAI such as TV-46000 can limit pain and discomfort owing to the smaller needle size, in turn reducing fear and anxiety in patients. In addition, it offers two interchangeable sites of administration (the back of the upper arm and the abdomen), which may provide further convenience to the patients when compared with the gluteal and deltoid sites of intramuscular LAI administration. The convenience of a prefilled syringe is also beneficial to healthcare professionals, as it makes administration easier, eliminates the need for reconstitution, and reduces risk of needlestick injury [7]. TV-46000 is the only risperidone LAI with a flexible dosing regimen that can be administered once every 2 months (q2m), offering more dosing options for clinicians.

Adhering to any long-term medication for a chronic disorder is challenging; with schizophrenia there are additional barriers such as stigma, lack of family support, and cognitive symptoms that exacerbate the challenge [8]. Approximately two-thirds of patients with schizophrenia exhibit poor adherence to oral antipsychotics, which increases risk of relapse [9]. Previously it has been shown that LAIs are associated with greater adherence and, subsequently, lower rates of relapse and lower risk of mortality and suicidality compared with oral antipsychotics in patients with schizophrenia. TV-46000 was developed to address nonadherence issues often associated with oral risperidone formulations [10, 11]. Previous phase 1 trials (RISPE1ZG15EU, SAD-10055, and BA-10148) demonstrated that TV-46000 provides a combination of immediate and sustained releases of risperidone over time, such that therapeutic concentrations are achieved within the first 24 h in patients and maintained with injections q1m or q2m [12, 13], therefore not requiring reconstitution steps, a loading dose, concomitant oral supplementation at initiation, or a complicated re-initiation regimen in the event of a missed dose [1]. In addition, the total active moiety (TAM; sum of concentrations of risperidone and its active metabolite [9-OH risperidone] corrected by molecular weight) exposure was comparable between administrations into upper-arm or abdominal injection sites, and rubbing the injection site after dose administration did not significantly increase relative bioavailability [12].

TV-46000 was approved by the US Food and Drug Administration (FDA) in April 2023 for the treatment of schizophrenia in adults [1] on the basis of the efficacy and safety results of two phase 3 clinical trials. The first of these trials was a randomized, double-blind, placebo-controlled, phase 3 trial in patients with schizophrenia (RIsperidone Subcutaneous Extended-release study [RISE]; NCT03503318). Among the 863 patients who enrolled, the time to impending relapse was significantly prolonged for those taking TV-46000 q1m (5.0 times) and q2m (2.7 times) compared with placebo. The most frequently reported treatment-related adverse events (AEs) were injection site nodules (3–7% of patients), weight increase (2–6%), and extrapyramidal disorder (0–5%) [2]. The second of these trials (Safety in Humans of TV-46000 subcutaneous INjection Evaluation study [SHINE]; NCT03893825) was designed to evaluate the long-term safety and tolerability of TV-46000. Among the 336 patients who were randomized, there were only six impending relapses (three each for q1m and q2m). The most frequently reported treatment-related AEs were injection site pain (2–7% of patients) and injection site nodules (3–4%) [14]. Overall, the safety profile of TV-46000 was consistent with other approved oral and injectable formulations of risperidone, with no new safety signals detected [2, 14].

Previously, a population pharmacokinetics (popPK) model was developed on the basis of the data obtained from 97 patients with schizophrenia or schizoaffective disorder enrolled in the phase 1 SAD-10055 study [15]. The model demonstrated that exposure of TAM and dopamine-receptor occupancy (D2RO), an important indicator of antipsychotic efficacy and safety, following TV-46000 q1m and q2m were comparable to that of oral risperidone doses of 2–5 mg/d [16–19].

The objective of the current analysis was to characterize the PK of TV-46000, based on pooled data from five clinical studies that

included three phase 1 and two phase 3 studies, and to further support clinical use aspects of TV-46000. Therefore, the time course of risperidone and its active metabolite, 9-OH risperidone, was modeled using a population approach, and potential effects of covariates on risperidone and 9-OH risperidone PK were investigated. In addition, D2RO levels were determined on the basis of a published D2RO PK/pharmacodynamic (PD) model [16].

METHODS

Datasets

TV-46000 PK data were obtained from five clinical studies (Table 1): three phase 1 (RISPE1ZG15EU, SAD-10055, and BA-10148) and two phase 3 studies (RISE and SHINE). For the SAD-10055 and BA-10148 phase 1 clinical studies, patients enrolled in the study were already stable on orally administered risperidone (henceforth oral risperidone). Upon enrolment, patients received oral risperidone according to the treatment they were assigned for 7 days, followed by a washout period of 7 days. Therefore, the majority of patients had undetectable plasma levels at the first injection of TV-46000. For the phase 3 clinical studies, patients were stabilized on oral risperidone for 12 weeks before being administered TV-46000 (or were rollover patients on TV-46000, in the case of the SHINE clinical study). The use and impact of prior antipsychotic treatments (i.e., oral risperidone) on PK following administration of TV-46000 were explored. Oral risperidone has limited effect on AUC or C_{max} following dosing of TV-46000 as exposure after 24 h of oral risperidone dose is marginal compared with exposure from TV-46000.

Phase 1 Studies

The RISPE1ZG15EU and other phase 1 studies were used in the model to better characterize the absorption/release following administration of TV-46000. The phase 1 study included dense sampling during absorption while the phase 3 studies included a sparse sampling scheme for PK characterization. Intense sampling in initial absorption/release phase from healthy subjects was important to characterize the PK adequately.

RISPE1ZG15EU was a two-part, open-label, non-randomized trial in healthy volunteers using TV-46000 administered via a syringe filled from a vial. Healthy subject data from study RISPE1ZG15EU contributed only 7% of the total number of subjects ($n = 50$ of 692). The study consisted of a single-ascending-dose part to assess the safety, tolerability, and PK of various doses administered in the upper arm, and a comparative part to investigate the safety, tolerability, and PK of abdomen administration and the effect of rubbing on the injection site.

SAD-10055 was an open-label study conducted in patients with schizophrenia or schizoaffective disorder that evaluated the safety, tolerability, and PK of sequential single and multiple ascending doses of TV-46000 administered in the upper arm or abdomen via a syringe filled from a vial.

BA-10148 was an open-label, parallel-design, single-dose study in patients with schizophrenia or schizoaffective disorder that examined the relative bioavailability of TV-46000 administered in the abdomen with a PFS versus a syringe filled from a vial. A PFS is a single-use syringe already prefilled with the correct dosage amount for administration, whereas filling from a vial requires clinicians to manually fill to the correct dose with each administration. Glass vials also require additional sterilization processes not necessary with PFSs.

Phase 3 Studies

RISE study was a randomized, double-blind, multicenter, placebo-controlled, relapse-prevention study comparing sc administration of TV-46000 q1m or q2m versus placebo q1m in patients with schizophrenia. Patients diagnosed with schizophrenia were stabilized on oral risperidone for 12 weeks and then randomized 1:1:1 to receive TV-46000 q1m, TV-46000 q2m, or placebo administered via a syringe filled from a vial [2].

SHINE study was a 56-week, open-label, multicenter study that evaluated the safety and

Table 1 TV-46000 clinical studies included in the popPK dataset

Study	Design	Dose	PK sampling times	Subjects treated with TV-46000
Phase 1 studies [12, 13]				
RISPE1Z-G15EU	Single-dose study targeting subtherapeutic plasma concentrations in healthy volunteers	Single dose 12.5–25 mg	Pre-injection on day 1 and 0.5, 1, 2, 3, 4, 6, 8, 12, 22, 24, 26, 30, 36, 48, and 72 h post injection Thereafter on days 4, 5, 7, 8, 9, 10, 11, 12, 14, 21, 28, 35, 42, 49, and 54	55
SAD-10055	Single dose and 3 consecutive monthly doses in patients with schizophrenia who are stable on oral risperidone	Single dose 50–225 mg q1m 75–150 mg	Pre-injection on day 1 and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 30, and 36 h post injection Thereafter on days 3, 4, 5, 6, 7, 8, 10, 12, 15, 18, 22, 25, 29, 36, 43, 50, 57, 64, 71, 78, and 84/85 For the multidose cohorts, additional PK samples were collected on days 92, 99, 106, and 112	96
BA-10148	Single-sequence study in parallel groups of patients with schizophrenia to assess the relative bioavailability of TV-46000 from prefilled syringe	Single dose 100-mg vial or prefilled syringe	Pre-injection on day 1 and 1, 2, 3, 4, 6, 8, 12, 24, 30, and 36 h post injection Thereafter on days 3, 4, 5, 6, 7, 9, 11, 13, 15, 18, 22, 25, 29, 36, 43, 50, 57, 64, 71, 78, and 85	Approximately 110
Phase 3 studies [2, 14]				
RISE (NCT03503318)	TV-46000 sc q1m and q2m and placebo sc in a 1:1:1 ratio. Oral conversion and stabilization stage (12 weeks), double-blind maintenance stage (up to approximately 13 months), and follow-up (8 weeks)	q1m 50–125 mg q2m 100–250 mg	Stage 1 (oral, at weeks 4, 8, 10, and 12), Stage 2 (TV-46000, at baseline, every 4 weeks for up to approximately 13 months, and at follow-up)	Approximately 596, including placebo
SHINE (NCT03893825)	Safety extension study of Study TV-46000-CNS-30072 TV-46000 sc q1m and q2m in a 1:1 ratio	q1m 50–125 mg q2m 100–250 mg	Stage 1 (oral, at weeks 4 and 12), Stage 2 (TV-46000, at baseline, every 4 weeks, and at follow-up)	Approximately 300 in Stage 2 (both rollover subjects from RISE and new subjects; only data available at the time of RISE database lock are included in the popPK analysis)

PK pharmacokinetics, *popPK* population pharmacokinetics, *q1m* once monthly, *q2m* once every 2 months, *RISE* RIsperidone Subcutaneous Extended-release study, *sc* subcutaneous, *SHINE* Safety in Humans of TV-46000 subcutaneous INjection Evaluation study

tolerability of TV-46000. Patients diagnosed with schizophrenia received TV-46000 q1m or q2m via PFS for up to 56 weeks [14]. SHINE included patients who were newly enrolled (randomized 1:1 to TV-46000 q1m or q2m), as well as those who rolled over from RISE. Patients randomized to TV-46000 in RISE continued to receive their assigned treatment in SHINE.

An integrated dataset was constructed from all clinical studies. The dataset included PK data during pretreatment with oral risperidone and following treatment with TV-46000. Patients who received at least one TV-46000 injection and had at least one measurable plasma concentration after TV-46000 administration were included in the dataset. Dense PK sampling was performed for phase 1 and sparse sampling for phase 3 studies. Time relative to first dose and time since the most recent dose were derived using actual sampling/dosing time data where available. When actual time data were missing, times were imputed on the basis of nominal time, and the corresponding record was flagged. Study ID, subject ID, dosing history (including actual date and time of administration), nominal and actual date and time of PK sample collections, risperidone and its active metabolite (9-OH risperidone) concentrations in plasma, and relevant covariates were available in the dataset.

Ethical Approval

This article is based on data from previously conducted studies and does not contain any new studies with human participants. All involved study centers of the original clinical trials received approval by local ethics committees, and informed consent was received for all patients. Consent was obtained during the original clinical trials, and no new consent forms were required/collected for this analysis.

Population PK Model Development

Previous analyses had indicated that the PK of TV-46000 were well described by a two-compartment structural model with a time-varying absorption rate described by a double Weibull function [15]. Although the previous model had been suitable for the analysis of dense phase 1 PK data, an alternative absorption model was considered for the analysis of combined phase 1 and phase 3 PK data. The starting point of the current analysis was the model reported by Ivaturi et al. [20], which described sc absorption by one depot dose and a double first-order absorption route. A sequential parent–metabolite model structure was developed with risperidone (the parent) as a one-compartment model with two parallel first-order release routes and first-order elimination. The PK of metabolite 9-OH risperidone was described by a one-compartment model, with first-order conversion from the parent and first-order elimination. The predicted risperidone concentrations were used as input into the metabolite central compartment using individual post hoc PK parameters from the parent model. Interindividual variability was evaluated for all parameters and described via exponential error models. Random-effect variance–covariance structures were evaluated, including partial and full-block structures; structures were deemed suitable if they provided statistically significant ($p<0.01$ χ^2 distribution, with 1 degree of freedom) improvement in objective function, improved model stability, and were identifiable as measured by the condition number. The "log-transformed, both-sides" approach was applied, using an additive residual error to describe the residual variability in the data. Model development was performed using the first-order conditional estimation with interaction method of the non-linear, mixed-effect modeling software (Version 7.4.3) [21].

A stepwise covariate analysis was performed to investigate the potential effects of intrinsic and extrinsic factors on sequentially developed parent and metabolite models. Intrinsic factors examined were age, body weight, body mass index (BMI), creatinine clearance, sex, and race. Extrinsic factors examined were injection volume (dose), injection site, and product presentation (vial or PFS). All continuous and categorical covariates were incorporated into the population model as follows:

Continuous:

$$P_i = P \bullet \left(\frac{\text{COV}i}{\text{COV median}} \right)^{\theta_i}$$

Categorical:

$$P_i = P \bullet (1 + \theta_i)^{\text{COV}_i}$$

where P_i is the individual PK parameter and P is a population estimate of parameters, COV_i is the covariate of subject I for the parameter P_i, COV median is the median of covariate for the subject population, and θ_i is a coefficient that reflects the covariate's effect on the parameter.

The robustness of parameter estimates and associated 95% CIs were evaluated via a nonparametric bootstrap procedure, consisting of repeatedly (1000 replicates) fitting datasets obtained by random sampling with replacement of the dataset used for model development.

The effect of a continuous covariate was considered to be clinically irrelevant if the median of the PK parameter estimate of any individual differed by less than 20% from an individual with an extreme covariate value (10th and 90th percentiles); for a categorical variable, the criterion was if the PK parameter estimate between categories of a covariate differed by less than 20%. Covariate effects were also considered clinically irrelevant if the reduction in unexplained variability between subjects was less than 5%.

Simulated TAM Exposure Following TV-46000 Dosing Regimens

The following simulations were conducted using the popPK model parameters:

- Simulations of TV-46000 TAM concentrations for different dosing regimens.
- Simulations of oral risperidone TAM concentrations (1–16 mg/d).
- Prediction of individual exposure parameters from TAM concentration–time profiles.

All simulations were performed using the R package RxODE (R-based Simulation of Differential Equation Models for Mixed Effects), version 0.9.2-1.

Model-Based PK Simulations of TV-46000 TAM Concentrations for Different Dosing Regimens

The sequential parent–metabolite model was used to simulate TAM concentrations for different TV-46000 dosing regimens (q1m at doses of 50, 75, 100, and 125 mg and q2m at doses of 100, 150, 200, and 250 mg, with the assumption that each month had 28 days). Demographic covariates were bootstrapped from a random sample of 500 participants from the TV-46000 phase 3 population. The simulated TAM exposures to daily exposure following oral administration of risperidone 2–5 mg/d were compared with simulated exposure following TV-46000 administration over the 28-day and 56-day dosing intervals.

Model-Based PK Simulations of Oral Risperidone TAM Concentrations (1–16 mg/d)

TAM concentrations at steady state were simulated for oral risperidone (1–16 mg/d) on the basis of a previously published model [22]. Similar to the model-based PK simulations of TV-46000 TAM concentrations, demographic covariates were also bootstrapped from a random sample of 500 participants from the TV-46000 phase 3 population. Metabolizer status was set to extensive, and no concomitant medication was assumed for simulated subjects.

Prediction of Individual Exposure Parameters from TAM Concentration–Time Profiles

The following exposure parameters were firstly derived from TAM concentration–time profiles at the individual participant level and then summarized using descriptive statistics: (1) area under the time–concentration curve at steady state (AUC_{ss}) calculated for a dosing interval (28 or 56 days for TV-46000 and one 24-h period for oral risperidone); (2) daily AUC_{ss} calculated as AUC_{ss} divided by the dosing interval of TV-46000; (3) average plasma concentration during the dosing interval at steady state ($C_{avg,ss}$)

calculated as AUC_{ss} divided by the dosing interval in hours (i.e., 24 h × 28 or 56 days for TV-46000 and 1 × 24 h for oral risperidone); (4) maximal plasma concentration at steady state ($C_{max,ss}$); and (5) trough plasma concentration at steady state ($C_{trough,ss}$). Simulated TAM exposures over the 28-day and 56-day dosing intervals served for comparison with daily exposure following oral administration of risperidone. In parallel, the D2RO profile was simulated from the TAM profile with a simple maximum effect (E_{max}) PK/PD model, where E_{max} = 100% and apparent equilibrium dissociation constant (k_d) was 10.1 ng/mL [22, 23].

RESULTS

Dataset

The model development and covariate analysis were based on data from 692 participants (2 participants were excluded as a result of self-administration of risperidone, and 41 participants as a result of PK samples below the lower limit of quantification) who received at least one TV-46000 injection in the phase 1 and phase 3 trials (Table 2). The model used data from the subset of participants with measurable plasma concentrations, including 267 patients and healthy volunteers from the phase 1 trials (50 from RISPE1ZG15EU, 97 from SAD10055, and 120 from BA-10148) and 425 patients from the phase 3 trials (352 from RISE and 73 from SHINE) (Table S1). Overall, participants were primarily male (70.4%), Black or African American (64.7%), and middle-aged (mean age, 47.4 years). The mean weight of participants was 86.3 kg, mean BMI was 28.7 kg/m^2, and mean creatinine clearance was 121 mL/min. Most participants received injections in the abdomen (68.5%) versus the upper arm (31.5%), and from vials (77.8%) versus PFS (22.2%).

Risperidone (Parent) PK Model and the Effect of Covariates

Using data from the phase 1 and phase 3 studies, the preliminary model [15] structure was reassessed and refined, and a stepwise covariate analysis was performed. The final parent (risperidone) PK model for TV-46000 was a one-compartment model, with double first-order release routes (fast absorption rate constant 1 [KA1] and slow absorption rate constant 2 [KA2], with transit rate constant and five transit compartments) and first-order elimination (Fig. 1, Table 3).

Statistically significant covariates were BMI, injection volume, administration site, sex, and age. Age and sex did not have clinically relevant effects on apparent clearance (CL/F) compared with the base model, and both were removed. After checking for successful minimization, a successful covariance step, and unbiased goodness-of-fit plots (Fig. S1), a BMI effect on KA1 and KA2 was retained in the model, as well as effects of administration site and injection volume on KA1. All parameters were estimated with good precision (relative standard error [RSE] < 35%).

In the final model (Fig. 1), KA1 decreased with increased injection volume. The effect of injection volume was pronounced at subtherapeutic dose levels of 12.5 mg and 25 mg (administration volume of 0.035 mL and 0.07 mL, respectively), while at therapeutic doses of 50 mg or higher (≥ 0.139 mL), the effect of administration volume was minimal. The balance between KA1 and KA2 shifted with increased BMI (KA1 decreased with increased BMI; KA2 increased with increased BMI). Upper-arm administration was associated with a 33% higher KA1 (i.e., faster release) than injection in the abdomen, though the change in TAM exposure was still relatively small.

9-OH Risperidone (Metabolite) PK Model and the Effect of Covariates

The final metabolite (9-OH risperidone) PK model for TV-46000 was a one-compartment model, with first-order input from the risperidone compartment and first-order elimination (Fig. 1, Table 3). The effect of sex on metabolite clearance (CLMO) was the only covariate identified to have a statistically significant impact based on the difference in objective function value; however, the impact on CLMO was small

Table 2 Intrinsic and extrinsic factors examined in stepwise covariate analysis

	Phase 1			Phase 3[a]		Total
	RISPE1ZG15EU ***N*** **= 50**	**SAD-10055** ***N*** **= 97**	**BA-10148** ***N*** **= 120**	**RISE** ***N*** **= 363**	**SHINE** ***N*** **= 103**	**Overall** ***N*** **= 733**
Age, years, mean (SD) [range]	35.5 (10.1) [19.0–54.0]	44.4 (8.84) [20.0–56.0]	47.4 (9.77) [21.0–60.0]	49.3 (10.8) [16.0–65.0]	49.4 (10.6) [16.0–64.0]	47.4 (10.9) [16.0–65.0]
Sex, *n* (%)						
Male	41 (82.0)	78 (80.4)	93 (77.5)	222 (61.2)	82 (79.6)	516 (70.4)
Female	9(18.0)	19 (19.6)	27 (22.5)	141 (38.8)	21 (20.4)	217 (29.6)
Race, *n* (%)						
Black or African American	3 (6.0)	93 (95.9)	101 (84.2)	218 (60.1)	59 (57.3)	474 (64.7)
White	38 (76.0)	4 (4.1)	13 (10.8)	138 (38.0)	41 (39.8)	234 (31.9)
Asian	5 (10.0)	0	1 (0.8)	3 (0.8)	1 (1.0)	10 (1.4)
Missing	4 (8.0)	0	5 (4.2)	4 (1.1)	2 (1.9)	15 (2.0)
Weight, kg, mean (SD), [range]	77.1 (11.3) [53.6–96.4]	87.3 (14.9) [57.8–113.0]	87.0 (16.1) [51.1–122.0]	86.0 (16.5) [42.0–132.0]	89.8 (17.7) [55.9–131.0]	86.3 (16.3) [42.0–132.0]
BMI, kg/m^2, mean (SD) [range]	25.1 (2.5) [19.5–30.1]	28.6 (4.4) [19.6–34.8]	28.3 (4.8) [18.5–35.4]	29.0 (4.9) [18.0–38.0]	29.9 (4.9) [19.3–38.0]	28.7 (4.8) [18.0–38.0]
Creatinine clearance, mL/min, mean (SD)	NA	115 (24.4)	119 (29.6)	120 (35.6)	128 (41.1)	121 (34.3)
Product presentation per patient, *n* (%)						
Vial	50 (100)	97 (100)	60 (50.0)	363 (100)	0	570 (77.8)
Prefilled syringe	0	0	60 (50.0)	0	103 (100)	163 (22.2)
	RISPE1ZG15EU ***N*** **= 50**	**SAD-10055** ***N*** **= 139**	**BA-10148** ***N*** **= 120**	**RISE** ***N*** **= 2678**	**SHINE** ***N*** **= 300**	**Overall** ***N*** **= 3287**
Injections per site, *n* (%)						
Arm	40 (80.0)	15 (10.8)	0	922 (34.4)	58 (19.3)	1035 (31.5)
Abdomen	10 (20.0)	124 (89.2)	120 (100)	1756 (65.6)	241 (80.3)	2251 (68.5)
Missing	0	0	0	0	1 (0.3)	1 (0.0)
Injection volume, mL, mean (SD)	0.0563 (0.0170)	0.352 (0.165)	0.278 (0)	0.303 (0.142)	0.333 (0.154)	0.303 (0.144)

BMI body mass index, *NA* not available, *RISE* RIsperidone Subcutaneous Extended-release study, *SHINE* Safety in Humans of TV-46000 subcutaneous INjection Evaluation study

[a]Demographic and clinical data for $n = 466$ participants from the phase 3 studies are described here; however, $n = 41$ samples were below the lower limit of quantification. Therefore, only $n = 425$ participants were included in development of the popPK model

(– 1.7%) compared with the base model, and it was removed from the model. After checking for successful minimization, successful covariance step, and unbiased goodness-of-fit plots (Fig. S2), the base model without a sex effect on CLMO was accepted as the final model. There were no clinically relevant covariate effects on

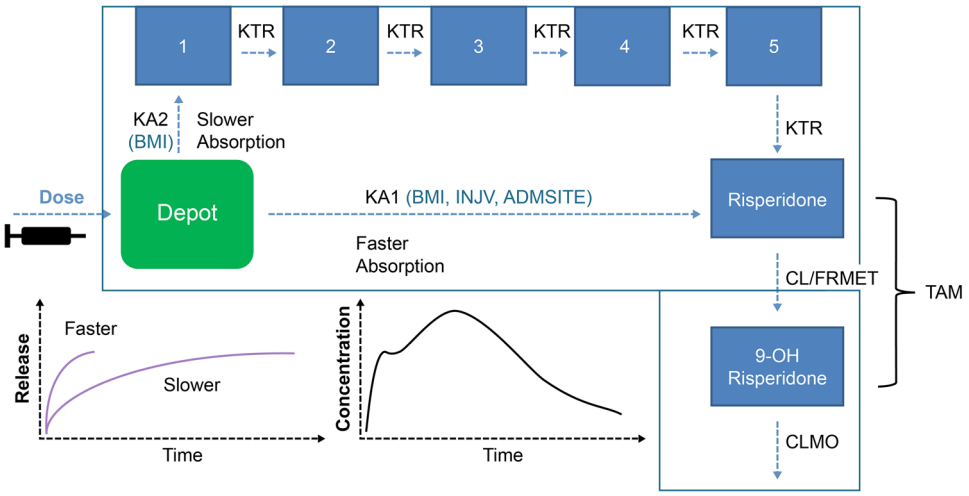

Fig. 1 Illustration of the PK model of the release of risperidone and active metabolite 9-OH risperidone following TV-46000. Variables in blue text are covariates included in the final PK model. *ADMSITE* administration site, *BMI* body mass index, *CL* (apparent) clearance, *CLMO* (apparent) metabolite clearance, *FRMET* fraction metabolized, *INJV* injection volume, *KA1* absorption rate constant 1, *KA2* absorption rate constant 2, *KTR* transit rate constant, *PK* pharmacokinetics, *TAM* total active moiety

the PK of 9-OH risperidone, and all parameters were estimated with good precision (RSE < 5%).

TAM Time–Concentration Simulations

Using these models, TAM concentration–time profiles were simulated for TV-46000 q1m and q2m across the range of available doses (Fig. 2).

Steady state was approached by approximately 3 months after initiation (86% and 88% of steady-state TAM exposure for q1m and q2m, respectively) and fully attained by approximately 6 months (i.e., >90% of steady-state TAM exposure) for both q1m and q2m. For example, median accumulation ratios for AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ were 2.0, 1.9, and 2.4, respectively, following q1m dosing with 75 mg, and 1.5, 1.4, and 1.5 following q2m dosing with 150 mg. Predicted TAM exposure parameters at steady state increased proportionally with increasing dose in the therapeutic dose range for both TV-46000 q1m and q2m (Table 4). Simulated TAM exposures over the 28-day and 56-day dosing intervals were comparable with daily exposure following oral risperidone 2–5-mg/d administration (Fig. 3, Table 4).

At corresponding doses of TV-46000, TAM AUC_{ss} following q2m dosing was twice that of the TAM AUC_{ss} following q1m dosing, as TV-46000 showed linearity in PK. Therefore, the average daily exposures with q1m and q2m were similar, supporting dosing interval interchangeability (Table 4). Furthermore, following TV-46000 administration, the proportion of trough values below the limit of quantification (BLQ) was relatively lower than it was following oral administration (e.g., 0.5% of observations were BLQ for TV-46000 75 mg q1m vs 13% for oral risperidone 3 mg once daily; Fig. 3). Although the site of administration was identified as a significant covariate in the parent (risperidone) PK model for TV-46000, no impact of the site of injection on the overall steady-state TAM exposure was observed (Fig. 4). In addition, the impact of early or late administration (± 1 week) on TAM exposure was small (Fig. S3).

Table 3 Final TV-46000 PK model parameter estimates for risperidone (parent) and 9-OH risperidone (metabolite)

Parameter	Estimate (95% CI)	%RSE	Bootstrap median (95% CI)
Risperidone (parent)			
CL/F, L/h	14.3 (13.4–15.1)	2.9	14.3 (13.4–15.1)
V/F, L	66.3 (60.6–71.9)	4.4	66.2 (61.1–72.0)
KA2, 1/h	0.000408 (0.000329–0.000486)	9.9	0.000409 (0.000340–0.000486)
KTR, 1/h	0.0252 (0.0228–0.0275)	4.8	0.0252 (0.0227–0.0275)
KA1, 1/h	0.000632 (0.000588–0.000676)	3.6	0.000631 (0.000591–0.000675)
KA1ADMSITE1	0.331 (0.109–0.553)	34.2	0.336 (0.147–0.546)
KA1BMI1	− 1.1 (− 1.460 to 0.745)	16.6	− 1.092 (− 1.482 to 0.716)
KA1INJV1	− 0.384 (− 0.469 to − 0.298)	11.3	− 0.384 (− 0.474 to − 0.297)
KA2BMI1	1.7 (0.992–2.410)	21.3	1.687 (0.798–2.552)
Random effects	**Estimate (95% CI)**	**%RSE (%shrinkage)**	**Bootstrap median (95% CI)**
IIV on KA2, %	254.2 (198.8–320.1)	5.2 (25.8)	252.8 (205.1–321.9)
Correlation IIV KA2 and KA1, %	42.8	14.7	43.7 (28.8–55.7)
IIV on KA1, %	51.0 (44.0–57.5)	6.0 (32.7)	51.0 (43.7–57.8)
IIV on CL, %	82.3 (75.3–89.3)	3.3 (6.6)	82.2 (75.9–88.9)
Residual error	**Estimate**	**%RSE (%shrinkage)**	**Bootstrap median (95% CI)**
EP, %	40.5	2.3 (5.8)	40.4 (38.5–42.2)
Parameter	**Estimate (95% CI)**	**%RSE**	**Bootstrap median (95% CI)**
9-OH risperidone (metabolite)			
CLMO, L/h	5.78 (5.52–6.04)	2.322	5.79 (5.54–6.06)
VMO, L	95.7 (88.5–103.0)	3.822	95.6 (89.0–103.1)
Random effects	**Estimate (95% CI)**	**%RSE (%shrinkage)**	**Bootstrap median (95% CI)**
IIV on CLMO, %	65.1 (58.9–71.1)	4.0 (5.5)	65.1 (59.4–71.4)
Residual error	**Estimate**	**%RSE (%shrinkage)**	**Bootstrap median (95% CI)**
EP, %	38.3	2.0 (2.7)	38.2 (36.7–40.0)

CL/F (apparent) clearance of parent, *CLMO* (apparent) clearance of metabolite, *EP* proportional residual error, *IIV* inter-individual variability, *KA1* absorption rate constant 1, *KA1ADMSITE1* administration site effect on KA1, *KA1BMI1* body mass index effect on KA1, *KA1INJV1* injection volume effect on KA1, *KA2* absorption rate constant 2, *KA2BMI1* body mass index effect on KA2, *KTR* transit rate constant, *RSE* relative standard error, *V/F* (apparent) volume of distribution of parent, *VMO* (apparent) volume of distribution of metabolite, which can also be interpreted as V/FRMET (fraction metabolized) fixed to 1

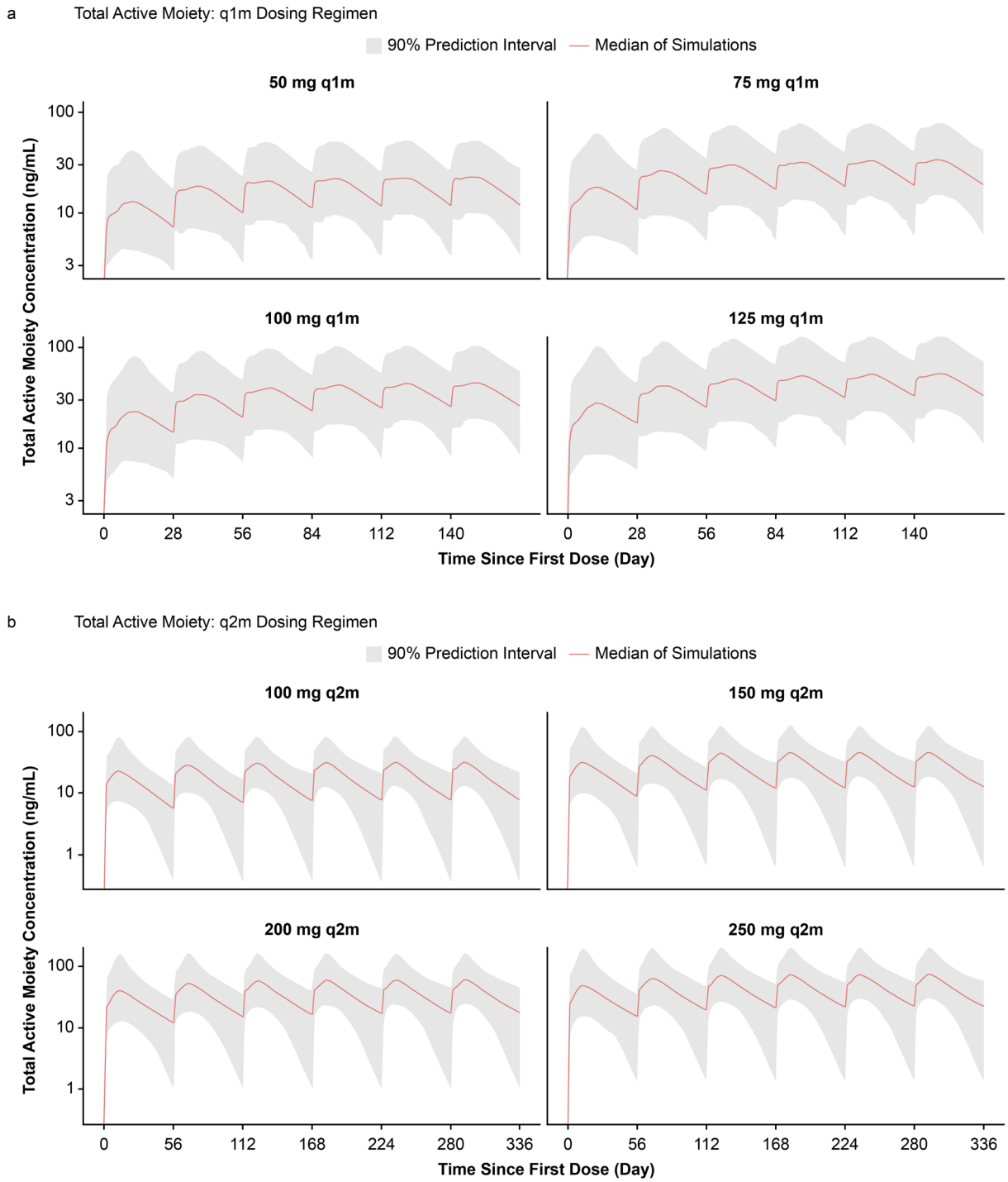

Fig. 2 Simulated TAM concentration–time profiles for (**a**) q1m and (**b**) q2m dosing. *q1m* once monthly, *q2m* once every 2 months, *TAM* total active moiety

Table 4 Model-derived median TAM PK parameters for TV-46000 and daily oral risperidone

Regimen	Dose	AUC_{ss} (ng × h/mL)	Daily AUC_{ss} (ng × h/mL)	$C_{avg,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$C_{trough,ss}$ (ng/mL)
Daily oral risperidone	2 mg/d	—	374	15.6	24.7	9.0
	3 mg/d	—	561	23.4	37.0	13.5
	4 mg/d	—	749	31.2	49.3	17.9
	5 mg/d	—	936	39.0	61.6	22.4
TV-46000 q1m	50 mg	13,306	475.2	19.8	25.1	12.1
	75 mg	19,951	712.5	29.7	36.4	19.5
	100 mg	26,521	947.2	39.5	47.5	26.8
	125 mg	33,141	1183.6	49.3	58.7	34.1
	100 mg	26,829	479.1	20.0	32.6	7.7
TV-46000 q2m	150 mg	40,152	717.0	29.9	47.2	12.8
	200 mg	53,321	952.2	39.7	61.4	17.6
	250 mg	66,634	1189.9	49.6	76.0	22.8

AUC area under the plasma concentration–time curve, AUC_{ss} AUC steady state, $C_{avg,ss}$ average plasma drug concentration at steady state, $C_{max,ss}$ maximum plasma drug concentration at steady state, $C_{trough,ss}$ trough plasma drug concentration at steady state, *PK* pharmacokinetics, *q1m* once monthly, *q2m* once every 2 months, *ss* steady state, *TAM* total active moiety

D2RO–Time Profile Simulations

Using the simulated TAM concentration–time profiles and published E_{max} PK/PD model [16], simulated D2RO–time profiles for TV-46000 were generally within the therapeutic window of 60–80% [16–19] during both dosing intervals (Fig. 5). Although D2RO levels with some doses deviated from the 60–80% range for short time periods (Fig. 5), the D2RO profile was within this range for most of the dosing interval.

DISCUSSION

The sequential parent–metabolite popPK model was developed with a different model (one-compartment model appropriate for sparse phase 3 PK data) than the previously published model, which was based on a phase 1 study of TV-46000 [15], including data from additional phase 1 studies and phase 3 trials. The model included single and multiple ascending doses, long-acting sc injection and oral administration, and sparsely and densely sampled PK data from a population of 692 participants from five studies with oral dose levels ranging from 2 to 5 mg and LAI levels from 12.5 to 250 mg. The parent (risperidone) model for TV-46000 described two parallel-release processes: a fast initial-release process that is potentially associated with the initial release from the sc depot, reaching therapeutic concentrations within 24 h, and a second, slower process that is likely associated with the in situ depot, releasing risperidone in a sustained manner over 28 days (q1m) or 56 days (q2m). Dual-release models have been used previously to describe the PK of other long-acting formulations of risperidone and 9-OH risperidone [20, 23].

The stepwise covariate analysis identified injection volume, BMI, and administration site (upper arm vs abdomen) as variables that had statistically significant effects on the release rate of risperidone in the sequential parent–metabolite model. The KA1 of the fast-release process

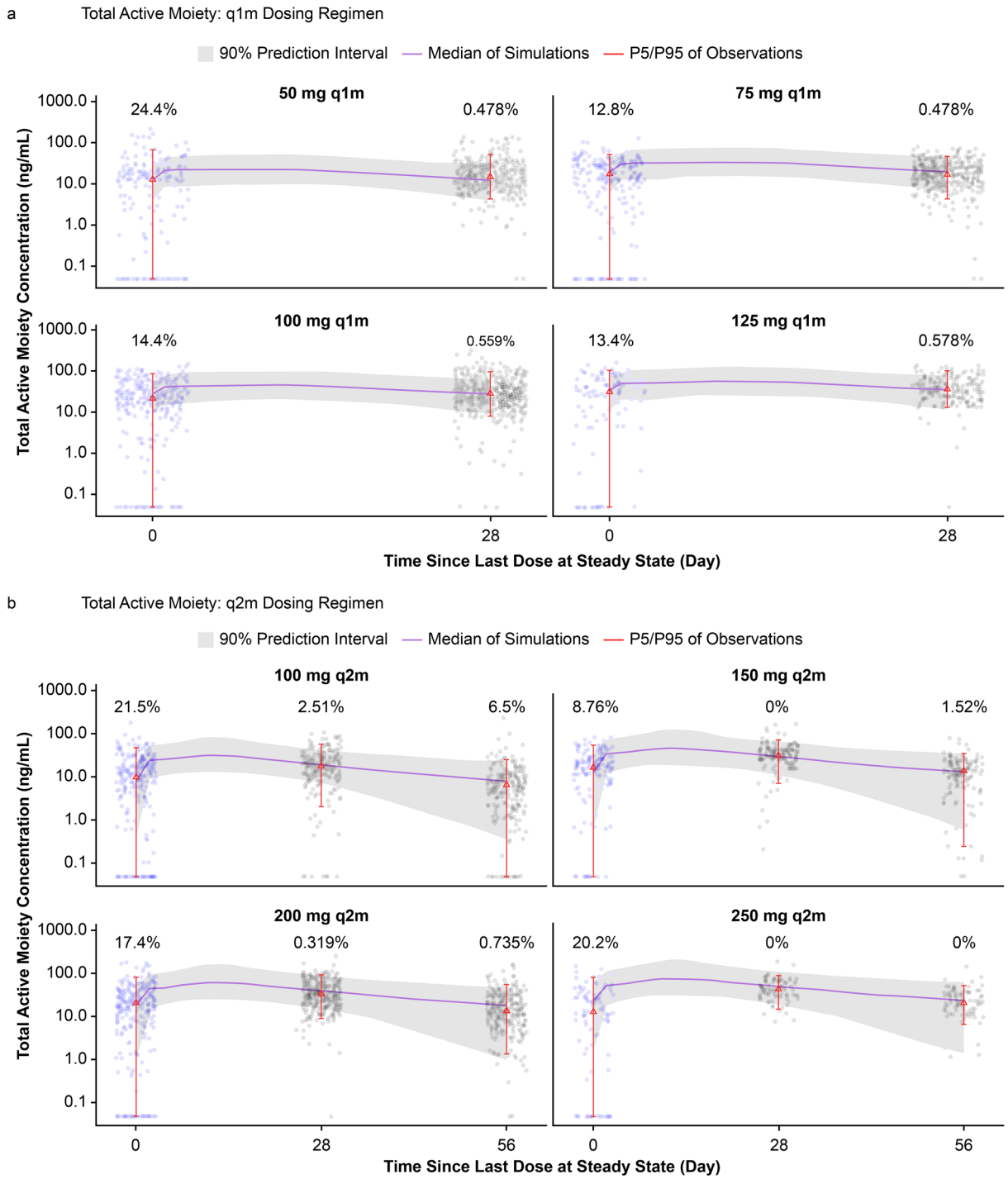

Fig. 3 Total active moiety concentrations—oral risperidone and (**a**) q1m and (**b**) q2m TV-46000 dosing in Study 30072 and Study 30078. Blue dots represent observed TAM concentrations following daily oral risperidone. Patients were stabilized on oral risperidone for 12 weeks. Thereafter, PK sampling was done at day 1 for oral risperidone. Gray dots represent observed TAM concentrations following TV-46000. PK sampling was done at the end of the dosing interval for TV-46000 q1m (28 days post dose) and at the middle and end of dosing interval for TV-46000 q2m (28 and 56 days post dose). *P5* 5th percentile, *P95* 95th percentile, *q1m* once monthly, *q2m* once every 2 months, *TAM* total active moiety

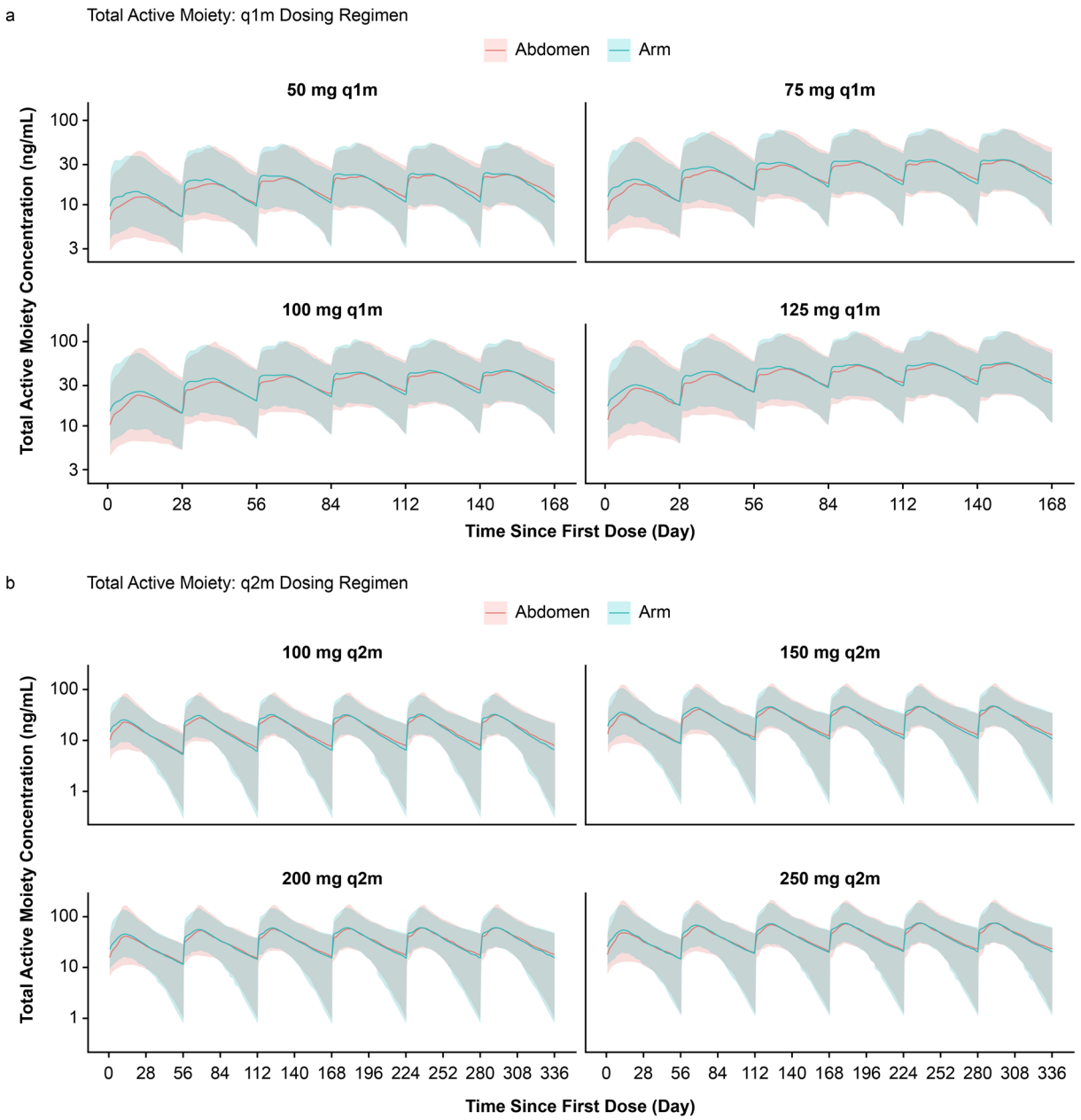

Fig. 4 Impact of injection site on TAM exposure of (**a**) q1m and (**b**) q2m TV-46000 dosing. Lines represent the median of simulations. Shaded areas represent 90% prediction interval. *q1m* once monthly, *q2m* once every 2 months, *TAM* total active moiety

decreased (slower release via the direct route) as injection volume increased. The effect of injection volume was pronounced at subtherapeutic doses (12.5 and 25 mg). However, at therapeutic doses (i.e., ≥ 50 mg), the effect of injection volume was minimal. Lower BMI was associated with higher KA1 values (faster release via the direct route) and decreased KA2 (slower release via the indirect route). This suggests that the slower release route is likely associated with distribution into subcutaneous fat, which is in line with the lipophilic profile of risperidone [21].

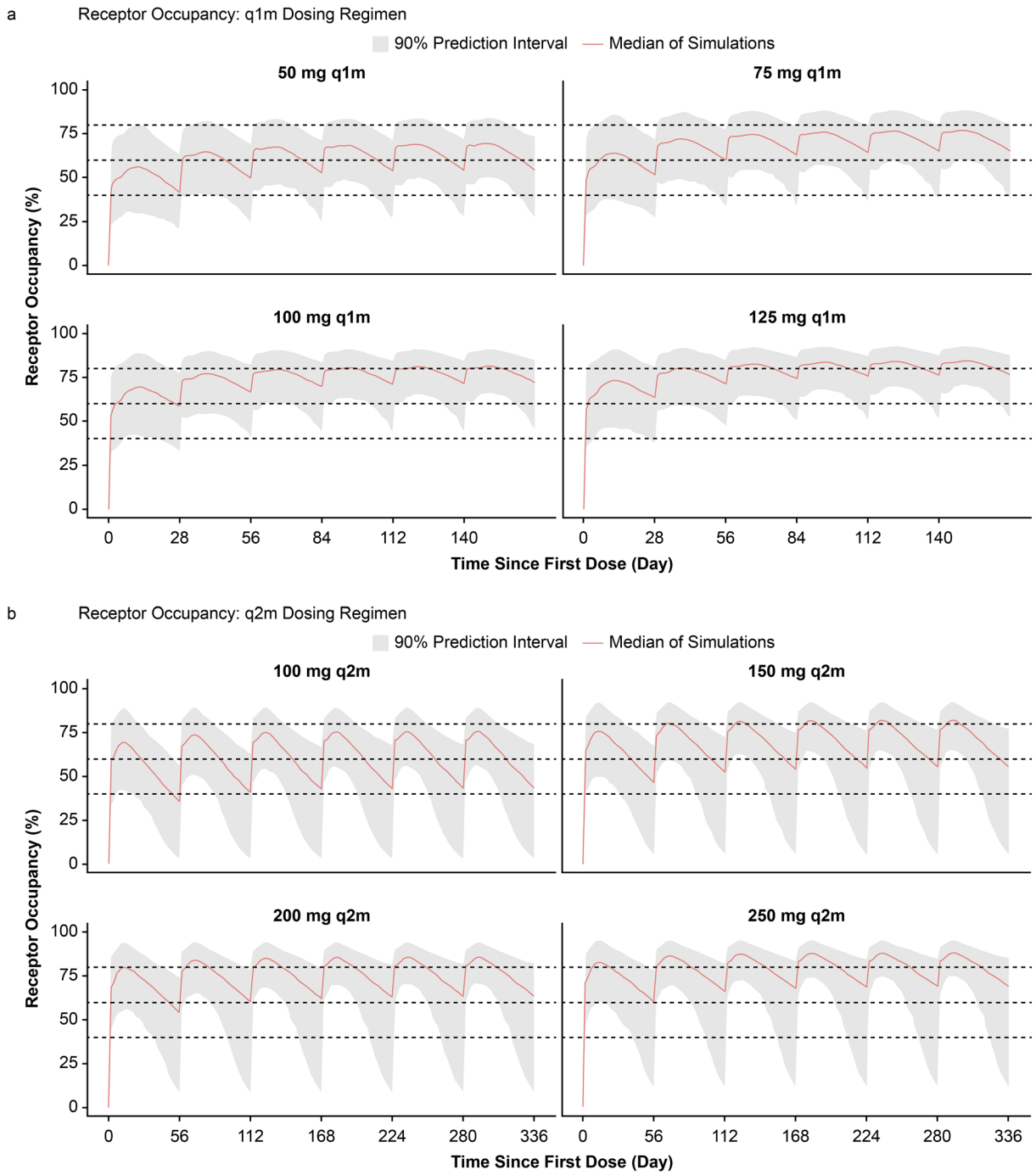

Fig. 5 D2RO–time profiles since first dose of TV-46000 for (**a**) q1m and (**b**) q2m dosing. Dashed reference lines at 40%, 60%, and 80%. *D2RO* dopamine-receptor occupancy, *q1m* once monthly, *q2m* once every 2 months

Injection of TV-46000 in the upper arm was associated with a higher KA1 compared with abdominal injection, which could be related to the difference in fat distribution between the upper arm and the abdomen. Although these covariates were statistically significant in the parent (risperidone) model, the reduction in unexplained variability between subjects was

less than 5%, suggesting no clinically relevant effect on the overall steady-state TAM exposure. This was also observed in the phase 1 data [15], indicating that the sites of injection can be interchangeable. This provides patients and clinicians with more options for injection site, as most prefer administration to the back of the upper arm, as well as the convenience of alternating between sites with each subsequent dose [7]. In addition, the impact of early or late administration of the next dose (±1 week) on TAM exposure was minimal, indicating resumption of treatment is straightforward (provided deviations are short), with likely minimal impact on clinical outcomes.

TAM-simulated exposure following TV-46000 administration demonstrated sustained release characteristics over time comparable with oral risperidone (for both q1m and q2m). At corresponding doses, TAM AUC_{ss} after TV-46000 q2m dosing was twice that of q1m dosing, while average daily exposures were similar, indicative of dose proportionality over the dose range tested (TV-46000 50–250 mg). TAM exposure was similar to that of oral risperidone 2–5 mg/d, and dose strengths for q1m (50, 75, 100, or 125 mg) and q2m (100, 150, 200 or 250 mg) provided comparable exposure over 28 days (q1m) and 56 days (q2m), depending on the dose. These findings support the interchangeability of the two dosing regimens (depending on patient and clinician needs or preferences) from a clinical and PK perspective. The choice between these options can be influenced by factors like patient preference, adherence, the severity of the illness, and logistical considerations. For instance, q1m administration allows healthcare providers to monitor patients more frequently, which can be beneficial in early detection of relapse signs, adjusting dosages, or addressing side effects. Alternatively, q2m injections offer greater convenience due to less disruption to daily life, are suitable for patients who have been stable on treatment for a significant period of time, require less monitoring, and have proven efficacy in maintaining stability. Q2m injections are also more cost-effective for healthcare systems owing to reduced clinic visits and resource utilization, while maintaining treatment efficacy. Both TV-46000 q1m and q2m are also within comparable peak-to-trough ranges compared with other LAI formulations [24, 25].

In addition to TAM exposure, a PK/PD model was applied to simulate D2RO from the predicted TAM concentrations. For both q1m and q2m regimens, the D2RO profile was mostly within the preferred range of 60–80% [16–19] during the intended dosing interval. These D2RO and popPK simulations support the appropriateness of the doses selected for clinical development and approved by the US FDA [1].The limitations mirror those of the previous phase 1 popPK model [15] and the RISE and SHINE studies [2, 14] from which the phase 3 data for the PK models were acquired, namely that the race and sex of participants were skewed towards African Americans and male patients, respectively and that patients aged > 65 years were excluded from the study. This may impact the generalizability of the popPK simulations performed here. However, the characteristics of the population included in the RISE and SHINE studies were consistent with some other phase 3 studies of risperidone LAIs, where the participants were also mostly male African Americans [26, 27]. Additionally, although factors such as age and sex affected the PK of TV-46000, these were not considered clinically relevant.

CONCLUSION

The PK of TV-46000 is characterized by a complex and multiphasic release profile, representing a rapid-release phase and a prolonged disposition/elimination process, representative of "flip–flop" kinetics. There is also a second, prolonged risperidone-release phase, which overlaps with the elimination phase. Because of this release-dependent elimination, therapeutic levels are maintained after injection for 28 to 56 days (depending on dose). Therapeutic concentrations are reached within 24 h after administration and by 3 months after initiation, and 86–88% of steady-state exposures are achieved and fully attained by 6 months for both q1m and q2m regimens. The sequential parent–metabolite popPK model demonstrated similar TAM exposure following TV-46000 administration to

both injection sites, supporting the interchangeability of administration sites (arm vs abdomen). The model also confirmed that TV-46000 q1m (50–125 mg) and q2m (100–250 mg) both provide dose-proportional TAM exposure adequate for achieving D2RO within the effective range [16–19] and comparable with corresponding doses of daily oral risperidone (2–5 mg/d), with lower maximum plasma concentrations. Although intrinsic factors such as age and sex did affect the PK of TV-46000, these effects were not considered clinically relevant. Furthermore, the product presentation (vial vs PFS) did not affect exposure. Taken together, the observed data, the developed model, and the performed simulations support TV-46000 as a LASCA that offers flexible dosing intervals (q1m or q2m) and administration sites (abdomen or upper arm) and does not require oral supplementation or loading dose(s).

ACKNOWLEDGEMENTS

This study was supported by Teva Branded Pharmaceutical Products R&D, Inc.

Medical Writing/Editorial Assistance. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Jean-Paul Fouche, PhD, and Jennifer C. Jaworski, MS, BCMAS, CMPP, and editing support by Kelsey Gribbon, MS, all of Ashfield MedComms, an Inizio company, and were funded by Teva Branded Pharmaceutical Products R&D LLC.

Author Contributions. Itay Perlstein: Conceptualization, Data interpretation, Investigation, Writing—reviewing and editing. Avia Merenlender Wagner: Conceptualization, Data interpretation, Investigation, Writing—reviewing and editing. Anna Elgart: Conceptualization, Data interpretation, Investigation, Writing—reviewing and editing. Anthe Zandvliet: Data curation, Data interpretation, Formal analysis, Methodology, Visualization, Writing—reviewing and editing. Farina Hellmann: Data curation, Data interpretation, Formal analysis, Methodology, Visualization, Writing—reviewing and editing. YuWei Lin: Data curation, Data interpretation, Formal analysis, Methodology, Visualization, Writing—reviewing and editing. Eline van Maanen: Data curation, Data interpretation, Formal analysis, Methodology, Visualization, Writing—reviewing and editing. Nele Plock: Data curation, Data interpretation, Formal analysis, Methodology, Visualization, Writing—reviewing and editing. Floris Fauchet: Data curation, Data interpretation, Formal analysis, Methodology, Visualization, Writing—reviewing and editing. Rajendra Singh: Conceptualization, Data interpretation, Investigation, Writing—reviewing and editing.

Funding. This study was supported by Teva Branded Pharmaceutical Products R&D LLC. The journal's Rapid Service Fee was funded by Teva Branded Pharmaceutical Products R&D LLC.

Data Availability. The data sets used and/or analyzed for the study described in this manuscript are available upon reasonable request. Qualified researchers may request access to patient-level data and related study documents, including the study protocol and the statistical analysis plan. Patient-level data will be de-identified and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please visit www.clinicalstudydatarequest.com to make your request.

Declarations

Conflict of Interest. This study was supported by funding from Teva Branded Pharmaceutical Products R&D LLC. Itay Perlstein has received consultancy fees from Teva Pharmaceuticals in relation to this study. Avia Merenlender Wagner, Anna Elgart, and Rajendra Singh are employees and/or shareholders of Teva Pharmaceuticals. Anthe Zandvliet, Farina Hellmann, YuWei Lin, Eline van Maanen, Nele Plock, and Floris Fauchet are employees of Certara, which has received payments from Teva Pharmaceuticals in relation to this study.

Ethical Approval. This article is based on data from previously conducted studies and does not contain any new studies with human participants. All involved study centers of the original clinical trials received approval by local ethics committees, and informed consent was received for all patients. Consent was obtained during the original clinical trials, and no new consent forms were required/collected for this analysis.

REFERENCES

1. Teva Neuroscience, Inc. Uzedy™ (risperidone) extended-release injectable suspension. Parsippany; 2024.

2. Kane JM, Harary E, Eshet R, et al. Efficacy and safety of TV-46000, a long-acting, subcutaneous, injectable formulation of risperidone, for schizophrenia: a randomised clinical trial in the USA and Bulgaria. Lancet Psychiatry. 2023;10(12):934–43.

3. Janssen Pharmaceutical Companies. Risperdal Consta® (risperidone) long-acting injection. Titusville; 2021.

4. Shandong Luye Pharmaceutical Co., Ltd. Rykindo® (risperidone extended-release injectable suspension for intramuscular [IM] use). Yantai, Shandong; 2023.

5. Indivior Inc. Perseris™ (risperidone) for extended-release injectable suspension. North Chesterfield; 2021.

6. Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. J Clin Psychiatry. 2016;77(Suppl 3):1–24.

7. Robinson DG, Suett M, Wilhelm A, et al. Patient and healthcare professional preferences for characteristics of long-acting injectable antipsychotic agents for the treatment of schizophrenia. Adv Ther. 2023;40(5):2249–64.

8. Kane JM, Correll CU. Optimizing treatment choices to improve adherence and outcomes in schizophrenia. J Clin Psychiatry. 2019;80(5):IN18031AH1C.

9. Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient Prefer Adherence. 2013;7:1171–80.

10. Lian L, Kim DD, Procyshyn RM, Cázares D, Honer WG, Barr AM. Long-acting injectable antipsychotics for early psychosis: a comprehensive systematic review. PLoS ONE. 2022;17(4):e0267808.

11. Lee S, Schwartz S. Adherence and persistence to long-acting injectable dopamine receptor blocking agent therapy in the United States: a systematic review and meta-analysis of cohort studies. Psychiatry Res. 2021;306:114277.

12. Merenlender Wagner A, Perlstein I, Elgart A, et al. Exposure-response analysis to assess the relationships between TV-46000 pharmacokinetic exposure parameters, prevention of impending relapse and adverse events. In: 34th Annual Psych Congress, October 29–November 1, 2021 ed. San Antonio, Texas; 2021.

13. Merenlender Wagner A, Elgart A, Perlstein I, et al. Phase 1 open-label study assessing the pharmacokinetics and safety of TV-46000, a novel long-acting subcutaneous injectable formulation of risperidone. Eur Neuropsychopharmacol. 2021;53(7):S339–40.

14. Kane JM, Eshet R, Harary E, et al. A long-term safety and tolerability study of TV-46000 for subcutaneous use in patients with schizophrenia: a phase 3, randomized, double-blinded clinical trial. CNS Drugs. 2024;38:625–36.

15. Perlstein I, Merenlender Wagner A, Gomeni R, et al. Population pharmacokinetic modeling and simulation of TV-46000: a long-acting injectable

formulation of risperidone. Clin Pharmacol Drug Dev. 2022;11(7):865–77.

16. Nordström AL, Farde L, Wiesel FA, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol Psychiatry. 1993;33(4):227–35.

17. Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L. Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. Am J Psychiatry. 1999;156(6):869–75.

18. Vanover KE, Davis RE, Zhou Y, et al. Dopamine D(2) receptor occupancy of lumateperone (ITI-007): a positron emission tomography study in patients with schizophrenia. Neuropsychopharmacology. 2019;44(3):598–605.

19. Uchida H, Takeuchi H, Graff-Guerrero A, Suzuki T, Watanabe K, Mamo DC. Dopamine D2 receptor occupancy and clinical effects: a systematic review and pooled analysis. J Clin Psychopharmacol. 2011;31(4):497–502.

20. Ivaturi V, Gopalakrishnan M, Gobburu JVS, et al. Exposure-response analysis after subcutaneous administration of RBP-7000, a once-a-month long-acting Atrigel formulation of risperidone. Br J Clin Pharmacol. 2017;83(7):1476–98.

21. Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM. Pharm Res. 1998;15(9):1463–8.

22. Korell J, Green B, Remmerie B, Vermeulen A. Determination of plasma concentration reference ranges for risperidone and paliperidone. CPT Pharmacometr Syst Pharmacol. 2017;6(9):589–95.

23. Gomeni R, Bressolle-Gomeni F, Fava M. Response surface analysis and nonlinear optimization algorithm for maximization of clinical drug performance: application to extended-release and long-acting injectable paliperidone. J Clin Pharmacol. 2016;56(10):1296–306.

24. Correll CU, Kim E, Sliwa JK, et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. CNS Drugs. 2021;35(1):39–59.

25. Sheehan JJ, Reilly KR, Fu DJ, Alphs L. Comparison of the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. Innov Clin Neurosci. 2012;9(7–8):17–23.

26. Nasser AF, Henderson DC, Fava M, et al. Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. J Clin Psychopharmacol. 2016;36(2):130–40.

27. Kane JM, Eerdekens M, Lindenmayer J, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry. 2003;160:1125–32.