

SUPPLEMENTARY MATERIAL

Switching Patients with Schizophrenia from Intramuscular Paliperidone Palmitate Once Monthly to TV-46000, a Long-Acting Subcutaneous Antipsychotic: Population Pharmacokinetic–Based Strategies

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Running heading: Switching from paliperidone once monthly to TV-46000, a long-acting subcutaneous antipsychotic

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Prior Presentations

Part of this work was previously presented at the Annual Psych Congress Elevate on May 30–June 2, 2024, in Las Vegas, NV;; at the 37th European College of Neuropsychopharmacology Congress on September 21–24, 2024, in Milan, Italy;; at the the Annual Psych Congress on October 29–November 2, 2024, in Boston, MA;; at the NEI Congress 2024, on November 7–10, 2024, in Colorado Springs, CO;; and at NEI Saturday Morning Live, on March 22, 2025, virtually

Table S1 TV-46000 clinical trials included in the popPK dataset [27]

Study	Design	Dose	Subjects treated with TV-46000, n	Participants used for generation of virtual populations, n		
Phase 1 studies						
RISPE1ZG15EU	Single-dose study, targeting subtherapeutic plasma concentrations in healthy volunteers	Single dose, 12.5–25 mg	55	NA		
TV-46000-SAD-10055	Single dose and three consecutive monthly doses in patients with schizophrenia who are stable on oral risperidone	Single dose, 50–225 mg; 75–150 mg q1m	96	NA		
TV-46000-BA-10148	Single-sequence study in parallel groups of patients with schizophrenia to assess the relative bioavailability of TV-46000 from pre-filled syringe	Single dose of 100-mg vial or pre-filled syringe	Approximately 110	NA		
Phase 3 studies						
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)	50–125 mg q1m 100–250 mg q2m	Approximately 596, including placebo	Placebo 61 30 68 22	q1m 50 mg: 47 75 mg: 46 100 mg: 68 125 mg: 22	q2m 100 mg: 60 150 mg: 32 200 mg: 67 250 mg: 21
SHINE (NCT03893825)	Safety extension study of TV46000-CNS-30072. TV-46000 sc q1m and q2m in a 1:1 ratio	50–125 mg q1m 100–250 mg q2m	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)	NA		

PK pharmacokinetic; *popPK* population pharmacokinetic; *q1m* once monthly; *q2m* once every 2 months; *sc* subcutaneous; *NA* not applicable

Table S2 Initiating TV-46000 4 weeks after the last dose of PP1m using a transition and maintenance switch strategy: simulated PK parameters

Switching scenario		PP1m C _{max} , ng/mL	TV-46000 median C _{max} , ng/mL (ratio of TV-46000: PP1m at steady state)		PP1m C _{min} , ng/mL	TV-46000 median C _{min} , ng/mL (ratio of TV-46000:PP1m at steady state)		PP1m C _{avg} , ng/mL	TV-46000 median C _{avg} , ng/mL (ratio of TV-46000:PP1m at steady state)	
PP1m dose switching from	TV-46000 dose switching to		1st dose	Steady state		1st dose	Steady state		1st dose	Steady state
117 mg	75 mg (50 mg for first 6 months) q1m	27.4	50 mg: 35.8 (1.3) 75 mg: 35.7 (1.3)	39.5 (1.4)	17.0	50 mg: 16.0 (0.9) 75 mg: 13.5 (0.8)	17.9 (1.0)	22.8	50 mg: 28.2 (1.2) 75 mg: 27.2 (1.2)	29.8 (1.3)
156 mg	100 mg (75 mg for first 6 months) q1m	36.0	75 mg: 48.3 (1.3) 100 mg: 48.6 (1.4)	52.6 (1.5)	23.0	75 mg: 22.0 (1.0) 100 mg: 21.6 (0.9)	26.3 (1.1)	30.2	75 mg: 39.1 (1.3) 100 mg: 38.5 (1.3)	40.9 (1.4)
234 mg	125 mg (100 mg for first 6 months) q1m	52.3	100 mg: 67.4 (1.3) 125 mg: 63.2 (1.2)	64.2 (1.2)	35.1	100 mg: 34.3 (1.0) 125 mg: 31.2 (0.9)	32.7 (0.9)	44.7	100 mg: 56.0 (1.3) 125 mg: 50.5 (1.1)	50.2 (1.1)
117 mg	150 mg (100 mg for first 2 months) q2m	26.8	100 mg: 44.5 (1.7) 150 mg: 52.4 (2.0)	50.5 (1.9)	16.7	100 mg: 12.3 (0.7) 150 mg: 12.4 (0.7)	11.0 (0.7)	22.4	100 mg: 28.0 (1.3) 150 mg: 32.0 (1.4)	29.5 (1.3)
156 mg	200 mg (150 mg for first 2 months) q2m	36.8	150 mg: 62.2 (1.7) 200 mg: 69.7 (1.9)	65.8 (1.8)	23.2	150 mg: 18.0 (0.8) 200 mg: 18.7 (0.8)	15.7 (0.7)	30.7	150 mg: 40.5 (1.3) 200 mg: 44.0 (1.4)	39.1 (1.3)
234 mg	250 mg (200 mg for first 2 months) q2m	52.5	200 mg: 86.2 (1.6) 250 mg: 89.9 (1.7)	81.2 (1.5)	34.9	200 mg: 28.3 (0.8) 250 mg: 28.2 (0.8)	21.2 (0.6)	44.8	200 mg: 58.1 (1.3) 250 mg: 58.6 (1.3)	49.6 (1.1)

For the transition and maintenance switch strategy, the patient initially receives a lower dose of TV-46000 q1m for 6 months or of TV-46000 q2m for 1 month and then moves to the higher TV-46000 dose comparable to oral risperidone

Fig. S1 Schematic of comparable-dose switching scenarios when switching from PP1m to (A) TV-46000 q1m or (B) TV-46000 q2m

a

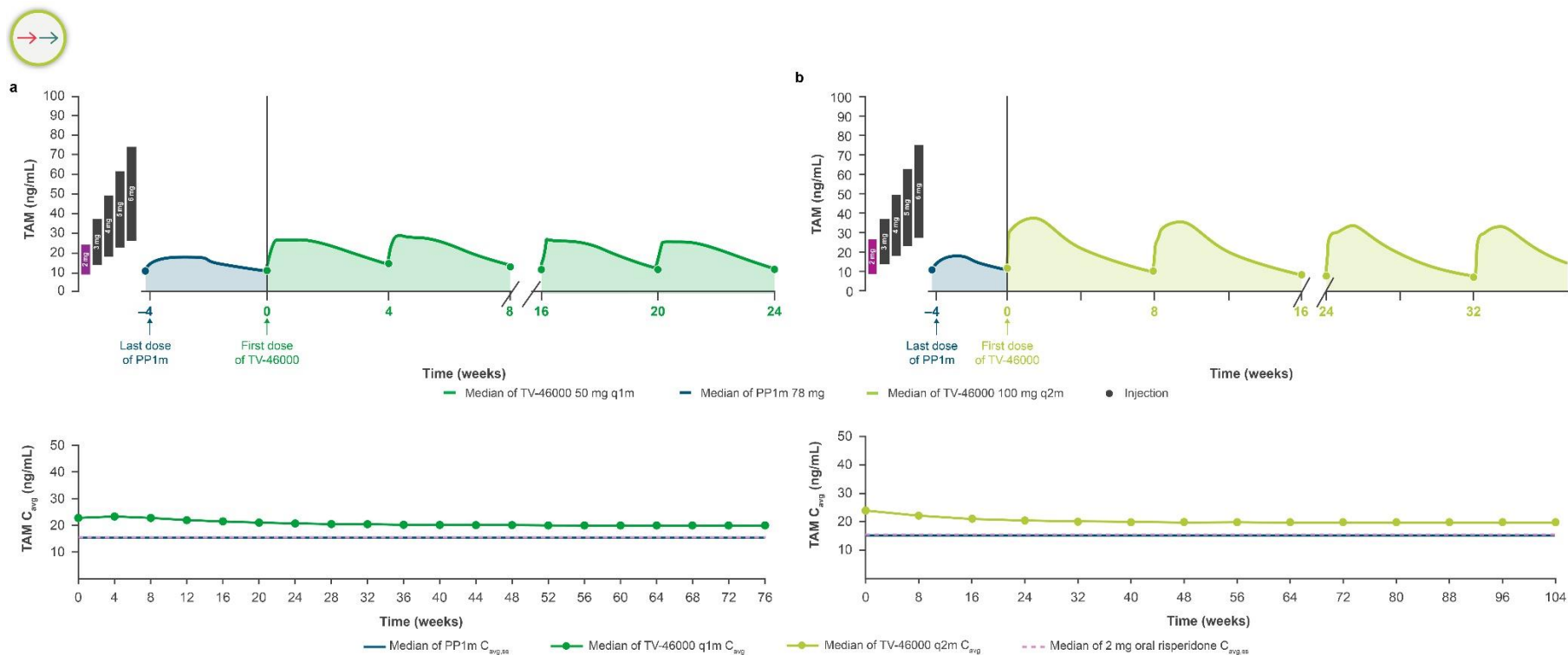
	PP1m dose	TV-46000 q1m dose
2 mg/d oral risperidone scenarios	78 mg	50 mg (Fig. S2)
3 mg/d oral risperidone scenarios	117 mg	75 mg (Fig. S3)
4 mg/d oral risperidone scenarios	156 mg	100 mg (Fig. S4)

b

	PP1m dose	TV-46000 q2m dose
2 mg/d oral risperidone scenarios	78 mg	100 mg (Fig. S2)
3 mg/d oral risperidone scenarios	117 mg	150 mg (Fig. S3)
4 mg/d oral risperidone scenarios	156 mg	200 mg (Fig. S4)

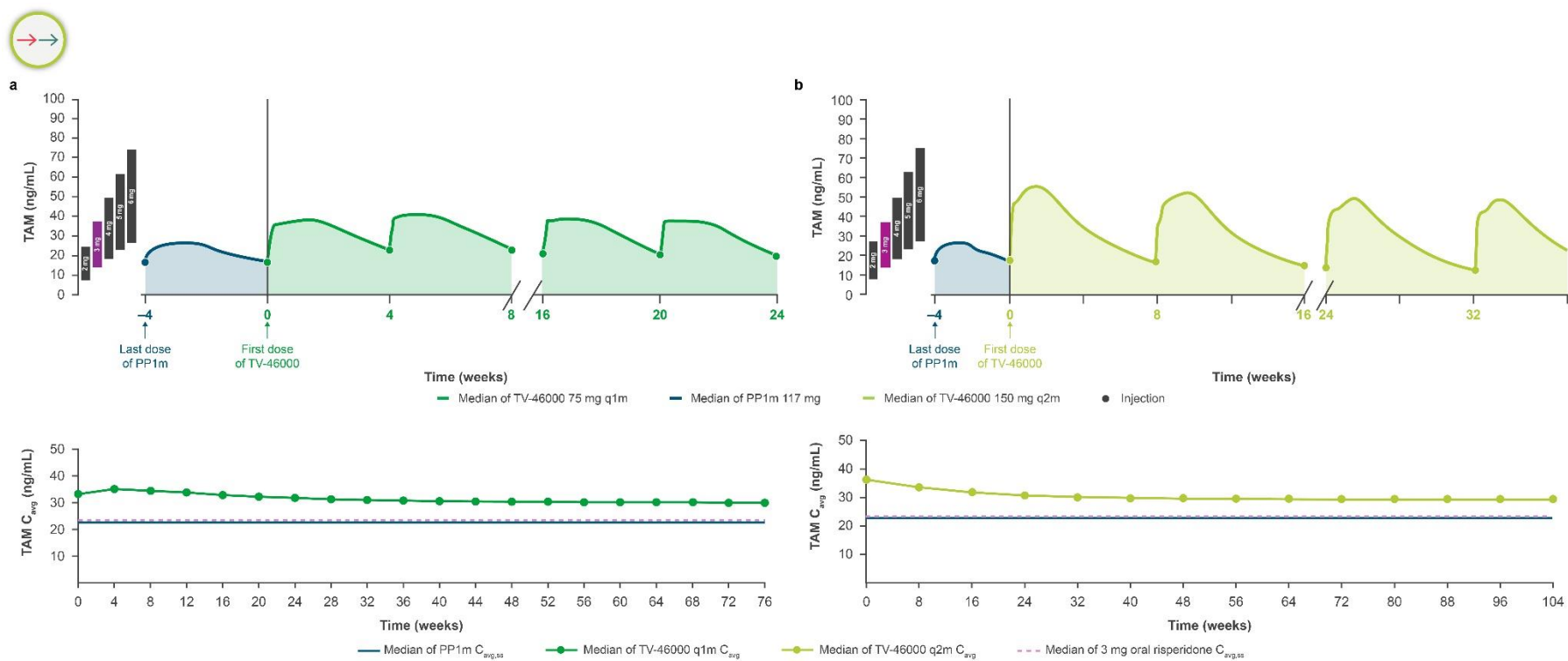
q1m once monthly; *q2m* once every 2 months

Fig. S2 Comparable-dose switching from PP1m 78 mg to (A) TV-46000 50 mg q1m and (B) TV-46000 100 mg q2m (administered in the back of the upper arm) 4 weeks after last dose of PP1m: representative TAM concentration simulations and average TAM



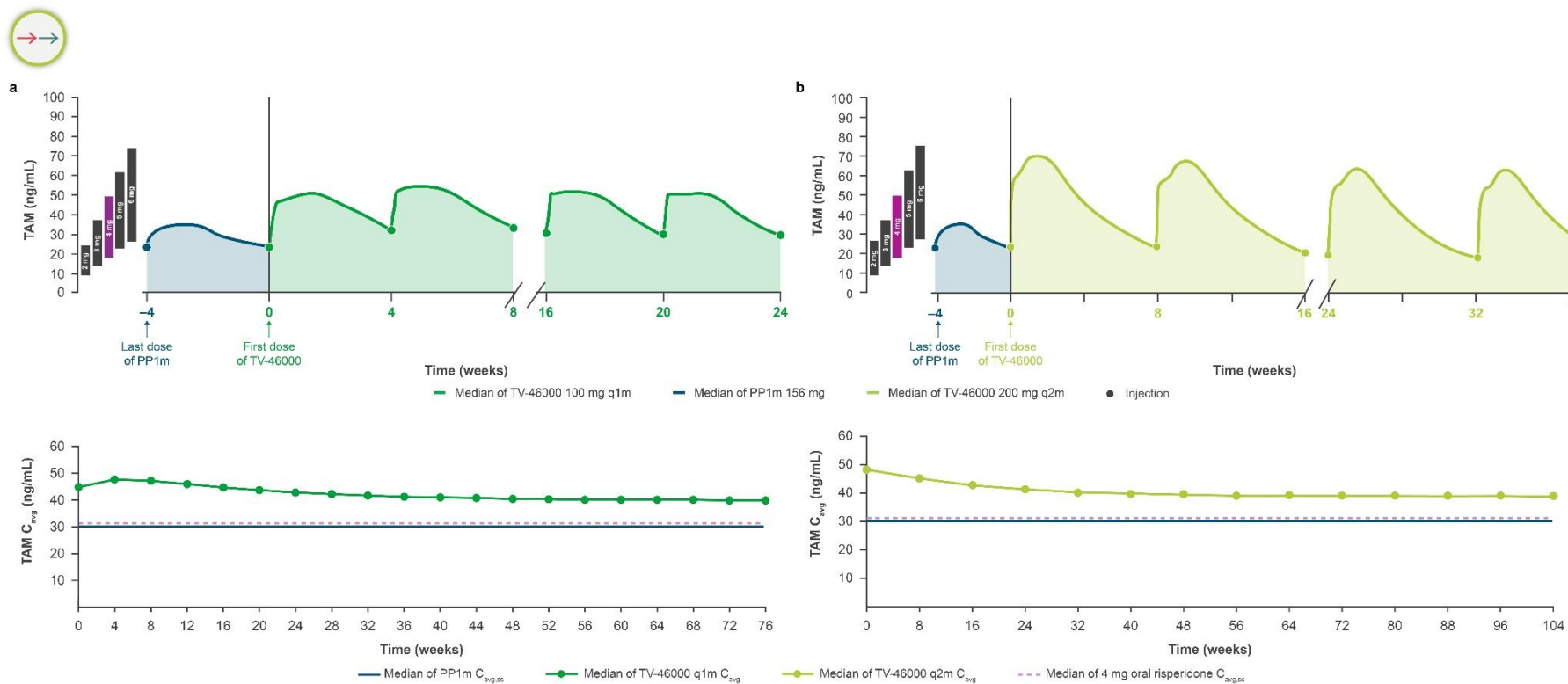
$C_{avg,ss}$ average plasma concentration at steady state; PP1m paliperidone palmitate once monthly; q1m once monthly; q2m once every 2 months; TAM total active moiety

Fig. S3 Comparable-dose switching from PP1m 117 mg to (A) TV-46000 75 mg q1m and (B) TV-46000 150 mg q2m (administered in the back of the upper arm) 4 weeks after last dose of PP1m: representative TAM concentration simulations and average TAM



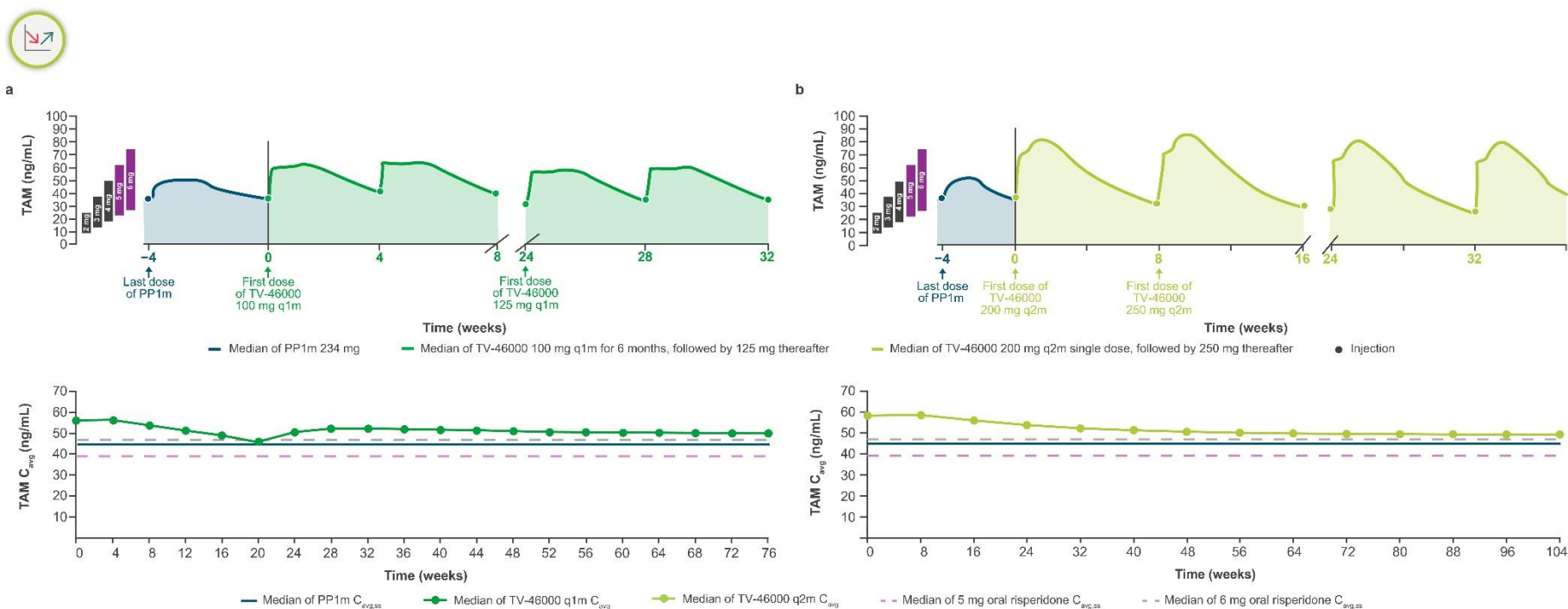
$C_{avg,ss}$ average plasma concentration at steady state; PP1m paliperidone palmitate once monthly; q1m once monthly; q2m once every 2 months; TAM total active moiety

Fig. S4 Comparable-dose switching from PP1m 156 mg to (A) TV-46000 100 mg q1m and (B) TV-46000 200 mg q2m (administered in the back of the upper arm) 4 weeks after last dose of PP1m: representative TAM concentration simulations and average TAM



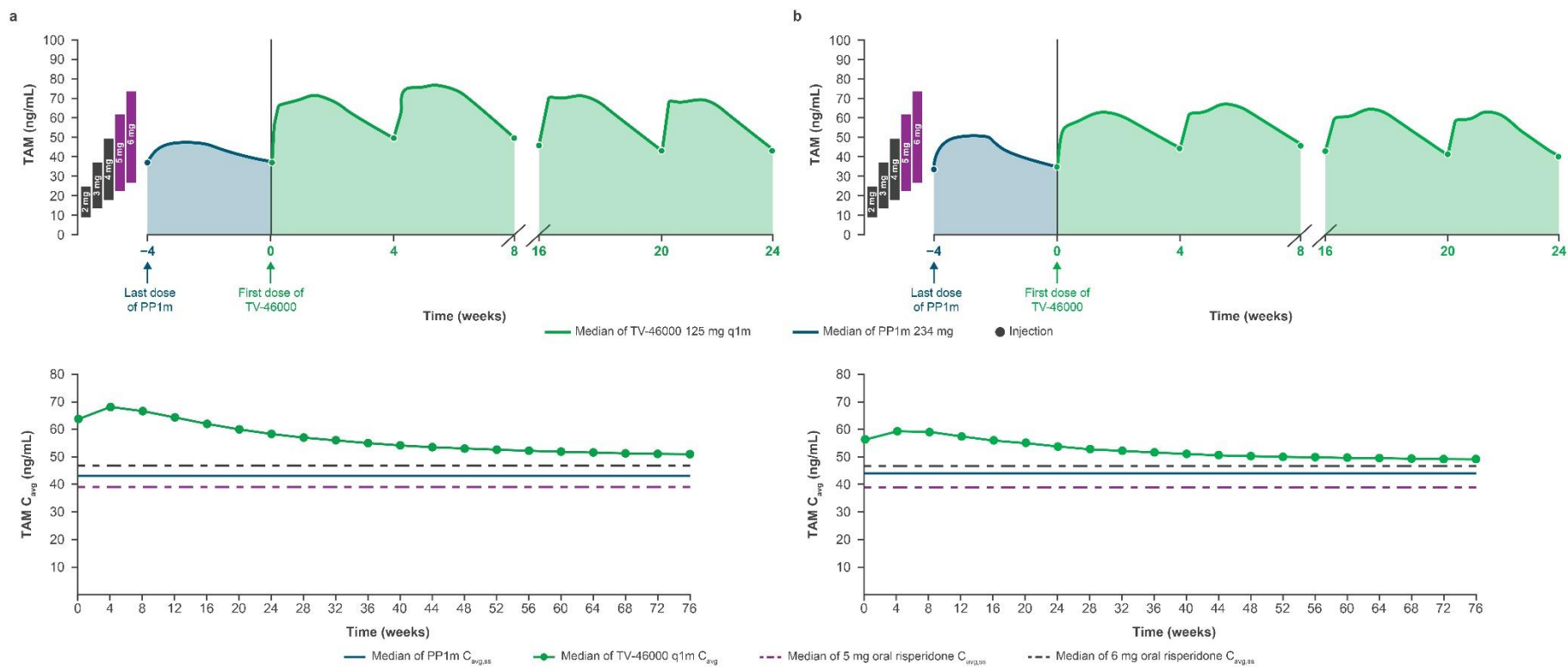
$C_{avg,ss}$ average plasma concentration at steady state; PP1m paliperidone palmitate once monthly; q1m once monthly; q2m once every 2 months; TAM total active moiety

Fig. S5 Switching from PP1m 234 mg to (A) TV-46000 100 mg q1m for 6 months followed by 125 mg thereafter and (B) TV-46000 single dose of 200 mg q2m, followed by 250 mg thereafter at 4 weeks after last dose of PP1m (administered in the back of the upper arm): representative TAM concentration simulations and average TAM



$C_{avg,ss}$ average plasma concentration at steady state; PP1m paliperidone palmitate once monthly; q1m once monthly; q2m once every 2 months; TAM total active moiety

Fig. S6 Impact of site of administration on TAM exposure when switching from 234 mg PP1m to 125 mg TV-46000 q1m: (A) PP1m gluteal to TV-46000 back of upper arm and (B) PP1m deltoid to TV-46000 abdomen



C_{avg,ss} average plasma concentration at steady state; q1m once monthly; TAM total active moiety