SUPPLEMENTARY MATERIAL

Efficacy and Safety of TV-46000 and Second-Generation Long-Acting Injectable Antipsychotics for Schizophrenia: A Systematic Literature Review and Network Meta-Analysis of Randomized Controlled Trials

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TABLES

Table S1 PICOS inclusion and exclusion criteria (SLR)

Domain	Inclusion criteria	Exclusion criteria
Population	• Adults and adolescents (≥13 years old) with schizophrenia • Clinically stable (receiving maintenance treatment)	• First episode patients • Patients on clozapine or treatment-refractory illness • A diagnosis of schizophrenia for <1 year
Treatment(s)	• Second-generation long-acting injectable antipsychotics approved in Canada – Risperidone – Aripiprazole – Paliperidone palmitate	• Long-acting second-generation injectable antipsychotics not approved in Canada (eg, aripiprazole lauroxil, olanzapine pamoate) • Injectable typical (first generation) antipsychotics (eg, haloperidol decanoate, fluphenazine decanoate, flupentixol decanoate, zuclopenthixol decanoate) • Oral antipsychotics
Comparator(s)	• Any comparator	• None
Outcomes	• Efficacy – Time to impending relapse – Impending relapse rate – Remission rate – Stability maintenance – Change in PANSS score – Change in CGI-S • Safety – Treatment-related AEs – AEs (weight gain, injection-site pain) – AE-related discontinuation – All-cause discontinuation – Adherence • Patient Reported – Drug Attitudes Inventory 10-item – Schizophrenia Quality of Life Scale – Personal and Social Performance Scale – EQ-5D • Other – Hospitalization rate – ER visit rate – Outpatient visit rate	• Studies that do not report any of the outcomes of interest
Study Design	• Randomized controlled trials	• Observational studies • Pre-clinical studies • Case reports • Case series • Letters • Single-arm • Reviews (eg, narrative, opinion, commentary) • Systematic reviews and meta-analyses
Language	• English	• Any other language
Date	• Jan 2000 – May 2023	• Pre-2000

AE adverse event, *CGI-S* Clinical Global Impression – Severity, *EQ-5D* European Quality of Life-Five Dimension, *ER* emergency room; *PANSS* Positive and Negative Syndrome Scale, *PICOS* population, intervention, comparators, outcomes, and study design

Table S2 Search strategy (NMAs)

Group 1: Disease and treatments	Group 2: Mode of therapy	Group 3: Study types
Schizophrenia AND Any of the following treatments: • All antipsychotics[a] • Risperidone • Aripiprazole • Paliperidone palmitate • Aripiprazole lauroxil[b]	Injectables OR Extended-Release Drugs OR Maintenance Drug Therapy	RCTs OR SLR, MA, NMA & ITC[c]

[a]All antipsychotics and neuroleptic agents were included to ensure that all drugs of interest would be captured in the search. Only the four drugs of interest were included during screening

[b]Aripiprazole lauroxil is not publicly funded in Canada and does not have a Health Canada label. Studies containing aripiprazole lauroxil were excluded during screening but tagged so that they could be reviewed in the future if needed

[c]The full texts of any relevant systematic reviews and meta-analyses were acquired, and the reference lists were hand-searched for any additional relevant studies not identified through the primary database search. They were excluded during screening but tagged so that the bibliographies could be reviewed

ITC indirect treatment comparison, *MA* meta-analysis, *NMA* network meta-analysis, *RCT* randomized controlled trial, *SLR* systematic literature review

Table S3 Data items extracted for the SLR

Publication characteristics	• Citation data (eg, title, author, year) • Trial identification details (eg, trial name, clinical trial ID)
Study design	• Treatment phase • Blinding • Enrollment date • Location • Objective • Study duration/follow-up length • Primary and secondary endpoints • Key population inclusion and exclusion criteria
Treatment details	• Dosing • Administration schedule • Length of treatment • Administration route (eg, intramuscular LAI, subcutaneous LAI)
Baseline characteristics	• Number of patients • Age • Sex • Weight • Body mass index • Time since diagnosis • Disease severity (eg, PANSS score, CGI-S)
Efficacy outcomes	• Time to impending relapse • Impending relapse rate • Remission rate • Stability maintenance • Change in PANSS score • Change in CGI-S
Safety outcomes	• Treatment-related AEs • Adverse events (eg, weight gain, injection-site pain, incidence of EPS [tardive dyskinesia, parkinsonism, akathisia]) • AE-related discontinuation • All-cause discontinuation ○ Adherence
Patient-reported outcomes	• Drug Attitudes Inventory 10-item • Schizophrenia Quality of Life Scale • Personal and Social Performance Scale • EQ-5D
Other outcomes	• Hospitalization rate • ER visit rate • Outpatient visit rate

AE adverse event, *CGI-S* Clinical Global Impression – Severity, *EPS* extrapyramidal symptoms, *EQ-5D* European Quality of Life-Five Dimension, *ER* emergency room, *LAI* long-acting injectable, *PANSS* Positive and Negative Syndrome Scale, *SLR* systematic literature review

Table S4 Studies eligible for inclusion in the SLR

Treatment	Trial	Number of records	Treatments arms	Blinding	Study duration	Key outcomes	Population stability status at randomization (as defined by study)	PANSS randomization criteria	Mean CGI-S score at baseline post randomization	Inclusion in NMA; reason for exclusion from NMA (if applicable)
Risperidone (LAI)	*Risperidone vs relevant comparator for NMA*									
	RISE	1 [1]	Risperidone SC (50-125 mg; monthly)	Double-blind	12 weeks + variable randomized phase	• **Time to relapse** • **CGI-I, CGI-SS** • Relapse rate • Stability, remission • Safety and pharmacokinetics • QoL, hospitalizations	Stable	≤80	3.3	Included
			Risperidone SC (100-250 mg; bi-monthly)						3.2	
			Placebo						3.3	
	SHINE	1 [2]	Risperidone SC (50-125 mg; monthly)	Double-blind	12 weeks + up to 56 weeks randomized phase	• **Safety** • Relapse rate • DAI-10, SQLS, EQ-5D, HCRU • Change in PASS, change in CGI-I, change in PSP	Stable	≤80	NR	Excluded; Study design and sample size limitations
			Risperidone SC (100-250 mg; bi-monthly)							
	Kane 2003	1 [3]	Risperidone IM (25 mg; bi-weekly)	Double-blind	12 weeks	• **Change in PANSS** • Change in CGI-S • Safety	NR	60-120	3.1	Excluded; Non-stable patients
			Risperidone IM (50 mg; bi-weekly)						3.1	
			Risperidone IM (75 mg; bi-weekly)						3.1	
			Placebo						3.1	
	Risperidone vs. non-relevant comparator for NMA									
	MacFadden 2010 [4]	2 [4, 5]	Risperidone IM (25-50 mg; bi-weekly)	Open-label	2 years	• **Time to relapse** • **Time in remission** • Safety	Stable	<100	NR	Excluded; Non-relevant comparator
			Aripiprazole PO (10-30 mg; daily)							
	NCT00256997	1 [6]	Risperidone IM (25, 37.5, or 50 mg; bi-weekly)	Open-label	2 years	• **Relapse rate from month 3 post-randomization** • Change in PANSS, CGI-S, CGI-C, QoL, PSP	Stable	NR	NR	Excluded; Non-relevant comparator
			PO AP (as per local practice)							

Treatment	Trial	Number of records	Treatments arms	Blinding	Study duration	Key outcomes	Population stability status at randomization (as defined by study)	PANSS randomization criteria	Mean CGI-S score at baseline post randomization	Inclusion in NMA; reason for exclusion from NMA (if applicable)
	Bai 2007	2 [7, 8]	Risperidone (25, 37.5, or 50 mg; bi-weekly) Risperidone PO (original dose; daily)	Single-blind	48 weeks	• Change in PANSS and CGI-S	Stable	≤80	4.0 3.9	Excluded; Non-relevant comparator
	Chue 2005 [9]	1 [9]	Risperidone IM (25, 50, or 75 mg; bi-weekly) Risperidone PO (2, 4, or 6 mg; daily)	Double-blind	20 weeks	• **Change in PANSS** • Change in CGI-S	Stable	≥50	NR	Excluded; Non-relevant comparator
PP1M (LAI)	*PP1M vs. relevant comparator for NMA*									
	Hough 2010	5 [10-14]	PP1M IM (25, 50, or 100 mg eq; monthly) Placebo	Double-blind	33 weeks + variable randomized phase	• **Time to relapse** • Change in PANSS, CGI-S, and PSP • Safety	Stable	≤75	3[c] 3[c]	Included
	Takahashi 2013	2 [15, 16]	PP1M IM (75-150 mg eq; monthly) Placebo	Double-blind	13 weeks	**Change in PANSS** Change in CGI-S Safety, pharmacokinetics	NR	60-120	4[c] 4[c]	Excluded; Non-stable patients
	Nasrallah 2010	1 [17]	PP1M IM (25 mg eq; monthly) PP1M IM (50 mg eq; monthly) PP1M IM (100 mg eq; monthly) Placebo	Double-blind	13 weeks	**Change in PANSS** Change in CGI-S, PSP Safety, pharmacokinetics	NR	70-120	5[c] 5[c] 4[c] 4[c]	Excluded; Non-stable patients
	NCT00604279	1 [18]	PP1M IM (50-150 mg eq; variable schedule) Risperidone IM (25-50 mg; variable schedule)	Open-label	13 weeks	• **Change in PANSS** • Change in CGI-S, PSP	NR	60-120	4.9 5.0	Excluded; Non-stable patients

Treatment	Trial	Number of records	Treatments arms	Blinding	Study duration	Key outcomes	Population stability status at randomization (as defined by study)	PANSS randomization criteria	Mean CGI-S score at baseline post randomization	Inclusion in NMA; reason for exclusion from NMA (if applicable)
	EUCTR2004-002694-22-AT	1 [19]	PP1M IM (25, 50, 75, or 100 mg; monthly) Risperidone IM (25, 37.5, or 50 mg; bi-weekly)	Double-blind	53 weeks	• **Change in PANSS** • Change in CGI-S, PSP • Symptomatic remission • Safety	NR	60-120	NR	Excluded; Non-stable patients
	PP1M vs. non-relevant comparator for NMA									
	Bozzatello 2019	1 [20]	PP1M IM (50-150 mg eq; monthly) Paliperidone ER (6-12 mg; daily)	Open-label	6 months	• **Change in TSQM, SWN-K, and SES** • Change in CGI-S, PSP	Stable	NR	4.9 4.5	Excluded; Non-relevant comparator
	PROSIPAL	1 [21]	PP1M (25-150 mg eq; monthly) Oral AP (variable dosing; daily)	Open-label	24 months	• **Time to relapse** • Relapse rate • Change in PANSS, CGI-S, PSP, EQ-5D • Percentage of treatment responders • Safety	Stable	70-120	3.9 3.8	Excluded; Non-relevant comparator
Aripiprazole (LAI)	*Aripiprazole vs. relevant comparator for NMA*									
	ASPIRE-US [22]	6[a] [22-27]	Aripiprazole IM (300 or 400 mg; monthly) Placebo	Double-blind	52 weeks	• **Time to relapse** • Change in PANSS and CGI-S • Safety	Stable	≤80	NR	Included
	QUALIFY	5 [28-32]	Aripiprazole IM (400 mg; monthly) PP1M IM (50-234 mg; monthly)	Open-label	28 weeks	• **Change in QLS total score** • CGI-S	Stable	NR	4 4	Included
	EULAST	1 [33]	Aripiprazole IM (400 mg; monthly) + PP1M (75 mg; monthly) Aripiprazole PO (15 mg; daily) + Paliperidone PO (6 mg; daily)	Open-label	19 months	• **Time to all-cause discontinuation** • Changes in different dimensions of psychopathological symptoms, global psychosocial functioning, hospitalizations, and side effects	NR	NR	4.4 4.3	Excluded; Non-stable patients

Treatment	Trial	Number of records	Treatments arms	Blinding	Study duration	Key outcomes	Population stability status at randomization (as defined by study)	PANSS randomization criteria	Mean CGI-S score at baseline post randomization	Inclusion in NMA; reason for exclusion from NMA (if applicable)
	Aripiprazole vs. non-relevant comparator for NMA									
	ASPIRE-EU [34]	4 [34-37]	Aripiprazole IM (400 mg; monthly)	Double-blind	38 weeks	• **Relapse rate** • Time to impending relapse • Rate of responders and patients in remission • Change in PANSS, CGI-S, and CGI-I scores • Safety	Stable	≤80	3.1	Excluded; Non-relevant comparator
			Aripiprazole PO (10-30 mg; daily)						3.1	
			Aripiprazole IM (50 mg; monthly)						3.0	
	Raoufinia 2017	2 [38, 39]	Aripiprazole Deltoid IM (400 mg; monthly)	Open-label	Up to 24 weeks	• **Pharmacokinetic assessment** • Safety	Stable	NR	NR	Excluded; Non-relevant comparator
			Aripiprazole Gluteal IM (400 mg; monthly)							
	Ishigooka 2015 [40]	1 [40]	Aripiprazole IM (400 mg; monthly)	Double-blind	52 weeks	• **Non-relapse rate** • Time to relapse • Change in PANSS and CGI-S scores • Rates of relapse, meeting stabilization, and remission • Safety	Stable	≤80	2.8	Excluded; Non-relevant comparator
			Aripiprazole PO (6-24 mg; daily)						2.7	
	Mallikaarjun 2013	2 [41, 42]	Aripiprazole IM (200 mg; monthly)	Open-label	24 weeks	• **Pharmacokinetic assessment** • PANSS, CGI-S • Safety	Stable	NR	3.2	Excluded; Non-relevant comparator
			Aripiprazole IM (300 mg; monthly)						3.1	
			Aripiprazole IM (400 mg; monthly)						3.3	
PP3M (LAI)	*PP3M vs. relevant comparator for NMA*									
	Berwaerts 2015 [43]	6[b] [43-48]	PP3M IM (175, 263, 350, or 525 mg eq; quarterly)	Double-blind	29 weeks + variable randomized phase	• **Time to relapse** • Change in PANSS, CGI-S, and PSP • Safety	Stable	<70	2.7	Included
			Placebo						2.8	
	Savitz 2016 [49]	9 [49-57]	PP3M IM (175, 263, 350, or 525 mg eq; quarterly)	Double-blind	48 weeks	• **Rate of patients who remained relapse-free** • Change in PANSS, CGI-S, and PSP	Stable	<70	2.9	Included

Treatment	Trial	Number of records	Treatments arms	Blinding	Study duration	Key outcomes	Population stability status at randomization (as defined by study)	PANSS randomization criteria	Mean CGI-S score at baseline post randomization	Inclusion in NMA; reason for exclusion from NMA (if applicable)
			PP1M IM (50, 75, 100, or 150 mg eq; monthly)			• Rates of clinical response, symptomatic remission • Safety			2.9	
	PP3M vs. non-relevant comparator for NMA									
	Najarian 2022	4 [58-61]	PP3M IM (350 or 525 mg eq; quarterly)	Double-blind	Up to 3 months + 12 months randomized phase	• **Time to relapse** • Change in PANSS, CGI-S, and PSP • Rates of symptomatic remission	Stable	<70	3	Excluded; Non-relevant comparator
			PP6M IM (100 or 150 mg eq; semi-annually)						3	

[a]Includes data from both the ASPIRE-US [22] and ASPIRE-EU [34] trials

[b]Includes data from both the Berwaerts 2015 [43] and Savitz 2016 [49] trials

[c]Median reported

Bolded outcomes are the primary outcomes in each trial

Non-relevant comparator refers to any comparator other than placebo or a second-generation LAI approved in Canade at the time of this study

Non-stable patients were indicated by PANSS scores at randomization >80 or mean CGI-S scores >4 at baseline

AP antipsychotic, *CGI-C* Clinical Global Impression – Change, *CGI-I* Clinical Global Impression – Improvement, *CGI-S* Clinical Global Impression – Severity, *CGI-SS* Clinical Global Impression of Severity of Suicidality, *DAI-10* Drug Attitudes Inventory 10-item Version, *eq* = equivalent, *EQ-5D* European Quality of Life-Five Dimension, *HCRU* healthcare resource utilization, *IM* intramuscular, *LAI* long-acting injectable, *NMA* network meta-analysis, *NR* not reported, *PANSS* Positive and Negative Syndrome Scale, *PO* oral, *PP1M* paliperidone palmitate 1-month, *PP3M* paliperidone palmitate 3-month, *PP6M* paliperidone palmitate 6-month, *PSP* Personal and Social Performance, *QoL* quality of life, *QLS* Quality of Life Scale, *SC* subcutaneous, *SES* Service Engagement Scale, *SLR* systematic literature review, *SQLS* Schizophrenia Quality of Life Scale, *SWN-K* Subjective Well-Being Under Neuroleptics, *TSQM* Treatment Satisfaction for Medication

Table S5. Data availability for outcomes selected for the NMAs

Treatment	Trial	Relapse rate at 6 months	Time to relapse	Change in PSP	AE-related discontinuation	Significant weight gain (≥7%)	Treatment-related AEs	Injection-site pain
TV-46000	RISE [1]	✓	✓	✓	✓	✓	✓	✓
PP1M	Hough 2010 [10]	✓	✓	✓	✓	✓	✓	×
Aripiprazole	ASPIRE-US [22]	✓	✓	✓	✓	✓	×	✓
	QUALIFY [28]	×	×	×	✓	✓	×	✓
PP3M	Berwaerts 2015 [43]	✓	✓	✓	✓	✓	✓	✓
	Savitz 2016 [49]	✓	✓	✓	✓	✓	✓	✓

AE adverse event, *NMA* network meta-analysis, *PSP* Personal and Social Performance

Table S6 Raw data for the NMAs

Study name	RISE [1]			ASPIRE-US [22]		Hough 2010 [10]		Berwaerts 2015 [43]		Savitz 2016 [49]		QUALIFY [28]	
Treatment	Placebo	TV-46000 q1m	TV-46000 q2m	Placebo	Aripiprazole q1m	Placebo	PP1M 25-100 mg eq	Placebo	PP3M	PP1M 50-150 mg eq	PP3M	PP1M	Aripiprazole q1m
Relapse rate at 6 months													
Sample size (average baseline to day 182)	130	155	142	77	184	110	143	101	124	455	428	NR	NR
Relapse events	39	10	16	33	23	59	28	31	12	35	23	NR	NR
Time to relapse													
HR (95% CI) Vs. comparator	–	0.20 (0.11 to 0.37) vs Placebo	0.375 (0.23 to 0.62) vs Placebo	–	0.20 (0.12 to 0.32) vs Placebo	–	0.28 (0.19 to 0.41) vs Placebo	–	0.26 (0.14 to 0.48) vs Placebo	–	0.87 (0.56 to 1.34) vs PP1M 50-150 mg eq	NR	NR
Change in personal and social performance													
Sample size	164	177	168	134[a]	269[a]	205	203	142	157	495	474	NR	NR
Change from baseline, LS mean (SD)	–3.59 (10.37)	–0.05 (10.38)	–0.43 (10.37)	–6.2 (11.03)[b]	–1.74 (9.72)[c]	–7.2 (13.03)	–1.5 (11.53)	–4.2 (9.70)	–0.5 (6.63)	1.9 (9.21)	1.3 (10.22)	NR	NR
AEs related to discontinuation													
Sample size	179	183	180	NR	NR	203	205	NR	NR	NR	NR	NR	NR
Estimated number of events at 26 weeks[d]	21[e]	16[e]	14[e]	NR	NR	2[e]	3[e]	NR	NR	NR	NR	NR	NR
Significant weight gain (≥7%)													
Sample size	179	183	180	NR	NR	193	200	145	160	493	494	NR	NR
Estimated number of events at 26 weeks[d]	17[e]	21[e]	16[e]	NR	NR	10[e]	13[e]	1[e]	16[e]	51[f]	46[f]	NR	NR
Treatment-related AEs													
Sample size	179	183	180	NR	NR	203	205	145	160	512	504	NR	NR
Estimated number of events at 26 weeks[d]	49[e]	47[e]	51[e]	NR	NR	57[e]	42[e]	34[e]	58[e]	133[f]	129[f]	NR	NR
Injection site pain													
Sample size	179	183	180	134	269	NR	NR	145	160	512	504	118	132
Number of events at study endpoint[g]	11	9	12	5	8	NR	NR	0	2	14	12	11	4

Notes: Hazard ratio (HR) values were rounded to two decimal places. When needed, HRs were inverted to align with "treatment vs. comparator" type of comparison.

[a]Not reported for this outcome. It was assumed to be baseline sample size

[b]Assumed as the average of the remaining placebo arms in the network

[c]Assumed as the average of the remaining active arms in the network

[d]Refers to the estimated number of events at Week 26 of the randomized, double-blind, maintenance phase

[e]Estimates based on median time of drug exposure and assuming constant incidence rate

[f]Estimates based on mean time of drug exposure and assuming constant incidence rate

[g]Refers to the number of events reported during the maintenance phase. Duration of drug exposure was variable across studies

AEs adverse events, *CI* confidence interval, *HR* hazard ratio, *LS* least squares, *NMA* network meta-analysis, *NR* not reported, *PP1M* paliperidone palmitate 1-month, *PP3M* paliperidone palmitate 3-month, *q1m* once monthly, *q2m* once every 2 months, *SD* standard deviation

Table S7 Differences in study characteristics

Outcome	Study design	Treatment/comparator doses	Time of drug exposure	Outcome definition
Relapse rate at 6 months	RISE [1] was the only study that did not include a depot-drug phase before randomization	Differences in PP1M doses. PP1M dose in Hough 2010 [10] was 25-100 mg eq, whereas PP1M dose in Savitz 2016 [49] was 50-150 mg eq	No key differences observed	The definition of relapse varied across studies with RISE [1] and ASPIRE-US [22] having a lower threshold for relapse compared with Hough 2010 [10], Berwaerts 2015 [43], and Savitz 2016 [49]. Specifically, the PANSS criteria for Hough 2010/Berwaerts 2015 [43]/Savitz 2016 [49] must be met for two consecutive visits[a], whereas for RISE/ASPIRE-US [22], it is only one visit.
Time to relapse				
Change in PSP			Treatment exposure varied across studies, with randomized phases that were event driven for most studies and had different pre-planned number of events for analyses. Duration of exposure presented in **Table 2**.	No key differences observed
AE-related discontinuation	RISE [1] and QUALIFY [28] did not include a depot-drug phase before randomization. QUALIFY was also not a double-blind and patients were randomized before the oral medication phase			
Significant weight gain (≥7%)				
Treatment-related AEs	RISE [1] was the only study that did not include a depot-drug phase before randomization			
Injection-site pain	RISE [1] and QUALIFY [28] did not include a depot-drug phase before randomization. QUALIFY was also not a double-blind and patients were randomized before the oral medication phase	No key differences observed	No key differences observed[b]	

[a]Two consecutive visits are between 3 and 7 days apart for Savitz 2016 [49]/Berwaerts 2015 [43]

[b]Analysis of injection-site pain was based on the reported percentage of patients with injection-site pain (regardless of time of drug exposure). Therefore, differences in time of drug exposure were not considered relevant for this outcome

AE adverse event, *PP1M* paliperidone palmitate 1-month, *PSP* Personal and Social Performance

Table S8. Differences in patient characteristics

Outcome	Eligibility criteria	Randomization criteria	Relevant baseline characteristics
Relapse rate at 6 months	No key differences observed	No key differences observed	RISE [1] had a higher mean age and Berwaerts 2015 [43] had a greater proportion of males
Time to relapse			
Change in PSP			
AE-related discontinuation		Differences in CGI-S score[a]. RISE [1] and ASPIRE-US [22] requested ≤4, while QUALIFY [28][b] requested ≥3 and ≤5	RISE [1] had a higher mean age and QUALIFY [28] had a higher mean CGI-S
Significant weight gain (≥7%)			RISE [1] had a higher mean age, Berwaerts 2015 [43] had a greater proportion of males, and QUALIFY [28] had a higher mean CGI-S
Treatment-related AEs		No key differences observed	RISE [1] had a higher mean age and Berwaerts 2015 [43] had a greater proportion of males
Injection-site pain		Differences in CGI-S score.[a] RISE[1] and ASPIRE-US [22] requested ≤4, while QUALIFY [28][b] requested ≥3 and ≤5	RISE [1] had a higher mean age, Berwaerts 2015 [43] had a greater proportion of males, and QUALIFY [28] had a higher mean CGI-S

[a]CGI-S not reported in Hough 2010, Berwaerts 2015 [43], and Savitz 2016 [49]

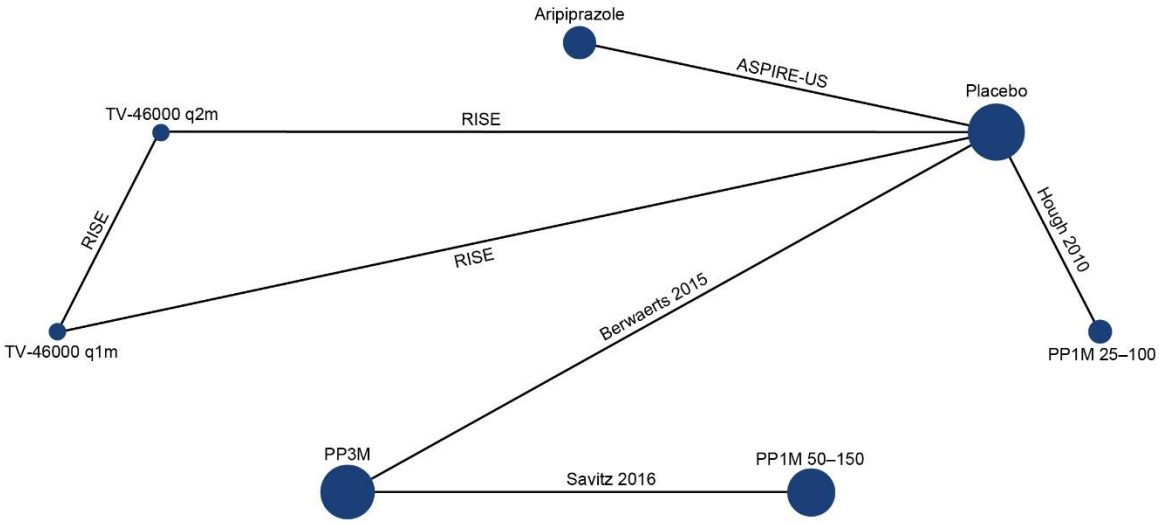
[b]For QUALIFY, inclusion criteria correspond to randomization criteria. For this table, differences that involved the QUALIFY study were included only in the randomization criteria column

AE adverse event, *CGI-S* Clinical Global Impression – Severity, *PSP* Personal and Social Performance

FIGURES

Fig. S1. Network diagrams for outcomes. **a.** Relapse rate, time to relapse, and change from baseline in personal and social performance score. **b.** Adverse event-related discontinuation. **c.** Significant weight gain (≥7%) and treatment-related adverse events. **d.** Injection-site pain.

a



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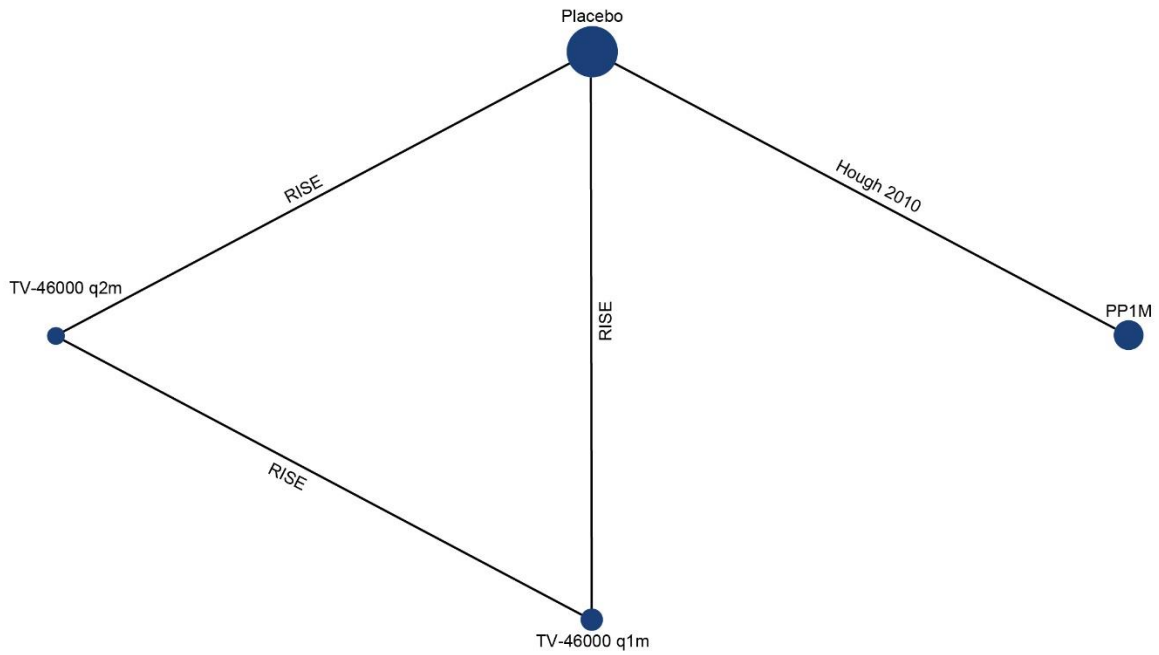

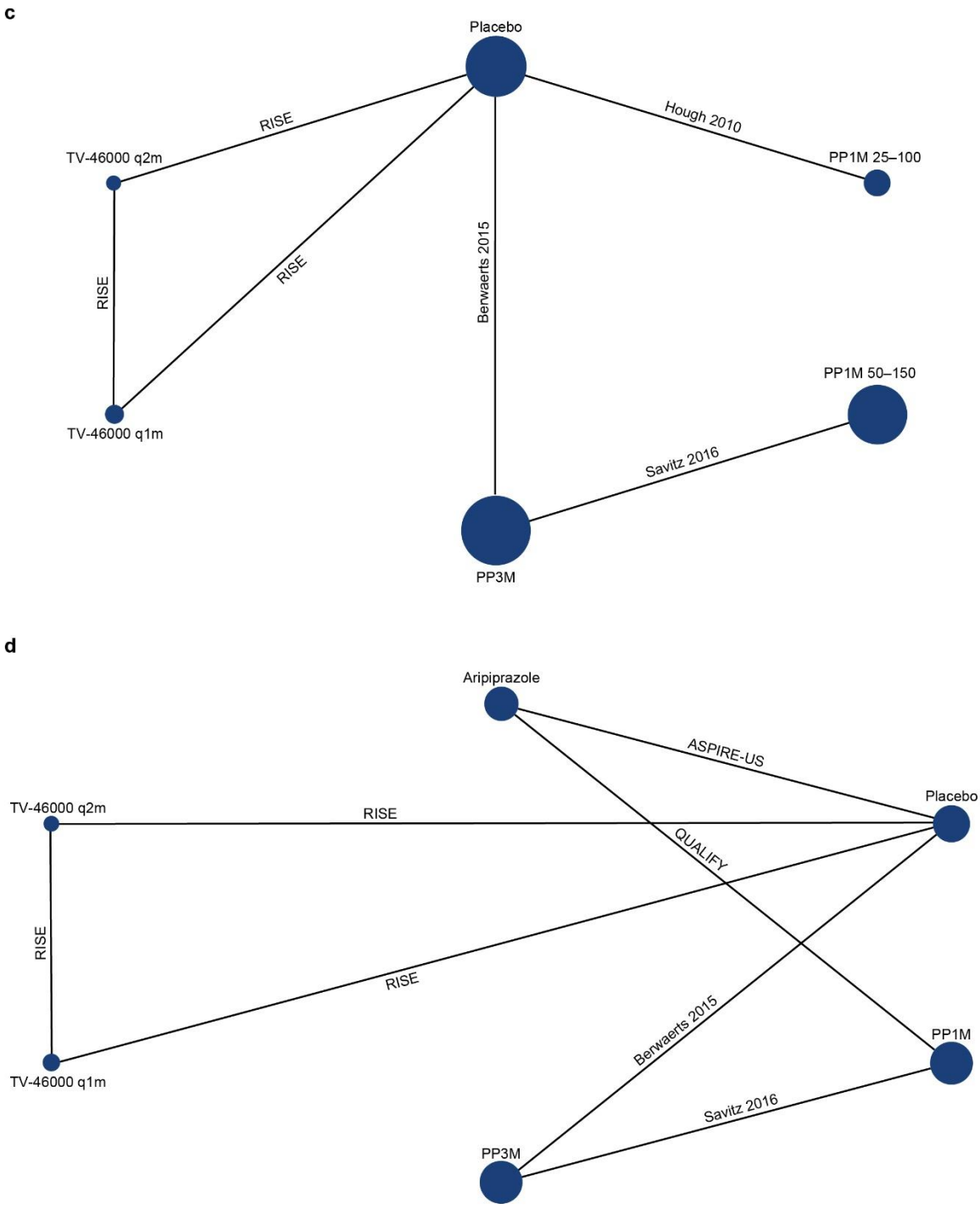

Each treatment is represented by a node, and comparisons between treatments are depicted by links between nodes. The size of a node reflects the sample size, and the width of the links reflects the number of studies connecting the treatments. Treatments with different doses were considered as separate nodes in the networks.

PP1M paliperidone palmitate 1-month, *PP3M* paliperidone palmitate 3-month, *q1m* monthly, *q2m* bi-monthly

Fig. S2 Random-effects NMA league tables. **a.** Relapse rate at 6 months (average population). **b.** Time to relapse. **c.** Change in personal and social performance. **d.** Adverse event–related discontinuation at 26 weeks. **e.** Significant weight gain (≥7%) at 26 weeks. **f.** Treatment-related adverse events at 26 weeks. **g.** Injection-site pain

a

TV-46000 q1m						
0.84 (0.04 to 17.88)	Aripiprazole					
0.78 (0.04 to 16.21)	0.93 (0.05 to 18.58)	PP1M 25–100				
0.7 (0.3 to 14.95)	0.83 (0.04 to 16.54)	0.9 (0.05 to 17.47)	PP3M			
0.59 (0.07 to 4.99)	0.7 (0.04 to 13.37)	0.75 (0.04 to 13.98)	0.84 (0.05 to 15.42)	TV-46000 q2m		
0.51 (0.02 to 24.16)	0.61 (0.03 to 27.42)	0.66 (0.03 to 28.19)	0.74 (0.15 to 6.98)	0.87 (0.05 to 36.01)	PP1M 50–150	
0.23 (0.02 to 1.46)	0.27 (0.02 to 1.56)	0.3 (0.03 to 1.61)	0.33 (0.03 to 1.72)	0.4 (0.04 to 1.83)	0.46 (0.01 to 2.31)	Placebo

b

Aripiprazole						
0.97 (0 to 6171.73)	TV-46000 q1m					
0.75 (0 to 5304.42)	0.76 (0 to 5456.17)	PP3M				
0.74 (0 to 4600.35)	0.75 (0 to 6006.38)	0.98 (0 to 8535.83)	PP1M 25–100			
0.64 (0 to 32970.62)	0.66 (0 to 36166.24)	0.86 (0 to 435.3)	0.89 (0 to 49996.46)	PP1M 50–150		
0.52 (0 to 3624.15)	0.54 (0 to 246.81)	0.72 (0 to 5285.76)	0.72 (0 to 5602.51)	0.83 (0 to 45972.98)	TV-46000 q2m	
0.2 (0 to 98.83)	0.21 (0 to 116.57)	0.27 (0 to 163.53)	0.28 (0 to 174.21)	0.31 (0 to 2487.83)	0.39 (0 to 182.94)	Placebo

c

PP1M 25–100						
1.26 (−3.4 to 5.95)	Aripiprazole					
1.39 (−3.97 to 6.66)	0.12 (−5.15 to 5.33)	PP1M 50–150				
2 (−2.59 to 6.51)	0.73 (−3.76 to 5.18)	0.6 (−2.14 to 3.37)	PP3M			
2.18 (−2.48 to 6.82)	0.93 (−3.68 to 5.53)	0.8 (−4.4 to 6.07)	0.19 (−4.25 to 4.66)	TV-46000 q1m		
2.59 (−2.15 to 7.3)	1.31 (−3.32 to 5.92)	1.2 (−4.08 to 6.48)	0.59 (−3.91 to 5.07)	0.39 (−2.87 to 3.6)	TV-46000 q2m	
5.7 (2.34 to 9.09)	4.45 (1.21 to 7.7)	4.31 (0.24 to 8.47)	3.71 (0.69 to 6.81)	3.52 (0.29 to 6.76)	3.13 (−0.17 to 6.41)	Placebo

d

TV-46000 q2m			
0.88 (0.07 to 10.41)	TV-46000 q1m		
0.63 (0.05 to 6.86)	0.72 (0.06 to 7.63)	Placebo	
0.41 (0.01 to 17.96)	0.46 (0.01 to 19.46)	0.63 (0.05 to 12.73)	PP1M

e

TV-46000 q2m					
0.93 (0.07 to 9.16)	Placebo				
0.75 (0.07 to 8.54)	0.81 (0.09 to 10.54)	TV-46000 q1m			
0.73 (0.02 to 22.7)	0.79 (0.08 to 10.38)	0.97 (0.03 to 28.63)	PP1M 25–100		
0.07 (0 to 1.86)	0.07 (0.01 to 0.93)	0.09 (0 to 2.34)	0.1 (0 to 2.61)	PP3M	
0.07 (0 to 3.42)	0.07 (0.01 to 1.96)	0.09 (0 to 4.28)	0.09 (0 to 4.67)	0.96 (0.29 to 6.81)	PP1M 50–150

f

PP1M 25					
0.78 (0.05 to 10.85)	TV-46000 q1m				
0.72 (0.07 to 2.87)	0.94 (0.1 to 3.1)	Placebo			
0.71 (0.05 to 9.85)	0.91 (0.14 to 5.57)	0.97 (0.32 to 9.26)	TV-46000 q2m		
0.5 (0.04 to 13.36)	0.64 (0.05 to 16.04)	0.65 (0.27 to 14.44)	0.7 (0.06 to 17.09)	PP1M 50	
0.49 (0.04 to 5.79)	0.64 (0.06 to 6.8)	0.66 (0.29 to 5.38)	0.7 (0.06 to 7.15)	1.01 (0.14 to 3.19)	PP3M

g

TV-46000 q1m					
0.79 (0.06 to 9.54)	Placebo				
0.7 (0.02 to 17.65)	0.89 (0.06 to 8.15)	Aripiprazole			
0.72 (0.06 to 8.97)	0.91 (0.08 to 11.74)	1.03 (0.04 to 42.72)	TV-46000 q2m		
0.15 (0 to 5.03)	0.19 (0.01 to 2.71)	0.22 (0.02 to 1.87)	0.21 (0 to 6.72)	PP1M	
0.14 (0 to 4.23)	0.18 (0.01 to 2.43)	0.2 (0.01 to 2.45)	0.2 (0 to 5.62)	0.93 (0.1 to 5.61)	PP3M

a, b, d, e, f, g. Pairwise comparisons from the random-effect model are shown in terms of relative risk (a, d, e, f, g) or hazard ratio (b) and 95% credible intervals (CrIs). Order on the table is determined by the average rank of a treatment. Treatments with the highest rank are found at the top left side of the table. Rank is determined by point estimates and does not indicate certainty of superiority or inferiority. A credible interval overlapping 1 is indicative of treatments that are comparable (grey cells). A credible interval that does not contain 1 indicates that there are significant differences between treatments (pink cells).
c. Pairwise comparisons from the random-effect model are shown in terms of mean difference and 95% credible intervals (CrIs). Order on the table is determined by the average rank of a treatment. Treatments with the highest rank are found at the top left side of the table. Rank is determined by point estimates and does not indicate certainty of superiority or inferiority. A credible interval overlapping 0 is indicative of treatments that are comparable (grey cells). A credible interval that does not contain 0 indicates that there are significant differences between treatments (pink cells).

Model specifications: a, b, c, e, f. 40,000 iterations, 40,000 burn-ins, 1 thinning. **d.** 80,000 iterations, 40,000 burn-ins, 2 thinning. **g,** 200,000 iterations, 100,000 burn-ins, 5 thinning.
PP1M paliperidone palmitate 1-month, *PP3M* paliperidone palmitate 3-month, *q1m* monthly; *q2m* bi-monthly

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