Benefit–risk assessment of paliperidone oral extended-release tablet versus monthly injectable for maintenance treatment of schizophrenia

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The purpose of this study was to conduct a post-hoc benefit–risk assessment of paliperidone palmitate once-monthly (PP1M) injectable versus oral paliperidone extended-release (ER) in schizophrenia maintenance treatment. The Benefit–Risk Action Team framework was used to structure the analysis based on patient-level data from two similar, double-blind, placebo-controlled relapse studies. Efficacy outcomes were relapse, psychiatric hospitalization, Clinical Global Impression–Severity scale, Personal and Social Performance (PSP) scale, and Positive and Negative Syndrome Scale (PANSS). Safety outcomes were extrapyramidal symptom–related adverse events, weight gain, prolactin-related adverse events, somnolence, orthostatic hypotension, anticholinergic use, fasting plasma glucose, and total cholesterol/high–density lipoprotein. For the first 8 weeks of maintenance treatment, most efficacy outcomes significantly favored PP1M compared with paliperidone ER. Per 1000 patients, there would be 165, 115, 85, and 53 fewer cases of PSP worsening, relapse, PANSS worsening, and hospitalizations, respectively. For the first 40 weeks, PSP worsening significantly favored PP1M (140 fewer cases). Relapse, PANSS, hospitalizations, and Clinical Global Impression–Severity scale showed a consistent pattern favoring PP1M but were not significant. Safety outcomes for both 8-week and 40-week periods demonstrated no statistically significant differences between groups. These analyses suggest a benefit–risk profile favoring PP1M over oral paliperidone ER throughout 40 weeks of treatment, particularly in early treatment. ***Int Clin Psychopharmacol*** **31:315–322**

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Introduction

Benefit–risk assessment is a key component of the regulation of medicines and subsequent medical treatment decisions (Levitan, 2011; Levitan *et al.*, 2011; Luteijn *et al.*, 2012; Quartey and Wang, 2012; US Food and Drug Administration, 2012, 2013). The assessment and communication of benefit–risk analysis is fundamentally important during drug development so as to identify the value of new products for public health and to better enable individual treatment decisions. Numerous regulatory and industry initiatives to standardize approaches to carrying out and communicating benefit–risk assessment are in development (European Medicines Agency, 2010; Coplan *et al.*, 2011; Levitan *et al.*, 2011; US Food and Drug Administration, 2012, 2013, 2015; Hermann *et al.*, 2015; Innovative Medicines Initiative, 2015; Mt-Isa *et al.*, 2015). One of the more commonly used methods is the Benefit–Risk Action Team (BRAT) framework (Coplan *et al.*, 2011; Levitan *et al.*, 2011; Noel *et al.*, 2012; Hughes *et al.*, 2015). This framework, developed by a multidisciplinary team sponsored by the Pharmaceutical Research and Manufacturers of America, provides a structured approach to benefit–risk assessment that addresses the practical complexities of real-world assessments.

Long-term maintenance therapy in schizophrenia is an important clinical and public health concern that requires a careful risk–benefit balance. Defining this balance for individuals with schizophrenia is complex because multiple efficacy and safety endpoints must be simultaneously considered. In addition, actual and perceived impact of therapy varies from patient to patient, and head-to-head treatment-comparison data are difficult to obtain. As a result, benefit–risk assessment for long-acting injectable (LAI) versus oral antipsychotics is of special interest because their differing adherence and pharmacokinetic profiles address other important clinical

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dimensions (Kane *et al.*, 2013; Kishimoto *et al.*, 2013, 2014). LAIs are increasingly valued for their ability to simplify dosing schedules, allow clinicians to monitor adherence, and potentially reduce the chance of noncompliance that can be associated with oral antipsychotics (Valenstein *et al.*, 2002). However, head-to-head trials comparing LAIs with their oral alternatives are limited.

In prior work, we conducted a comparative-effectiveness analysis of paliperidone palmitate once-monthly (PP1M) and oral extended-release (ER) paliperidone for the maintenance treatment of schizophrenia in adults during ~1 year of treatment (Markowitz *et al.*, 2013). Using similar methods for each outcome, this current post-hoc analysis applied the BRAT framework to provide a benefit–risk comparison of LAI (PP1M) and oral ER formulations of paliperidone in the maintenance treatment of schizophrenia in adults.

Methods

BRAT framework

The BRAT framework is a structured approach to pharmaceutical benefit–risk assessment that facilitates the selection, organization, summarization, and communication of evidence relevant to benefit–risk decisions (Coplan *et al.*, 2011; Levitan *et al.*, 2011; Noel *et al.*, 2012). It was chosen for the current analysis because the complexity and number of endpoints considered for this assessment required more focus on assessment setup, data selection, and endpoint definitions than on quantitative modeling (Hallgreen *et al.*, 2014; Hughes *et al.*, 2015). The approach and endpoints used here are similar to that of a recent application of the BRAT framework to LAI antipsychotics (Detke *et al.*, 2014).

Source data

In the absence of head-to-head trials, we analyzed patient-level, long-term efficacy and safety data from the double-blind (DB) maintenance phase of two similar randomized, DB, placebo-controlled, schizophrenia relapse-prevention studies of paliperidone ER (NCT00086320) (Kramer *et al.*, 2007) and PP1M (NCT00111189) (Hough *et al.*, 2010). Both of the original studies were approved by the institutional review board at each site and were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. The nearly identical, four-phase designs (i.e. run-in/transition, stabilization, DB, and an optional open-label extension) of these two studies allowed for a statistical comparison of results. Inclusion, exclusion, stabilization, and relapse criteria were comparable between the two studies (Kramer *et al.*, 2007; Hough *et al.*, 2010). Other sources of data were considered for this comparative work, including meta-analyses of relapse studies in the literature. None were pursued, however, because of widely varying patient inclusion criteria and differences in endpoint definitions, particularly variations in the definitions and measurement of relapse.

In both the Kramer *et al.* (2007) and Hough *et al.* (2010) studies, once patients were stabilized, they were randomly assigned to the DB phase and continued active treatment or received matching placebo until relapse, withdrawal from the study, or study completion. Both studies were terminated early on the basis of a preplanned interim analysis (Table 1). At the time the studies were stopped, 91 patients in the paliperidone ER study (35 in the run-in phase and 56 in the stabilization phase) and 76 patients in the PP1M study (all in the stabilization phase) were considered to have completed the study according to protocol. The two studies had similar but slightly different criteria for determining stabilization. To match the randomization criterion across studies for this comparative analysis, 25 patients were excluded from the PP1M study because they did not meet the more stringent measures of both the Positive and Negative Syndrome Scale (PANSS) score of up to 70 and the Clinical Global Impression–Severity (CGI-S) score of up to 4 (i.e. not ill to moderately ill) that were used as stabilization criteria in the paliperidone ER study. The end result was 104 patients on paliperidone ER and 193 patients on PP1M in the double-blind phase for this analysis (Table 1).

Selection of benefit and risk outcomes

Key benefits and risks associated with atypical antipsychotics were identified from the literature, package inserts (i.e. the expected safety events), and consultation with clinical experts. These outcomes are shown in the value tree in Fig. 1, a hierarchical depiction of outcomes important for characterizing possible schizophrenia treatments. Precise definitions are shown in Table 2. The goal was to include all outcomes needed to conduct a benefit–risk assessment.

Benefit outcomes included maintenance of symptom improvement measured by both core schizophrenia symptoms (assessed by the PANSS) and clinician judgment of the patient's symptoms (assessed by the CGI-S), relapse (both time to relapse and proportion relapsed), patient functioning [using the Personal and Social Performance (PSP) scale], and psychiatric hospitalization (Table 2). The final set of safety outcomes assessed was selected based on data availability and overall impact of the event (i.e. frequency plus clinical consequences). Stroke and syncope were not included because they had very low incidence; stroke was also considered by the authors as a potential rather than an identified endpoint (European Medicines Agency, 2008) for schizophrenia populations, and those at high risk for stroke were excluded from the two studies. Hyperprolactinemia was not included because the majority of patients with elevated prolactin levels had no prolactin-related adverse

Table 1 Disposition of patients in paliperidone ER and PP1M studies[a]

	Paliperidone ER study		PP1M study	
Screening [*N* (%)]	*N* = 628 patients 98 (16) screen failures		*N* = 951 patients 102 (11) screen failures	
Run-in/transition phase [*N* (%)]	*N* = 530 patients (8 weeks)		*N* = 849 patients (9 weeks)	
	183 (35) withdrew 35 (7) remained at study termination		168 (20) withdrew	
Stabilization phase [*N* (%)]	*N* = 312 patients (6 weeks)		*N* = 681 patients (24 weeks)	
	49 (16) withdrew 56 (18) remained at study termination 2 (1) had no efficacy data as of study termination		195 withdrew 76 remained at study termination 25 were excluded to align endpoints with those in the paliperidone ER study	
	Placebo	Paliperidone ER	Placebo	PP1M
Double-blind phase [*N* (%)]	*N* = 101 patients	*N* = 104 patients	*N* = 192 patients	*N* = 193 patients
	42 (42) completed	61 (59) completed	75 (39) completed	132 (68) completed
	52 (51) relapsed	23 (22) relapsed	90 (47) relapsed	32 (17) relapsed
	7 (7) withdrew[b]	20 (19) withdrew[c]	27 (14) withdrew[d]	29 (15) withdrew[e]

Patients remained in the double-blind phase until they experienced a relapse, withdrew from the study, or the study was completed. Based on significant efficacy, both studies were terminated early. At the time the studies were stopped, a total of 91 patients in the paliperidone ER study and 76 patients in the PP1M study were in the stabilization phase and were considered to have completed the entire study per protocol. Patients in the PP1M study who did not fulfill the more stringent stabilization criteria used in the paliperidone ER study ($n = 25$) were excluded from this analysis in order to standardize the study criteria.

AE, adverse event; ER, extended release; PP1M, paliperidone palmitate once-monthly.

[a]All patients who entered the double-blind phases and had efficacy data as of study termination are included in the 8-week and 40-week analyses, irrespective of whether or when they relapsed or withdrew.

[b]Seven withdrawals: one AE, one death, two lost to follow-up, and three other.

[c]20 withdrawals: 12 withdrew consent, three AEs, two lost to follow-up, one violation of study drug protocol, and two other.

[d]27 withdrawals: 15 withdrew consent, two AEs, and 10 other.

[e]29 withdrawals: 12 withdrew consent, three AEs, and 14 other.

events and because neither of the studies provided results of serum prolactin to the investigators to avoid unintentional unblinding. Sexual functioning endpoints were not included because neither study included these measures other than as spontaneously reported events.

Definition of outcomes

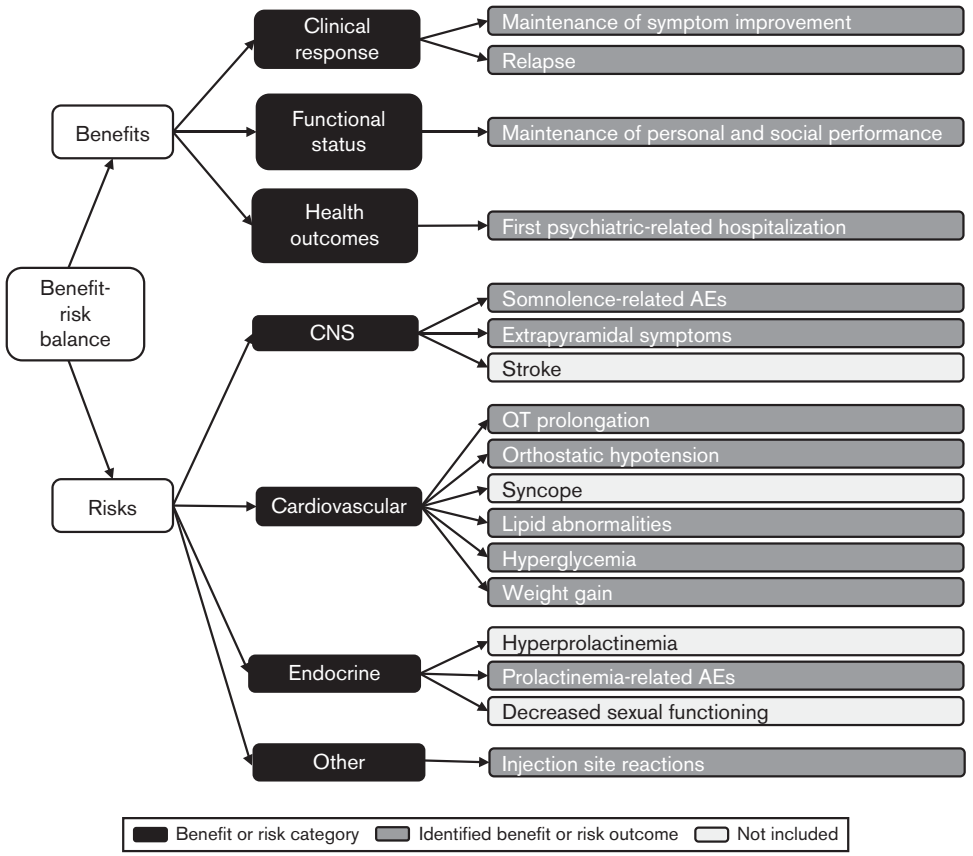
All efficacy endpoints were defined so as to identify loss in stability during the DB maintenance phase after patients had been stabilized (Table 2). To simultaneously interpret large numbers of endpoints, continuous efficacy endpoints were collapsed into dichotomous variables. Time to relapse (days) was also compared. Thresholds for dichotomization were set according to a clinically meaningful worsening of an event, such as the percentage of patients who had a decrease in PSP score from more than 70 at baseline to 70 or less at endpoint (Nasrallah *et al.*, 2008; Fleischhacker *et al.*, 2014). Patients with events that met this threshold at any point following baseline were considered to have worsened, even if the patient reverted to normal values later in the study.

Statistical methods

Because most outcome events occurred at greater frequency at the start of the DB maintenance phase, the analysis was carried out at both 8 and 40 weeks from DB baseline. The 8-week measure was chosen to mitigate the high withdrawal rate in schizophrenia studies. Forty weeks was chosen as a consistent long-term follow-up period for both studies because neither had a predetermined follow-up time and almost no event for any outcome occurred after 40 weeks. All patients who entered the double-blind phases and had efficacy data as of study termination are included in both the 8-week and 40-week analyses, irrespective of whether they completed, withdrew, or relapsed within the double-blind phases. If a patient had at least one event from Table 2 while still in the double-blind phase, that event contributed toward the corresponding endpoint.

The standard approach for an indirect comparison of two therapies accounts for some differences between trials by placebo adjustments of the outcome measures. However, as noted by Markowitz *et al.* (2013), the median time to first relapse in the placebo group of the PP1M study was longer than that for the placebo group of the paliperidone ER study [paliperidone ER/paliperidone palmitate (PP) hazard ratio (HR), 2.25; 95% confidence interval (CI), 1.59–3.18; $P < 0.0001$]. Other endpoints also showed differential effects for their respective placebo groups. This is likely because the PP1M formulation used in the stabilization phase remained in plasma for several months [median apparent half-life ($t_{½}$) = 25–49 days, depending on dose], whereas the oral formulation cleared from plasma in a few days (median $t_{½} = 23$ h). Placebo-corrected comparisons are therefore not meaningful because of the marked differences in pharmacokinetics between the formulations. For this reason, the active

Fig. 1



Value tree for benefit–risk assessment of atypical antipsychotics for the treatment of schizophrenia. Maintenance of symptom improvement is assessed with both Positive and Negative Syndrome Scale and Clinical Global Impression–Severity outcomes. Extrapyramidal symptoms were assessed using anticholinergics and extrapyramidal symptom–related adverse events. Lipid abnormalities and hyperglycemia were assessed with total cholesterol/high-density lipoprotein and fasting plasma glucose, respectively. AEs, adverse events; CNS, central nervous system; QT, measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.

arms were compared directly using patient-level data as described by Markowitz *et al.* (2013). This approach is justified because of the similarity of design and baseline patient characteristics between the trials.

For dichotomous endpoints, the mean (95% CI) risk differences between PP1M and paliperidone ER per 1000 patients (PP minus ER) were calculated over the periods 0 to 8 weeks and 0 to 40 weeks. Results are scaled to this hypothetical population so as to better reflect the benefits and risk on a population level. This risk difference can be interpreted as the additional number of patients from this hypothetical population who would experience an event of interest when treated with PP1M compared with paliperidone ER. A negative value indicates that fewer events occur in the population treated with PP1M and a positive value indicates that fewer events occurred with paliperidone ER; 95% CIs were intended to show statistical differences. When the 95% CI does not include 0, the difference was considered statistically significant. No adjustments were made for multiplicity. For time to relapse, HRs and 95% CIs were assessed using a Cox proportional hazards model.

Results

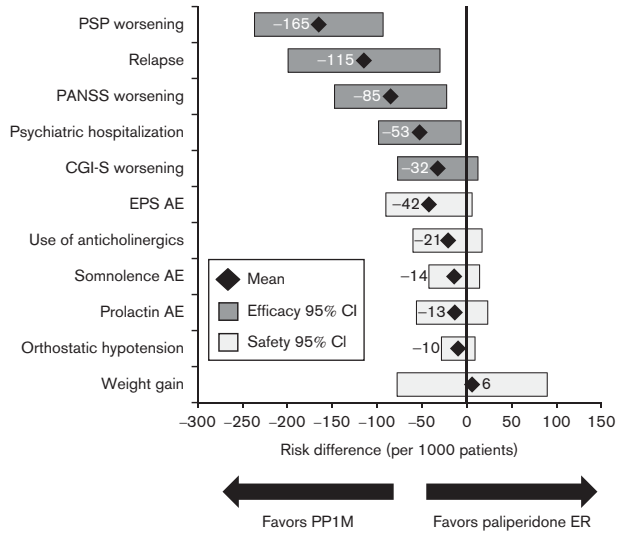
Baseline demographic and clinical characteristics of the two study populations were comparable and have been reported previously (Markowitz *et al.*, 2013). Briefly, the mean patient age at diagnosis was similar in the PP1M and paliperidone ER treatment arms (26.3 and 27.1 years, respectively), as were baseline PANSS total scores (mean 50.8 and 51.0, respectively) and the mean number of previous hospitalizations for psychosis (2.6 and 2.9, respectively) (Markowitz *et al.*, 2013). The proportions of patients who were mildly ill (47.7 and 47.1%, respectively) or moderately ill (10.9 and 10.6%, respectively),

Table 2 Definitions of efficacy and safety outcomes

Outcomes	Measure and definition[a]
Efficacy outcomes	
CGI-S worsening	Proportion of patients with DB baseline CGI-S = normal (1) to moderately ill (4) whose CGI-S score increased to markedly ill (5) to extremely ill (7)
PANSS worsening	Proportion of patients whose PANSS score ≤ 70 at DB baseline with total PANSS score > 70 and increased by 25% from DB baseline
PSP worsening	Proportion of patients with total PSP > 70 at DB baseline who have PSP ≤ 70
Psychiatric hospitalization	Proportion of patients with psychiatric hospitalization after DB baseline started
Relapse	Proportion of patients who relapsed[b]
Time to relapse	Time to relapse (days)
Safety outcomes	
EPS-related AEs	Proportion of patients with EPS-related AEs after DB baseline started
FPG worsening	Proportion of patients with FPG < 100 mg/dl at DB baseline who had ≥ 1 measurement of FPG ≥ 100 mg/dl after DB baseline started
Injection-site reactions[c]	Proportion of patients with injection-site reaction pain, redness, swelling, or induration rated as moderate or severe
Orthostatic hypotension[d]	Proportion of patients without orthostatic hypotension at DB baseline who had ≥ 1 event of orthostatic hypotension after DB baseline started
Prolactin-related AEs	Proportion of patients with prolactin-related AEs after DB baseline started
Somnolence-related AEs	Proportion of patients with somnolence-related AEs after DB baseline started
TC/HDL ratio worsening	Proportion of patients with TC/HDL ratio ≤ 5.0 (male) or ≤ 4.5 (female) at DB baseline who had ≥ 1 measurement of TC/HDL ratio > 5.0 (male) or > 4.5 (female) in patients after DB baseline started
Use of anticholinergics	Proportion of patients not taking anticholinergics at DB baseline who were prescribed anticholinergics after DB baseline
Weight gain	Proportion of patients with > 7% weight gain from DB baseline

AEs, adverse events; BPM, beats per minute; CGI-S, Clinical Global Impression–Severity; DB, double-blind; EPS, extrapyramidal symptom; FPG, fasting plasma glucose; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; TC/HDL ratio, total cholesterol/high-density lipoprotein ratio.
[a]All measurements other than time to relapse were performed using percentage of patients who had ≥ 1 occurrence of the defined event by 8 and 40 weeks in the DB period.
[b]Relapse defined as ≥ 1 of the following: psychiatric hospitalization; a 25% increase in PANSS score for two consecutive assessments in patients who scored > 40 at DB baseline or a 10-point increase in patients who scored ≤ 40 at randomization; deliberate self-injury, violent behavior; suicidal or homicidal ideation; PANSS items P1, P2, P3, P6, P7, or G8 score ≥ 5 for two consecutive assessments for patients whose score was ≤ 3 at DB baseline or score ≥ 6 for two consecutive assessments for patients whose score was 4 at DB baseline.
[c]Study personnel blinded to the treatment assignment evaluated the injection site within 1 h after injection for pain, redness, swelling, and induration using a four-point scale (absent, mild, moderate, or severe).
[d]Orthostatic hypotension defined as difference from supine to standing pulse of > 15 BPM and systolic blood pressure of ≤ −20 mmHg.

Fig. 2



Risk differences (per 1000 patients) for key benefit–risk endpoints from 0 to 8 weeks (PP1M vs. paliperidone ER). Diamonds and the adjacent numbers show the point estimates; horizontal bars show 95% confidence intervals. Dark gray bars indicate the efficacy endpoints. Light gray bars indicate the safety endpoints. QT interval prolongation, fasting plasma glucose, and total cholesterol/high-density lipoprotein are not shown because no events occurred in either group. AE, adverse event; CGI-S, Clinical Global Impression–Severity; CI, confidence interval; EPS, extrapyramidal symptom; ER, extended release; PANSS, Positive and Negative Syndrome Scale; PP1M, paliperidone palmitate once-monthly; PSP, Personal and Social Performance.

Table 3 Treatment arm and treatment differences for key endpoints from 0 to 8 weeks (PP1M vs. paliperidone ER)

	Events per 1000 patients		
Endpoint	PP1M	Paliperidone ER	Risk difference per 1000 patients (95% CI)[a]
Benefits			
PSP worsening	0	165	**−165 (−237 to −93)**
Relapse	78	192	**−115 (−199 to − 30)**
PANSS worsening	21	106	**−85 (−147 to −22)**
Psychiatric hospitalization	5	58	**−53 (−98 to −7)**
CGI-S worsening	16	48	−32 (−77 to 12)
Harms			
EPS-related AE	16	58	−42 (−90 to 6)
Use of anticholinergics	6	26	−21 (−58 to 17)
Somnolence-related AE	5	19	−14 (−42 to 14)
Prolactin-related AE	16	29	−13 (−50 to 23)
Orthostatic hypotension	0	10	−10 (−28 to 9)
Weight gain	140	134	6 (−78 to 90)
TC/HDL ratio worsening	0	0	–
FPG worsening	0	0	–

AE, adverse event; CGI-S, Clinical Global Improvement-Severity; CI, confidence interval; EPS, extrapyramidal symptom; ER, extended release; FPG, fasting plasma glucose; LAI, long-acting injectable; PANSS, Positive and Negative Syndrome Scale; PP1M, paliperidone palmitate once-monthly; PSP, Personal and Social Performance; TC/HDL ratio, total cholesterol/high-density lipoprotein ratio.
[a]Risk differences in bold are statistically significant at the 5% level, with no adjustment for multiplicity.

according to CGI-S scores, were also similar (Markowitz *et al.*, 2013).

In 1000 patients treated for 8 weeks with PP1M versus paliperidone ER, there would be 165 (95% CI, 93–237) fewer PSP worsening events for PP1M, 115 (95% CI, 30–199) fewer relapses, 85 (95% CI, 22–147) fewer PANSS worsening events, and 53 (95% CI, 7–98) fewer hospitalization events (Fig. 2 and Table 2). No significant difference was identified for CGI-S worsening, with 32 (95% CI, –12 to 77) fewer events for PP1M. PANSS worsening and CGI-S worsening were both highly correlated with relapse, according to the definition of relapse and the correlation between CGI-S and PANSS (Leucht *et al.*, 2006). Time to relapse also strongly favors PP1M with an HR of 5.38 (95% CI, 2.21–13.12). In contrast, all harms assessed showed no statistical difference between treatments; all 95% CIs included 0 (Table 3 and Fig. 2). No QT interval prolongation, fasting plasma glucose, or total cholesterol/high-density lipoprotein events occurred in either group during weeks 0 to 8.

For treatment over a 40-week period for 1000 patients, there would be 140 (95% CI, 55–225) fewer PSP worsening events for PP1M (Fig. 3 and Table 4). Collectively, all other benefits evaluated showed a numerical advantage for PP1M treatment; 95% CIs included 0 and were not statistically significant (Fig. 3). Time to relapse strongly favored PP1M, with an HR of 2.52 (95% CI, 1.46–4.35) compared with paliperidone ER (Markowitz *et al.*, 2013). Safety outcomes were not different between treatments. No QT interval prolongation events occurred in either group during weeks 0 to 40.

Injection-site reaction pain was moderate in 1% of patients during the double-blind phase of the PP1M study (no cases were severe) and no injection-site reactions had moderate or severe redness, swelling, or induration (data not shown). Using the units of Tables 3 and 4, in 1000 patients, 10 would experience moderate injection-site reaction pain with paliperidone palmitate, whereas of course none would experience such pain with oral paliperidone ER.

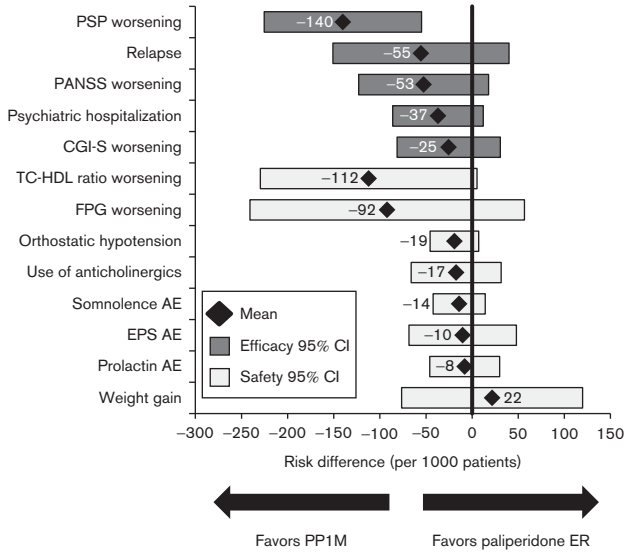
An additional consideration for benefit–risk assessment is the impact of formulation on adherence. Although results from the two clinical trials do not provide information on adherence in real-world use and the preplanned early terminations of both studies further complicates interpretation, the duration of exposure and withdrawal rates provide some indication of the degree to which patients choose to stay in the trials. The median (range) duration of exposure in the DB phases was 170 days (1–407 days) for PP1M versus 45 days (3–330 days) for paliperidone ER. Withdrawal rates were 15% for PP1M and 19% for paliperidone ER (Table 1). Both measurements suggest

Table 4 Treatment arm and treatment differences for key endpoints from 0 to 40 weeks (PP1M vs. paliperidone ER)

Endpoint	Events per 1000 patients		Risk difference per 1000 patients (95% CI)[a]
	PP1M	Paliperidone ER	
Benefits			
PSP worsening	64	204	**–140 (–225 to –55)**
Relapse	166	221	–55 (–151 to 40)
PANSS worsening	63	115	–53 (–123 to 18)
Psychiatric hospitalization	21	58	–37 (–86 to 12)
CGI-S worsening	42	67	–25 (–81 to 31)
Harms			
TC/HDL ratio worsening	92	204	–112 (–230 to 5)
FPG worsening	265	357	–92 (–241 to 57)
Orthostatic hypotension	0	19	–19 (–46 to 7)
Use of anticholinergics	22	40	–17 (–66 to 31)
Somnolence-related AE	5	19	–14 (–42 to 7)
EPS-related AE	57	67	–10 (–69 to 48)
Prolactin-related AE	21	29	–8 (–46 to 30)
Weight gain	218	196	22 (–76 to 120)

AE, adverse event; CGI-S, Clinical Global Impression–Severity; CI, confidence interval; EPS, extrapyramidal symptom; ER, extended release; FPG, fasting plasma glucose; LAI, long-acting injectable; PANSS, Positive and Negative Syndrome Scale; PP, paliperidone palmitate once-monthly; PSP, Personal and Social Performance; TC/HDL ratio, total cholesterol/high-density lipoprotein ratio.
[a]Risk differences in bold are statistically significant at the 5% level, with no adjustment for multiplicity.

Fig. 3



Risk differences (per 1000 patients) for key benefit–risk endpoints from 0 to 40 weeks (PP1M vs. paliperidone ER). Diamonds and the adjacent numbers show the point estimates; horizontal bars show 95% confidence intervals. Dark gray bars indicate the efficacy endpoints. Light gray bars indicate the safety endpoints. QT interval prolongation is not shown because no events occurred in either group. AE, adverse event; CGI-S, Clinical Global Impression–Severity; CI, confidence interval; EPS, extrapyramidal symptom; ER, extended release; FPG, fasting plasma glucose; PANSS, Positive and Negative Syndrome Scale; PP1M, paliperidone palmitate once-monthly; PSP, Personal and Social Performance; QT, measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; TC/HDL ratio, total cholesterol/high-density lipoprotein ratio.

that adherence on PP1M is greater than adherence on paliperidone ER.

Discussion

Despite the paucity of clinical trial data directly comparing the oral and 1-month injectable formulations of paliperidone, a comparative effectiveness analysis and the BRAT framework enabled comparisons of benefits and risks across two similarly conducted clinical trials. The results of this post-hoc benefit–risk analysis support the value of PP1M therapy in long-term schizophrenia treatment. This benefit manifests much more in the first 8 weeks of treatment than at 40 weeks; however, differential withdrawal between the PP1M and paliperidone ER arms may have shifted results to favor paliperidone ER as the studies progressed. Data suggest a benefit for PP1M versus paliperidone ER when used as maintenance treatment in stable patients with schizophrenia. There were fewer functioning (PSP) and symptomatic (PANSS) worsening events, and fewer relapses and hospitalizations in early treatment, with the benefit for fewer PSP events continuing throughout at least 40 weeks. The safety risk profile for the long-acting nature of PP appeared similar to that of paliperidone ER over the period studied, although 1% of PP1M patients experienced moderate pain at the injection site.

The analysis has several limitations, many of which are addressed in the comparative effectiveness analysis on which this work is partly based (Markowitz *et al.*, 2013). Both studies were stopped early as a result of significant benefit of the active treatment arms over placebo; thus, the median duration of exposure in the DB phases of the studies was markedly different (171 days for the PP1M study and 44 days for the paliperidone ER study), making equivalent long-term comparisons impossible. The combined run-in/transition/stabilization phases were 33 weeks for the PP1M study versus 14 weeks for the paliperidone ER study. The dose range in the paliperidone ER study was 3–15 mg/day (mean dose 10.8). This includes doses above the currently approved range (3–12 mg/day). In contrast, the allowable dose range in the PP1M study was 39–156 mg (mean dose 82.8). This equates to roughly 2–8 mg/day (mean dose 4.2) of paliperidone ER and is narrower than the approved range of 39–234 mg (Janssen Pharmaceuticals Inc., 2015). Potentially, the lower dose equivalent used with PP1M could have shifted safety to favor PP1M and shifted efficacy to favor paliperidone ER. The dose difference is in good part due to trial design and the requirement to establish a loading dose. These challenges were addressed, where possible, with analytic adjustments to the patient-level data, including alignment of stabilization criteria, development of binary categorical variables, and use of two discrete time periods for analysis. Placebo correction could not be accurately conducted because concentrations were measurable in the plasma for several months for the LAI group versus several days for the oral group after withdrawal from active treatment in the DB phase. A direct comparison would be required to confirm the results of this analysis. Although most patients remained in both trials at 8 weeks, differences in outcomes observed between observations at weeks 8 and 40 can be challenging to interpret because of missing data and the possibility that the observed 'missingness' was not randomly distributed across treatment arms. In particular, because the PP1M study active arm retained a greater percentage of patients after 8 weeks than did the paliperidone ER study, the only changes possible in the rate differences between 8 and 40 weeks are additional events for PP1M, potentially pushing the rate differences toward favoring paliperidone ER for both benefit and harm items. This suggests that the shifts in risk differences from 8 to 40 weeks may be a reflection of differential withdrawal rather than the treatments themselves. Another limitation is that the studies from which these data were generated were restrictive in terms of patient selection criteria; therefore, data presented here cannot be confidently generalized to all patients with schizophrenia. Finally, there may also be a greater placebo effect with the LAI formulation than with an oral formulation. Mitigation of this limitation would require a direct comparison between treatments along with a placebo arm.

Conclusion

The combination of a comparative approach for multiple endpoints and the BRAT framework enabled meaningful comparisons of benefits and risks between the two different clinical trials. The benefit–risk data suggest an advantage in efficacy for PP1M versus paliperidone ER, with no increase in safety risk in early treatment that may lessen with time. This suggests that benefit exceeds risk for PP1M compared with paliperidone ER when used as maintenance treatment in stable patients with schizophrenia.

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Conflicts of interest

B. Levitan, I. Turkoz, and S. Gopal are employees of Janssen Research and Development, LLC, and are Johnson & Johnson stockholders. M. Markowitz was an employee of Janssen Scientific Affairs, LLC, at the time of this analysis and is a Johnson and Johnson stockholder. He is now with the Department of Biopharma Development Solutions, CNS Practice, UCB Biosciences Inc., Raleigh, NC, USA. D.-J. Fu and L. Alphs are employees of Janssen Scientific Affairs, LLC, and are Johnson & Johnson stockholders.

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