INVEGA® (paliperidone ER)
INVEGA - Comparison to Oral Risperidone

SUMMARY

- Paliperidone is the major active metabolite of RISPERDAL® (risperidone). INVEGA (paliperidone extended-release [ER]) utilizes OROS® (osmotic controlled release system) technology, which uses osmotic pressure to deliver paliperidone at a controlled rate.[1]
- INVEGA is metabolized by 4 primary metabolic pathways, none of which account for more than 10% of the dose, and 59% of the dose is excreted largely unchanged in urine.[1] In contrast, RISPERDAL is extensively metabolized in the liver.[2]
- The recommended dose of INVEGA is 6 mg once daily. Unlike RISPERDAL, INVEGA can be initiated at an effective dose without the need for initial titration. Additionally, no dose adjustment is recommended with INVEGA for patients with mild to moderate hepatic impairment.[1]
- Since cytochrome P450 enzymes (3A4 and 2D6) are minimally involved in the metabolism of paliperidone, INVEGA has less potential for clinically significant cytochrome P450 pharmacokinetic drug interactions compared to RISPERDAL.[1,3]
- Patients with schizophrenia who were suboptimally responsive to risperidone reported improved medication satisfaction after 4, 6, or 8 weeks of treatment with INVEGA.[4,5]
- In a 6-day, randomized, double-blind, phase 1 study, patients with stable schizophrenia experienced similar prolactin elevations on treatment with INVEGA 12 mg/day or risperidone 4 mg/day, and fluctuations in plasma drug concentrations were lower in the INVEGA group compared with risperidone (fluctuation index: 38% vs. 125%).[6]
- Results from a post-hoc analysis of three 6-week, double-blind, placebo-controlled studies demonstrated that INVEGA (fixed doses of 3-12 mg/day) was superior to placebo for improving acute symptoms and personal and social functioning in patients with schizophrenia who received prior treatment with risperidone within 2 weeks of randomization.[7]
- According to the results of a database comparison, INVEGA 6-12 mg/day may be similarly efficacious to risperidone 4-6 mg/day with some tolerability benefits.[8]
- In a pharmacokinetic simulation comparing virtual patients receiving either INVEGA 6 mg/day or risperidone 4 mg/day with varying degrees of adherence, the plasma concentration of paliperidone more consistently remained within the target concentration range at all tested degrees of adherence.[9]

CLINICAL STUDIES

Double-Blind Comparative Studies

Prospective Double-blind Studies Comparing Paliperidone ER and Risperidone

Trial Design	Results
Yoon et al (2012)[10] A randomized, prospective, double-blind, placebo- and active-controlled, parallel trial assessed the effects of multiple doses of PAL and RIS in healthy volunteers on secondary negative symptoms and cognitive performance (n=32). Participants received PAL 6 mg/day (n=11), RIS 3 mg/day (n=11), or placebo (n=12) daily for 3 days.	• Mean age was 28.97 years and 53.1% of the participants were male. Subjective negative symptoms: • After adjusting for mental and physical sedation, significant differences in NIDSS were observed in the cognition subscale (P<0.05). • Post-hoc results showed significant differences in cognition subscale and total NIDSS scores in the PAL group vs RIS group (P<0.05). Objective negative symptoms: • Global scores for alogia and blunted effect on the SANS showed a significant group time interaction.

	Post-hoc results showed a significant difference from baseline to first dose between the PAL and RIS groups ($P<0.05$) • Post-hoc results also showed change in total and mental sedation scores of PAL and RIS groups were significantly different from baseline to third medication dose ($P<0.05$) • Most common AE in any group: sedation, decreased salivation, headache, dysphoric mood-Two serious adverse events were reported in RIS group (vomiting and sedation).
Canuso et al (2010)[5] A 6-week, prospective, multicenter, randomized, double-blind initiation study to assess the observed change in MSQ (Medication Satisfaction Questionnaire) scores in patients with schizophrenia. Patients were either in the immediate (n=100) or a delayed initiation group (n=101). Those assigned to immediate initiation received PAL for a total of 6 weeks; those assigned to a delayed initiation continued their baseline dose of RIS for 2 weeks and then received PAL beginning on Day 15 and continuing for 4 weeks. Patients received an initial dose of PAL 6 mg/day, adjusted flexibly up to 12 mg/day.	• MSQ scores improved significantly from baseline to Week 6 endpoint (+2.4; $P<0.001$) for the immediate initiation and delayed initiation groups combined. In addition, at Week 2 a higher percentage of patients receiving PAL reported "satisfaction" compared with patients receiving RIS: 67.7%, vs. 45.3%, respectively ($P=0.002$). • A total of 53.3% of patients experienced a TEAE (treatment-emergent adverse event). The most frequently reported TEAEs included: insomnia (9.1%), constipation (7.6%), headache (7.6%), and somnolence (6.6%). • At Week 2, Extrapyramidal Symptoms Rating Scale Akathisia scores improved significantly among patients receiving PAL (-0.3) compared with RIS (-0.0; $P=0.027$).
Berwaerts et al (2010)[6] A 6-day, randomized, double-blind, parallel-group, phase 1 study to compare the prolactin exposure following administration of PAL 12 mg/day with RIS 4 mg/day in stable patients with schizophrenia (N=76). After a 1-week, open-label, placebo washout period, patients were randomized to 1 of 3 treatment groups: • Day 1: placebo; Days 2-6: PAL 12 mg/day • Days 1-6: PAL 12 mg/day • Day 1: RIS 2 mg/day; Days 2-6: RIS 4 mg/day	• On Day 1 the concentration of the active fraction of RIS (risperidone + paliperidone) peaked earlier (2.7 hours) compared with paliperidone (21.8 hours). Both groups reached a steady state by Day 6. At Day 6, the mean C_{max} of paliperidone was 19% lower than the active fraction of RIS (46.1 ng/mL vs. 56.8 ng/mL), while the AUC_{0-24} was similar in the PAL and RIS groups (896 ng•hr/mL vs. 760 ng•hr/mL). PAL demonstrated lower peak-to-trough variability in plasma drug concentrations compared with RIS, as measured by the fluctuation index (38% and 125%, respectively). • On Day 6, the AUC_{0-24} of prolactin was similar in the PAL and RIS group (1389 ng•hr/mL vs. 1306 ng•hr/mL), although the fluctuation index of prolactin was higher in the RIS group. • Overall, 40% of PAL-treated patients and 50% of RIS-treated patients reported a TEAE. The most common AE was extrapyramidal disorder in the PAL group (12%) and insomnia in the RIS group (18%). No potentially prolactin-related AEs were reported.
Rossenu et al (2008)[11] A comparison of the rate of measured orthostatic hypotension between the 2 mg RIS immediate-release group and the 12 mg PAL group on Day 1, as a component of the study described immediately above.[6] Orthostatic hypotension was defined as a decrease of >20 mmHg systolic or >10 mmHG diastolic blood pressure within 3	• The lower and upper limits of the 95% CI for the difference (1.18 mmHg) in the least-squared means between PAL and RIS immediate-release groups were -4.07 mmHG and 2.02 mmHG, respectively. Since this change did not exceed the pre-specified lower limit of -10 mmHg, these results established the orthostatic tolerability of 12 mg of PAL as non-inferior to 2 mg of RIS immediate-release.

minutes after standing. After a 1-week, open-label, placebo washout period, patients were randomized to 1 of 3 treatment groups: • Day 1: placebo; Days 2-6: PAL 12 mg/day • Days 1-6: PAL 12 mg/day • Day 1: RIS 2 mg/day; Days 2-6: RIS 4 mg/day	• Over the first 5 days of active treatment, the incidence of orthostatic hypotension varied between 39% (average from the 2 PAL groups) and 53% (RIS immediate-release group).
Abbreviations: NIDSS, Neuroleptic-Induced Deficit Syndrome Scale; PAL, paliperidone ER; RIS, risperidone; SANS, Scale of the assessment of negative symptoms; TEAE, Treatment-emergent adverse event.	

Open-Label Switching Studies

Prospective Open-label Studies in Patients Switched to Paliperidone ER from Risperidone

Trial Design	Results
Schreiner et al (2014)[12] • Prospective, open-label study that assessed the efficacy and tolerability of PAL in patients with non-acute schizophrenia previously unsuccessfully treated with other antipsychotics (N=1,812) including RIS (n=694) and olanzapine (n=396). • PAL 3-12 mg/day, flexibly dosed, for up to 6 months. Recommended dose was 6 mg/day, and patients were transitioned to the effective dose without titration. • Mean mode PAL dose: 7.1 mg/day. For patients who switched due to lack of efficacy, the primary endpoint was a ≥20% increase in PANSS total score from baseline to study endpoint. • For all other patients, the primary endpoint was noninferiority to the previous antipsychotic therapy defined as ≤5 point difference in the mean PANSS total score from baseline to study endpoint.	• 56.6% of patients switched to PAL due to lack of efficacy, 27.0% due to lack of tolerability, 9.1% due to lack of compliance, and 7.3% for other reasons. • Duration of treatment with PAL: 149.6±58.6 days Patients switching due to lack of efficacy (n=998): • 61.3% had improvement of ≥20% in PANSS total score from baseline to study endpoint. • Mean PANSS total score decreased from 85.4 at baseline to 70.1 at study endpoint (P=0.0001). Patients switching for other reasons: • Mean change from baseline to study endpoint in PANSS total score was -8.4 in the lack of tolerability group (n=475), • 18.4 in the lack of compliance group (n=155), and -9.5 in the other reasons group (n=128). Noninferiority was confirmed for each group (P<0.0001) showing that efficacy was maintained after switching to PAL. • 55.6% of patients in the lack of tolerability group, 72.3% in the lack of compliance group, and 55.5% in the other reasons group had ≥20% improvement in PANSS total score from baseline to study endpoint. Adverse Events: • The most common TEAEs were insomnia (9.2%), anxiety (7.2%), somnolence (4.2%), and depression (3.9%) • Prolactin-related AEs (79) were reported in 73 patients and included amenorrhea (n=21), galactorrhea (n=18), erectile dysfunction (n=12), decreased or disordered libido/orgasm (n=11), sexual dysfunction (n=9), menstrual problems (n=5), and breast pain, breast discharge, and gynecomastia (1 each) • Mean ESRS total score improved significantly from baseline (P<0.0001) in patients who switched from oral RIS. Mean increase from baseline in body weight was 0.4±4.3 kg (P=0.0071) in patients who switched from oral RIS.

	• A ≥7% increase from baseline in body weight occurred in 9% of patients who switched from oral RIS.
Yang et al (2014)[13] • A 6-week, open-label study conducted to evaluate the steady-state plasma concentrations, clinical response, and safety profiles in schizophrenic patients who were switched from RIS to PAL (n=25). • Following a screening period where patients were on a stable dose of RIS for 1 week, they were then switched to PAL 6 mg/day for 6 weeks. Dose of PAL could be adjusted between 3 and 12 mg/day during the 6-week period. Mean RIS dose prior to switch: 4.0 mg/day Mean PAL dose: 9.6 mg/day	• Plasma levels for RIS (RIS + 9-hydroxyrisperidone) were significantly higher versus PAL (9-hydroxyrisperidone) (19.7 ng/mL vs. 15.9 ng/mL, respectively; *P*<0.001). • PANSS score decreased 34.3 points from Day 1 to Week 6 (*P*<0.001). • CGI scores were significantly reduced from 'markedly ill' to 'mildly ill' from Day 1 to Week 6 (*P*<0.001) • No difference in SAS and BAS scores was observed between Day 1 and Week 6. One patient dropped out due to EPS symptoms while receiving PAL 12 mg/day.
Gattaz et al (2014)[4] An open-label, prospective, single-group study evaluating the efficacy, tolerability, and safety of switching to flexibly-dosed PAL in patients with schizophrenia who had unsuccessful treatment outcomes on RIS (n=218). Study included a 26-week main phase followed by a 26-week extension phase. • Flexibly-dosed PAL 3-12 mg/day. Mean PAL dose at Week 26: 7.9 mg/day. • Previous RIS was either immediately discontinued or tapered off over the first 4 weeks of the study.	• PANSS total score decreased by 24.7 points at Week 26 (*P*<0.0001) and by 29.9 points at Week 52 (*P*<0.0001) compared to baseline. PANSS total score was significantly decreased at the first post-baseline visit (Week 4) by 15.6 points (*P*<0.0001). • PSP score significantly improved from baseline to Weeks 26 (8.7 points, *P*<0.0001) and 52 (14.9 points, *P*<0.0001). • Patient-reported treatment satisfaction increased from 11.7% to 41.3% for those reporting "very good" and from 38.5% to 43.2% for those reporting "good" at Week 52. • PSQI and CGI-S scores improved significantly from baseline to Week 52 (*P*≤0.0001). • Adverse events were reported by 67% of patients during the main phase and 44% during the extension phase. The most common AEs (incidence ≥4%) were insomnia, increased body weight, anxiety, somnolence, headache, depression, akathisia, and agitation. • Serum prolactin levels increased by 5.6 ng/mL from baseline to Week 26 but decreased by 0.4 ng/mL from baseline to Week 52. • SRS total score decreased by 0.4 from baseline to Week 26 and by 0.49 from baseline to Week 52.
Suzuki et al (2014)[14] Preliminary results from an open-label, 12-week study in elderly patients (>60 years old) with schizophrenia who were switched from RIS to PAL due to inadequate response (N=17). The primary endpoint was the change in cognitive function which was assessed using the Brief Assessment of Cognition in Schizophrenia (Japanese version; BACS-J). EPS symptoms were assessed using DIEPSS, AIMS, and BAS scores. PAL 3-6 mg/day, flexibly dosed	Efficacy 12 weeks after switching to PAL: • One (digit sequencing) of the 6 tasks measured by the BACS-J was significantly improved (*P*=0.009), but there was no significant improvement in the BACS-J composite score. • There was no change in the PANSS total score, PANSS subscales, or CGI-S score. • There were significant improvements in the DIEPSS (*P*=0.03) and BAS (*P*=0.006). • There was an improvement in 41.2% of patients on the BAS, 64.7% of patients on the AIMS, and 76.5% of patients on the DIEPSS.

Mean dose of RIS at baseline: 4.1 mg/day-Mean dose of PAL at 12 weeks: 6.2 mg/day	
Kim et al (2013)[15] An open-label, prospective, 48-week study evaluated the efficacy, safety, and tolerability of PAL in adult patients diagnosed with schizophrenia who were previously on any oral antipsychotic for at least 2 weeks prior to trial initiation (N=184). Patients were stratified based on previous antipsychotic received (RIS or non-RIS group). Patients received PAL 3 to 12 mg/day. Previous oral antipsychotic medications were immediately discontinued or tapered down over a 4-week period. Mean doses of PAL at endpoint: • RIS patients (n=91): 8.3 mg/day • Non-RIS patients (n=93): 8.7 mg/day	• PANSS total score decreased from 78.3 to 65.5 in the RIS group and from 79.1 to 65.4 in the non-RIS group from baseline to endpoint (P<0.001 for both groups). The between-group differences were not significant. • PSP total score improved 8.2 points in the RIS group and by 8.8 points in the non-RIS group from baseline to endpoint (P<0.001 for both groups). • CGI-S overall severity score decreased by 0.6 points in both the RIS and non-RIS groups (P<0.001 for both groups). • Total AEs were reported by 68.5% of patients (63.7% in the RIS group and 73.1% in the non-RIS group). The most common AEs in the RIS and non-RIS groups were akathisia (16.5% and 20.4%), increased weight (9.9% and 18.3%), and muscle rigidity (9.9% and 11.8%), respectively. • DIEPSS total score improved from 2.5 to 1.4 in the RIS group (P<0.001) and from 2.2 to 1.6 in the non-RIS group (P=0.033). • Significant prolactin elevation was observed in women in the non-RIS group after switching to PAL, with the change in prolactin level being significantly lower for women in the RIS group.
Suzuki et al (2013)[16] -This open-label, flexible-dose, naturalistic, observational trial evaluated the efficacy and safety of switching to PAL from RIS in elderly patients with schizophrenia (n=27). -Patients were either switched to PAL (n=13) or remained on RIS as the control group (n=14). -Patients who switched were started on PAL 3-6 mg/day dependent on their previous antipsychotic dose. The previous drug was tapered down over a week and patients reached their optimal dose of PAL within 2 weeks.	• PANSS total scores decreased significantly from baseline to 24 weeks in both the PAL and control groups (-9.3 and -12.5, respectively). No significant difference was observed between the groups (P=0.27). Percent of treatment responders: 15.4% and 21.4% in the PAL and control groups, respectively. • Change from baseline in CGI-S score: -0.8 for PAL (P<0.005); -0.4 for control (P=NS) • A significant change from baseline was observed in the DIEPSS for the PAL (P<0.05) group, but not for the control group. • The most common AEs were insomnia, anxiety, agitation, somnolence, and headache.
Kim et al (2012)[17] A 12-week, randomized, parallel-group, open-label, flexible-dose study was conducted to investigate the cognitive benefit of PAL in patients with schizophrenia who were previously receiving RIS (n=58). Primary outcome measure was neurocognitive function (measured via a computerized battery) Secondary efficacy measures included total PANSS score, Social and Occupational Functioning Scale (SOFAS) and Calgary Depression Scale for Schizophrenia.	• Mean age was 34.1 years and 34.5% of the participants were female • Changes in short-term delayed recall of verbal learning test were significantly greater in PAL-switch group than in RIS-continuation group (P=0.042). No significant changes in other neurocognitive domains were observed. • A significant increase in SOFAS was observed the PAL group (P=0.044). No statistically significant changes in other secondary efficacy measures were seen. • Adverse events reported >10% of patients were menstrual disturbances (amenorrhea and oligomenorrhea). However, they were not significantly different between the groups.

Patients continued RIS therapy (n=26) or switched from RIS to PAL 3-12 mg/day (n=32). Patients who switched to PAL therapy were tapered off RIS while PAL was titrated simultaneously in the first 2 weeks of the study.	• There were no statistically significant differences from baseline to endpoint in laboratory measures (cholesterol profiles, glucose, alanine transaminase, and prolactin). • In PAL group, 12.5% of patients experienced ≥7% increase in body weight compared to 0% in the RIS group. The mean change in body weight from baseline to endpoint was not significantly different (RIS: +0.5 kg, PAL: +0.9 kg.
Fernández-Mayoralas et al (2012)[18] A 16-week, open-label study was conducted to assess the use of PAL in children with severe behavioral problems due to ADHD or generalized developmental disorders that were partially refractory to treatment with RIS and psychoeducation (n=18). Participants switched to PAL 3 mg daily with breakfast. Concomitant medications were steady for at least 3 months prior to switching to PAL. The mean RIS dose was 1.8 mg/day with 1.2 years as the average treatment duration.	• Mean age was 13.4 years and 83% of the participants were male. • Pretreatment vs. posttreatment difference in CGI-S score was statistically significant (1.72, *P*<0.001). • 78% of patients showed improvements in CGI-I score after 4 months of PAL therapy. Marked improvement (CGI-I, 1-2) was seen in 50% of the cases, while subtle improvements (CGI-I, 3) were observed in 28%. • The severity of aggressive behavior, as assessed (by the Overt Aggression Scale [OAS]) decreased significantly after treatment with PAL: 2.7 vs. 1.5 (*P*<0.001). • 11% of cases had more sleepiness with PAL than with RIS resulting in discontinuation for 1 patient.
Abbreviations: AEs, adverse events; AIMS, Abnormal Involuntary Movement Scale; BACS-J, Brief Assessment of Cognition in Schizophrenia - Japanese version; BAS, Barnes Akathisia Scale; CGI-S, Clinical Global Impression-Severity; DIEPSS, Drug-induced Extrapyramidal Symptoms Scale; EPS, Extrapyramidal Symptoms; ESRS, Extrapyramidal Symptom Rating Scale; PAL, paliperidone ER; PANSS, Positive and Negative Syndrome Scale; PSQI, Pittsburgh Sleep Quality Index; RIS, risperidone; SAS, Simpson-Angus Scale; TEAE, treatment-emergent adverse event.	

Retrospective Studies

Retrospective Comparisons of Paliperidone ER and Risperidone

Trial Design	Results
Turkoz et al (2011)[8] A comparative analysis of randomized, double-blind, placebo-controlled, short-term (4 to 8 week) clinical studies assessing the efficacy and safety of PAL or RIS as monotherapy in adult patients with schizophrenia was performed. Three PAL studies (total n=1193) and 3 RIS studies (total n=929) were identified and met the inclusion criteria for this analysis. Patients included in this analysis received either PAL 6-12 mg/day or RIS 2-4 mg/day. These doses were compared as they are expected to provide similar systemic drug exposure profile. PAL 6-12 mg/day was also compared to patients who received RIS 4-6 mg/day as these dose ranges yielded a favorable risk/benefit ratio based on clinical trials.	• A total of 575 patients (PAL: 179; RIS: 179; placebo: 217) were included in the final analysis. • The PAL group showed a greater improvement in the PANSS total score and CGI-S score at the endpoint compared to the RIS 2-4 mg/day group (*P*<0.05 and *P*<0.001, respectively). • A total of 55.1% of patients in the PAL group achieved the response rate threshold compared to 40.7% of patients in the RIS 2-4 mg/day group (*P*<0.05). • Change in PANSS total score and response rates were not significantly different in the PAL group compared to the RIS 4-6 mg/day group. Improvement on the CGI-S scale was greater for the PAL group compared to the RIS 4-6 mg/day group (*P*<0.05). • Placebo-adjusted adverse events that were more common in the PAL group compared to the RIS 2-4 mg/day group were sinus tachycardia and tachycardia, while those more common in the RIS 2-4 mg/day group were somnolence, restlessness,

	nausea, anxiety, salivary hypersecretion, and akathisia. • Placebo-adjusted adverse events that were more common in the PAL group compared to the RIS 4-6 mg/day group were insomnia and sinus tachycardia, while those more common in the RIS 4-6 mg/day group were somnolence, restlessness, nausea, anxiety, salivary hypersecretion, akathisia, nasal congestion, and dizziness.
Jones et al (2010)[19] A meta-analysis of 20 placebo-controlled trials of atypical antipsychotics to assess the relative effectiveness and tolerability of PAL as compared with those of RIS, olanzapine, quetiapine, and aripiprazole in adult patients with schizophrenia was conducted. Patients received placebo (n=1,634) or atypical oral antipsychotics (n=3,679): PAL (n=851), RIS (n=553), olanzapine (n=642), quetiapine (n=605), or aripiprazole (n=1,028). Data were extracted from published data of randomized, placebo-controlled studies in addition to unpublished data for risperidone and paliperidone ER. Inclusion criteria specified that the dose be within the recommend dose range for each product (PAL, 3-12 mg/day; RIS, 4-8 mg/day; olanzapine, 10-20 mg/day; quetiapine, 150-750 mg/day; aripiprazole, 10-30 mg/day). Evaluation of tolerability used the following dose ranges: RIS, 4-6 mg/day, olanzapine, 5-20 mg/day.	• PAL demonstrated greater improvement in incremental efficacy (-12.7), as measured with PANSS total score, than RIS (-12.1) and the antipsychotic class (-11.6). PAL demonstrated greater improvement in PANSS negative score (-2.8) than RIS (-2.2) and the antipsychotic class (-2.4). • The mean change in CGI-S score was similar between PAL (-0.7), RIS (-0.8), and the antipsychotic class (-0.5). • Tolerability outcomes suggested that PAL was associated with lower odds of withdrawal for any reason and lower odds of weight gain than all of the atypical antipsychotics, including RIS. Although the odds ratios varied among the atypical antipsychotics, PAL had lower odds of somnolence and agitation than RIS and the atypical class. The odds ratio for withdrawal due to AEs was lower with PAL than RIS. • The authors concluded that, although there was considerable variability across studies in every parameter considered, PAL demonstrated a unique efficacy and tolerability profile compared with those of other oral atypical antipsychotics.
Nazirizadeh et al (2010)[20] A retrospective analysis comparing intra- and inter-patient variability in serum trough concentrations between PAL and RIS. Primary data were collected from 217 patients who received PAL during a prospective, naturalistic study. The retrospective analysis included 30 patients from a single center who received PAL (n=13) or RIS (n=17). Patients received a mean dose of 9.1 mg/day of PAL and a mean dose of 5.1 mg/day of RIS.	• No significant differences in intra- or inter-patient variability in serum trough concentrations of paliperidone, risperidone, or 9-hydroxyrisperidone were observed, with an intra-individual variability of 35% for paliperidone and 32% for the risperidone active moiety. • In patients with CGI-I scores of at least much improved, the 25th-75th percentile of paliperidone serum levels was 20-52 ng/mL; this corresponded closely to the optimal range of 20-60 ng/mL that is recommended for risperidone/9-hydroxyrisperidone plasma concentrations. • Side effects were not significantly correlated with doses or serum concentrations of paliperidone. • The authors concluded that therapeutic monitoring of paliperidone concentrations is useful for treatment optimization, and that a target range of 20-60 ng/mL would probably be appropriate for both paliperidone and risperidone.
Canuso et al (2008)[7] A post-hoc analysis of pooled data from three 6-week, double-blind, placebo-controlled studies described by Meltzer et al (2006)[21] was conducted to assess the	• Significant improvement in mean PANSS total score (-14.1; -6.4; *P*=0.011), 2 out of 5 PANSS factor scores (negative symptoms *P*=0.007, disorganized thoughts *P*=0.002), mean CGI-S score (-0.7; -0.2; *P*=0.002), and mean PSP score (+6.9; -3.5;

effects of PAL versus placebo in patients previously treated with RIS within 2 weeks of study entry and for a duration of at least 4 weeks. Patients received PAL 3-12 mg/day or placebo. The prior RIS mean final doses were 4.2 mg/day and 4.1 mg/day, while the mean prior duration of treatment was 418.8 days and 527.0 days in the PAL and placebo groups, respectively.	*P*<0.001) was observed at endpoint in patients receiving PAL versus placebo, respectively. • Patients reporting at least 1 TEAE: PAL (70%); placebo (80%). Discontinuations due to AEs: PAL (2.1%); placebo (5.4%). Serious AEs: PAL (6.3%); placebo (5.4%) • Adverse events that were reported in ≥10% of patients in either group were: headache (16.2% PAL, 16.1% placebo), insomnia (14.1% PAL, 16.1% placebo), and agitation (8.5% PAL, 10.7% placebo). • EPS-related AEs: PAL (18.3%); placebo (12.5%) • Mean SAS score did not change significantly from baseline to endpoint in either group. Mean weight changes were +0.7 kg and -1.3 kg in the PAL and placebo groups, respectively (*P*<0.001). From screening to endpoint, mean prolactin levels increased significantly (*P*=0.004) in the PAL group and decreased significantly (*P*<0.0001) in the placebo group. No patients reported potentially prolactin-related AEs.
Abbreviations: CGI-S, Clinical Global Impressions of Severity; PAL, paliperidone ER; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; RIS, risperidone; SAS, Simpson Angus Scale; TEAE, Treatment-emergent adverse event.	

Simulations

Simulated Comparisons of Paliperidone ER and Risperidone

Trial Design	Results
DeVane et al (2009)[9] Pharmacokinetic simulations were conducted to examine the impact of 3 different adherence rates on the plasma concentration of PAL and RIS in 4,000 virtual patients. The simulation used data from 2 population pharmacokinetic models: PAL developed from 21,183 individual plasma drug concentrations, and 2) one for RIS developed from 5,359 plasma drug concentrations. Virtual patients received 12 weeks of either PAL 6 mg/day or RIS 4 mg/day. The investigators defined the target drug concentration range (10-17 ng/mL for paliperidone; 26-46 ng/mL for the active moiety of risperidone [risperidone + 9-hydroxy-risperidone]) as the concentration that corresponds to 70-80% D_2 receptor occupancy.	In simulations assuming 100% compliance for both PAL and RIS, 24.2% of virtual patients receiving PAL showed consistent plasma concentrations in the target range, compared with 4.7% of patients receiving RIS. Assuming 67% compliance (2 doses deleted within a window of 6 days prior to evaluation), 10.4% of PAL-treated virtual patients displayed plasma concentrations consistently in the target range, compared with 2.6% of RIS-treated patients. Finally, assuming 33% compliance, the plasma concentration of 3.4% and 1.0% of virtual patients receiving PAL and RIS, respectively, always remained within the target range.
Abbreviations: PAL, paliperidone ER; RIS, risperidone.	

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 04 April 2024.

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