Rassegna

Paliperidone extended-release in the short- and long-term treatment of schizophrenia

Paliperidone a rilascio prolungato nel trattamento della schizofrenia a breve e a lungo termine

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SUMMARY. Paliperidone is a second-generation antipsychotic drug belonging to the class of benzisoxasole derivatives. Paliperidone is the major active metabolite of risperidone (9-OH-risperidone) and, as such, is comparable to the latter in terms of pharmacodynamic properties. However, due to its peculiar characteristics, paliperidone may be particularly useful in the treatment of schizophrenic patients. In this critical review of the literature the efficacy and tolerability in the short- and in the long-term have been evaluated in patients with schizophrenia. Taking into account the tolerability and efficacy data, together with the use of innovative sustained-release formulation, with a peculiar pharmacokinetic profile that allows single daily administration, paliperidone can be considered a valid option both for the short and the long-term treatment of schizophrenia.

KEY WORDS: paliperidone extended-release, schizophrenia, short-term treatment, long-term treatment, tolerability.

RIASSUNTO. Il paliperidone è un farmaco antipsicotico di seconda generazione appartenente alla classe dei derivati benzisossazolici. Il paliperidone è il principale metabolita attivo del risperidone (9-OH-risperidone) e, in quanto tale, è paragonabile a quest'ultimo quanto a proprietà farmacodinamiche. Tuttavia, date le sue peculiari caratteristiche, il paliperidone potrebbe essere particolarmente utile nel trattamento dei pazienti affetti da schizofrenia. In questa revisione critica della letteratura sono state valutate l'efficacia e la tollerabilità nel trattamento a breve e a lungo termine della schizofrenia. Considerando i dati di efficacia e tollerabilità, combinati all'uso di una innovativa formulazione a rilascio prolungato, con un peculiare profilo farmacocinetico che permette una singola somministrazione giornaliera, il paliperidone può essere una valida opzione per il trattamento della schizofrenia sia a breve che a lungo termine.

PAROLE CHIAVE: paliperidone a rilascio prolungato, schizofrenia, trattamento a breve termine, trattamento a lungo termine, tollerabilità.

INTRODUCTION

Paliperidone, i.e. the (±)-3-[2-[4-86-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyil]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, is a second-generation antipsychotic drug belonging to the class of benzisoxazole derivatives. Its molecular formula and its molecular weight are $C_{23}H_{27}FN_4O_3$ and 426,49, respectively[1].

Paliperidone is the major active metabolite of risperidone (9-OH-risperidone): therefore, the two drugs are largely comparable in terms of pharmacodynamic properties. Due to some special features, paliperidone appears quite different from risperidone at a clinical level. For example, the drug has been developed in an extended-release formulation based on an osmotic-controlled release oral delivery system (OROS) and this advanced pharmaceutical technology, which uses the osmotic pressure to deliver the drug, ensures a steady release over a 24-hour period and a reduction of the peak-to-trough fluctuations in plasma concentrations. This allows once-daily administration without the need for an initial dose titration and, theoretically, a reduction of adverse events risk. Moreover, paliperidone, unlike risperidone, is not subjected to a significant hepatic metabolism and is excreted largely unchanged through the kidneys. Therefore, paliperidone is unlikely to have clinically significant interactions with other molecules and may be particularly useful for patients with hepatic impairment[2].

OROS TECHNOLOGY

Among the various OROS technologies developed since the 70s, paliperidone uses the longitudinally compressed tablet (LCT) multilayer formulation. The LCT is designed to ensure a gradual increase in plasma drug concentration so

treatment can be initiated with a therapeutically effective dosage since the first day, without the need for an initial dose titration. The system of administration is constituted by an osmotically active trilayer core, surrounded by a semi-permeable coating membrane. Two layers contain the drug and the excipients while the third, which is flexible, contains the osmotically active components. The convex side of the tablet presents two laser-drilled orifices. The controlled rate of drug administration can be changed according to the components used in the OROS technology[3].

In an aqueous environment, such as the gastrointestinal tract, the outer coating disintegrates rapidly and the water is absorbed through the semi-permeable membrane that regulates both the flow and the penetration rate into the tablet core, determining the rate of drug delivery. The hydrophilic polymers of the core hydrate and swell, creating a gel containing paliperidone that is pushed outside through the orifices. The biologically inert components of the tablet and the shell are not absorbed and the insoluble residues, similar to a tablet, are eliminated in the stool[3,4].

PHARMACOKINETIC PROFILE

After a single oral dose of paliperidone, the plasma concentration gradually rises reaching a peak plasma concentration (Cmax) after approximately 24 hours. Following the administration of a single daily dose, a steady state is reached within 4-5 days of treatment in most patients. Due to the peculiar delivery system, the peak-to-trough plasma level fluctuations are minimal, resulting in 38% for a dose of 12 mg of paliperidone extended-release (ER) compared to 125% with a dose of 4 mg of risperidone immediate-release[5].

The presence or absence of food during paliperidone administration may increase or reduce the drug concentration. For example, a study conducted in healthy volunteers treated with 12 mg of paliperidone showed that, when compared with an administration under fasting condition, taking a high-fat breakfast changes the pharmacokinetic parameters increasing the plasma concentration (Cmax) and the area under the curve (AUC) of 60% and 54% respectively[4]. Therefore, patients should be advised to take paliperidone either always in a fasting condition or always after breakfast.

Based on the analysis of population, the apparent distribution volume is 487 l. The plasma protein binding of paliperidone is 74% and relates mainly to the α1-acid glycoprotein and albumin[1].

The paliperidone metabolism has been studied on both extensive metabolizers and poor metabolizers of CYP2D6 substrates: after a week from the administration of a single oral dose of 1 mg of ^{14}C-paliperidone immediate release, 91,1% of the radioactivity, 80% in urine and about 11% in feces, was on average excrete. In urine, approximately 59% was excreted unchanged[1].

The pharmacokinetic profile was similar in both extensive and poor metabolizers. Therefore, the distinction between extensive and poor metabolizers seems scarcely significant[6].

Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, in vivo results indicate that these isozymes play a limited role in the metabolism of the drug. In vitro studies using human liver microsomes also showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by various P450 cytochrome isoenzymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 and CYP3A5. Due to its limited hepatic metabolism, paliperidone is not deemed to cause clinically important pharmacokinetic interactions with drugs metabolized by P450 cytochrome[1]. Moreover, in a study of patients with moderate hepatic impairment (class B according to Child-Pugh classification), plasma concentrations of a single oral dose of paliperidone immediate-release resulted to be quite similar to those found in subjects with normal hepatic function: on this basis, it can be reasonably assumed that no dose adjustment is necessary in subjects with moderate hepatic impairment[7].

The impact of the administration of a single dose of 3 mg of paliperidone ER was also studied at renal level in subjects with varying degrees of kidney failure. The elimination of paliperidone decreased with decreasing creatinine clearance, as demonstrated by the fact that in subjects with mild, moderate or severe kidney failure the total clearance and the terminal elimination half-life were reduced by 32%, 64% and 71%, and 24, 40 and 51 hours in subjects with mild, moderate and severe kidney failure, respectively. Therefore, in patients with impaired renal function, the dose of paliperidone should be individualized based on creatinine clearance values. Finally, no dose adjustments are needed based on age, race, sex and smoking status[1].

PHARMACODYNAMIC PROFILE

Paliperidone is a powerful antagonist of dopamine D2 receptors and is also characterized by a predominant 5HT2A antagonist activity. In addition, it acts as an antagonist at α1 and α2 adrenergic and H1 histaminergic receptors but has no affinity for cholinergic muscarinic or β1 and β2 adrenergic receptors[1].

The dissociation off-rate from human cloned D2 receptors in tissue culture cells of paliperidone is faster than that risperidone (60 seconds and 27 minutes, respectively): the inclusion of paliperidone in the group of antipsychotics that rapidly dissociate from D2 receptors due to their bond lability (such as amoxapine, aripiprazole, clozapine, perlapine, quetiapine and remoxipride) may explain its favorable profile on extrapyramidal adverse events[8] and some clinical differences from risperidone. The occupancy of D2 receptors following paliperidone administration has been assessed in three PET studies. Two of these studies[9] evaluated D2 receptor occupancy following the administration in healthy volunteers of a single dose of two formulations of paliperidone, immediate release 1 mg and ER 6 mg. D2 receptor occupation was 64-83% following the administration of 1 mg of paliperidone immediate-release and 75-78% after administration of 6 mg of paliperidone ER[9]: since an antipsychotic effect in the absence of appreciable extrapyramidal effects is associated with a D2 receptor occupancy of 65-80%[10,11], it can be assumed that the effective dose of paliperidone ER, which guarantees a D2 receptor occupancy above 60%, should be at least 3 mg/day[2].

In the third PET study[12], D2 receptor occupancy was assessed at 2 and 6 weeks in striatal and extra-striatal region in 13 patients with schizophrenia treated with paliperidone ER 3 mg (n=6), 9 mg (n=4) and 15 mg (n=3). D2 receptor occu-

pancy, measured in the striatum with [^{11}C]raclopride and in the temporal cortex with [^{11}C]FLB, was 54.2-85.5% and 34.5-87.3% respectively. No significant differences between striatum and temporal cortex were found. These evidences showed also that paliperidone ER at doses of 6-9 mg determined a 70-80% D2 receptor occupancy, both into the striatum and the cortex: this occupancy rate couples clinical efficacy with low risk of adverse extrapyramidal events.

OBJECTIVE

The aim of this review is to provide a selection of evidences from the literature to describe the efficacy of paliperidone ER use in different phases of schizophrenia, both in short and long-terms. The secondary aim is to evaluate the tolerability of these molecule and the treatment satisfaction in patients.

MATERIALS AND METHODS

Electronic searches were performed on PubMed. To ensure a better comparison between the data gathered, we selected similar studies in inclusion and exclusion criteria: all studies were conducted on adult patients with a diagnosis of schizophrenia (according to the DSM-IV[13] or DSM-IV-TR[14] criteria). Patients should not present a substance abuse or dependence disorder in the past six months or aggressive behavior. Other exclusion criteria were a history of hypersensitivity to paliperidone, previous acute dyskinesia or neuroleptic malignant syndrome, any medical illness that could interfere with the pharmacokinetics of the drugs, pregnancy or breastfeeding. To obtain a more complete view, we extended the results to more phases of the disease. Randomized controlled trials, pooled analysis and post-hoc analysis have all been considered. More details of the studies are shown in Table 1.

SHORT-TERM STUDIES

Initial studies

The short-term efficacy and safety of paliperidone ER were evaluated in various studies (Table 2).

The first three controlled studies[15-17] are characterized by a largely overlapping experimental design: indeed, they were multicenter, double-blind, randomized, parallel-group, 6-week studies, and included, in addition to the placebo arm, also an olanzapine arm, and selected patients utilizing identical criteria. During a 5-day screening period, patients meeting the selection criteria discontinued previous medications, including antipsychotics, antiparkinsonian drugs, herbal products and OTCs, for 3 days before randomization. The participants to the trial had to remain hospitalized from day 1 of the double-blind phase for at least 14 days; later, they could also be followed as outpatients with weekly visits until to the end of the 6-week period. The efficacy measures included the Positive and Negative Syndrome Scale (PANSS)[18], the PANSS Marder factors[19] and the Clinical Global Impression-Severity scale (CGI-S)[20], while the patient's personal and social functioning were assessed at baseline and endpoint using the Personal and Social Performance scale (PSP)[21], which evaluate: socially useful activities, interpersonal and social relationships, self-care, disturbing and aggressive behaviors (each of the four domains is assessed on the basis of six degrees of severity: absent, mild, manifest, marked, severe, very severe)[22].

In the first 6-week trial[15], 444 patients were randomized in 4 arms: placebo, paliperidone ER at fixed dose of 6 or 12 mg and olanzapine at fixed dose of 10 mg; 432 patients were included in Intent-to-treat (ITT) group and, at the endpoint, the mean reduction from the baseline PANSS total score was higher for both the doses of paliperidone ER compared with placebo (respectively $p=0.006$ and $p<0.001$). Paliperidone ER 6 mg and 12 mg showed greater improvements than placebo also in positive ($p<0.005$), negative ($p=0.007$) and uncontrolled hostility/excitement Marder factors (p£0.025). In addition, paliperidone ER 12 mg showed greater improvement than placebo in Marder conceptual disorganization factor ($p<0.001$). Patients in the olanzapine group improved from baseline to endpoint in PANSS total score to a similar extent as the paliperidone ER groups. Furthermore, olanzapine was associated with a decrease in all Marder factor scores at endpoint. It should be noted that olanzapine was used only as an arm for the sensitivity analysis and was not made a direct comparison with paliperidone ER groups. The first difference from placebo in PANSS total score ($p<0.05$) was evident from the fourth day of treatment with paliperidone ER 6 mg and from the fifteenth day with paliperidone ER 12 mg. In all cases the improvements were maintained throughout the double-blind phase. A superiority of paliperidone ER over placebo was observed at endpoint also in the CGI-S for paliperidone ER 6 and 12 mg (respectively $p=0.009$ and $p<0.001$): in particular, a smaller percentage of patients in treatment with paliperidone ER 6 and 12 mg was classified as "marked", "severely ill" or "extremely severe" (26.1% in paliperidone ER 6 mg and 20.7% paliperidone ER 12 mg). In the olanzapine group, 70.5% patients were classified as "marked", "severely ill" or "extremely severe" at baseline compared with 29.6% at endpoint. As regards personal and social functioning at endpoint, paliperidone ER differed from placebo only at a dose of 6 mg ($p=0.007$). Moreover, at endpoint, the rate of patients treated with paliperidone 6 and 12 mg showing an improvement in one or more categories, compared to placebo, was higher (50.6% in paliperidone ER 6 mg, 46.2% in paliperidone ER 12 mg, 37.5% in placebo). For the olanzapine group the endpoint change on the PSP scale was 7.6 points, with 47.3% of patients improved by at least one category.

In the second short-term study[16] 630 patients were enrolled and, of those, 628 were included in the ITT group. Paliperidone ER was administered at fixed doses of 6, 9 or 12 mg while olanzapine dose was 10 mg. For all paliperidone ER doses a PANSS total score improvement over placebo ($p<0.001$) was registered at endpoint, with an average reduction of 17.9, 17.2 and 23.3 in patients treated respectively with paliperidone ER 6, 9 and 12 mg. By contrast, patient included in the placebo arm present a mean PANSS total score reduction of 4.1 points. Paliperidone ER 6, 9 and 12 mg was more effective ($p<0.001$) than placebo on all Marder factors (positive symptoms, negative symptoms, conceptual disorganization, uncontrolled hostility/excitement, depression/anxiety). The first differences in PANSS total score between paliperidone ER and placebo were apparent from day 4 for the 12 mg dose and from day 8 for the 6 and 9 mg doses. The patients' amount with

Table 1. Main characteristics of the studies.

Authors	Type of study	N	Baseline characteristic	Duration
Marder et al.[15(A)]	MC, DB, RM, PAC, PG, DR study	444 patients, 432 patients included in ITT	Acute episode (PANSS TS 70-120)	6 weeks
Kane et al.[16(B)]	MC, DB, RM, PAC, PG, DR study	630 patients, 628 included in ITT	Acute episode (PANSS TS 70-120)	6 weeks
Davidson et al.[17(C)]	MC, DB, RM, PAC, PG, DR study	732 patients in the screening phase, 605 in ITT	Acute episode (PANSS TS 70-120)	6 weeks
Meltzer et al.[23(*)]	Pooled analysis of 3 MC, DB, RM, fixed-dose, PC studies	1306 patients	Acute episode (PANSS TS 70-120)	6 weeks
Patrick et al.[24(*)]	Pooled analysis of 3 MC, Phase III, PC	1306 patients (834 in the OLE)	Acute episode (PANSS TS 70-120)	6 weeks
Canuso et al.[25(*)]	Post-hoc analysis from 3 MC, DB, RM, PC, PG studies	198 patients	Acute episode (PANSS TS 70-120)	6 weeks
Canuso et al.[26(*)]	Post-hoc analysis from 3 MC, DB, RM, PC, fixed-dose studies	270 patients	Acute episode with predominant negative symptoms (PANSS TS)	6 weeks
Canuso et al.[27(*)]	Post-hoc analysis of pooled data from 3 DB, PC, and 1-year OL studies	1193 patients from ITT (1184 enrolled) and 774 in OL	Acute episode (PANSS TS 70-120)	6 weeks + 1 year (OL)
Canuso et al.[28(*)]	Post-hoc analysis from three Phase III, MC, DB, RM, PC, PG studies	1193 patients (193 enrolled)	Acute episode with predominant affective symptoms (PANSS TS)	6 weeks
Canuso et al.[29]	RM, DB, PC study	399 patients	Acute exacerbation (PANSS and CGI)	6 weeks
Schmauss et al.[32]	Single arm, OP study	295 patients screened (294 enrolled)	Acute episode (as evaluated by PANSS TS ≥70)	6 weeks
Kim et al.[33]	RM, PG, OP, flexible-dose	58 patients	Symptomatically stable, previously in Ris monotherapy	12 weeks
Kim et al.[38]	OP, prospective, non-comparative study	169 patients	Patients needed to switch to another antipsychotic	48 weeks
Mauri et al.[39]	OP, single-arm, MC study	133 patients enrolled (132 in ITT population)	Symptomatic but not highly acute (PANSS TS 70-100)	13 weeks
Kotler et al.[40]	Subgroup analysis of patients from a MC, open-label, single-arm study	396 patients	Non-acute patients unsuccessfully treated with Ola	6 months
Zhang et al.[41]	OLE phase of a RM, double blind, PC, parallel group study	201 patients in the run-in phase, 106 in the OLE phase	Schizophrenic patients who had completed run-in, stabilization and DB phases	24 weeks
Shi et al.[42]	Open, single-arm, MC prospective study	92 patients	PANSS TS ≥70,	24 weeks
Kramer et al.[45]	MC, RM, DB, PC trial	530 patients (205 in the final analysis)	Acute episode (PANSS TS 70-120)	52 weeks
Emsley et al.[48(*)]	Pooled analysis from three international, MC, OLE studies	1083 patients	Acute episode (PANSS TS 70-120)	52 weeks
Yang et al.[55]	Non-RM, OP, single-arm, phase-4, MC, prospective study	1693 patients	Schizophrenia	8 weeks

DB: double-blind; DR: dose-response; MC: multicenter; OL: open-label; Ola: olanzapine; OLE: open-label extension; PAC: PB- and active-controlled; PC: PB-controlled; PG: parallel-group; Ris: risperidone; RM: randomized; TS: total score.
(*) These studies are analysis from the same sample, derived from (A), (B), (C).

Table 2. Short term studies: assessments and main findings.

Authors	Assessment	Main effect of treatment with paliperidone
Marder et al.[15(A)]	Patients were assigned to Pali ER at fixed dose (n:112, 6 mg/die; n:112, 12 mg/die), Ola 10 mg (n:110) or PB (n:110)	Compared to PB: reduction in PANSS TS, positive, negative scores; uncontrolled hostility/excitement Marder factors; CGI-S
Kane et al.[16(B)]	Patients were assigned to Pali ER at fixed dose (n:123, 6 mg/die; n:122, 9 mg/die; n:129, 12 mg/die), Ola (n:128) or PB (n:126).	Compared to PB: reduction in PANSS TS, all Marder factors, CGI-S
Davidson et al.[17(C)]	Patients were assigned to receive fixed oral dosages of Pali ER (n:127, 3 mg/die; n:124, 9 mg/die; n:113, 15 mg/die), Ola 10 mg (n:127) or PB (n:605).	Compared to PB: improvement in PANSS TS), all Marder factors, CGI-S and PSP scale scores
Meltzer et al.[23(*)]	Patients were assigned to Pali ER (n:123, 3 mg/die; n:234, 6 mg/die; n:245, 9 mg/die; n:240, 12mg/die; n:113, 15 mg/die) or PB (n:351)	Compared with PB: improvement in PSP
Patrick et al.[24(*)]	Patients were assigned to Pali ER (n:123, 3 mg/die; n:234, 6mg/die; n:245, 9 mg/die; n:240, 12 mg/die; n:113, 15 mg/die) or PB (n:351)	Compared with PB: improvement in PANSS TS, two Marder PANSS factors (negative symptoms, conceptual disorganization), CGI-S, PSP TS
Canuso et al.[25(*)]	Patients were assigned to fixed doses of Pali ER (n:17, 3 mg; n:49, 6 mg; n:35, 9 mg; n:41, 12mg) or PB (n:56).	Compared with PB: improvement in PANSS TS, Marder PANSS factors, CGI-S, PSP
Canuso et al.[26(*)]	Patients were assigned to Pali ER (n:28, 3 mg/die; n:53, 6 mg/die; n:50, 9 mg/die; n:64, 12 mg/die) or PB (n:75)	Compared to PB: better response in PANSS TS, CGI-S, PSP TS
Canuso et al.[27(*)]	Effects of Pali ER compared to PB were evaluated in patients based on the time of the diagnosis: ≤3 years (n:189 Pali ER; n:70 PB) or >3 years (n:645, Pali ER; n:280, PB).	Compared to PB: improvement in PANSS TS, CGI- S and PSP
Canuso et al.[28(*)]	Patients with prominent affective symptoms received Pali ER (n:20, 3 mg/die; n:41, 6 mg; n:31, 9 mg; n:48, 12 mg/die) or PB (n:53)	Decrease in PANSS (TS and Subscales scores), Marder factor scores and CGI-S. Improvements in PSP functioning scores, sleep quality and daytime drowsiness
Canuso et al.[29]	Patients were assigned to Pali ER (n:160, 9-12 mg/die), Que (n:159, 600-800 mg/die) or PB (n:80).	Compared to PB: improvement in PANSS TS, Marder factors and CGI-S; most of the patients showed an improvement on at least 1 category on the PSP scale
Schmauss et al.[32]	Adults hospitalized with an acute exacerbation of schizophrenia were prospectively treated with open-label flexibly-dosed (3 to 12 mg/die) of Pali ER (n:294)	Decrease in PANSS (TS and Subscale scores), Marder factor scores and CGI-S. Improvements in PSP functioning scores, sleep quality and daytime drowsiness
Kim et al.[33]	26 patients continued Ris treatment and 32 patients were switched to Pali ER (3-12 mg/die)	Compared to Ris-continuation group: greater changes in the trial A6 of the verbal learning tests and increased in SOFAS
Kim et al.[38]	Previous antipsychotic agents (n=81, Ris; n=88, non-Ris) were switched to Pali ER treatment	Compared to Ris and non-Ris group: improvement in PANSS TS, CGI-S and PSP scores
Mauri et al.[39]	Symptomatic patients were switched to flexible doses (3 to 12 mg/die) of Pali ER (n:132)	Decrease in both in PANSS (TS and Subscales scores) and CGI-S scores. Improvement PSP, SWN-20 and DAI-30 scores, as well as the quality of sleep and the daytime drowsiness
Kotler et al.[40]	Adult patients with nonacute schizophrenia who had been treated unsuccessfully with oral Ola were switched to flexible doses (3 - 12 mg/die) of Pali ER (n=396)	Improvements in PANSS (TS and Subscales scores) and Marder factor scores (changes appeared to be significant for subgroups of patients switching for lack of efficacy, tolerability and adherence). Improvements in CGI-S and in PSP
Zhang et al.[41]	Regardless to the treatment in the DB phase, all patients in the OLE were treated with flexibly doses (3-12 mg/day) of Pali ER (n:47, Pali ER/Pali ER; n:59, PB/Pali ER)	Compared to PB/Pali ER: improvements in PANSS (TS, Subscales and factor scores). Less improvements in CGI-S and PSP scores
Shi et al.[42]	Patients dissatisfied with efficacy or lack of treatment (n:92)	A significantly decrease in PANSS TS, positive symptoms scores, negative symptoms scores, general pathology scores and in CGI-S scores. PSP scores improved, as well as the MCCB (in 6/9 individual subtests, 6/7 cognitive domains and in total cognitive scores) improved

Ola: olanzapine; OLE: open-label extension; Pali ER: paliperidone ER; PB: placebo; Que: quetiapine; Ris: risperidone; TS: total score.
(*)These studies are analysis from the same sample, derived from (A), (B), (C).

a reduction in endpoint PANSS total score greater than or equal to 30% in the paliperidone ER treatment groups was almost twice as compared as placebo (56% in paliperidone ER 6 mg, 51% in paliperidone ER 9 mg, 61% in paliperidone ER 12 mg, 30% in placebo; p<0.001). Furthermore, 22% of patients treated with paliperidone ER 6 mg, 23% of those treated with paliperidone ER 9 mg and 32% of those treated with paliperidone ER 12 mg presented a reduction in the PANSS total score greater than or equal to 50% as compared as the 15% of subjects receiving placebo. In the olanzapine group, 52% and 26% of patients showed a reduction respectively greater than or equal to 30% and 50%. At all doses of paliperidone ER, a significant improvement was observed in the CGI-S (p<0.001) compared to placebo. In particular, at the endpoint fewer patients treated with paliperidone ER were classified as "marked" or "severely ill" on the CGI-S (paliperidone ER 6 mg, 62.6% at baseline compared to 21.3% at endpoint, paliperidone ER 9 mg, 57.3% at baseline compared to 23.0% at endpoint, paliperidone ER 12 mg, 64.4% at baseline compared to 16.3% at endpoint; placebo 59.5% at baseline compared to 50.8% at endpoint). Among patients taking olanzapine, 64.1% of them were classified as "marked" or "severely ill" at baseline, compared with 23.5% at endpoint. A significant improvement in personal and social functioning was observed in all patients treated with paliperidone ER regardless of the dosage: 9.1, 8.1, 11.5 points on the PSP scale for paliperidone ER 6 mg, 9 mg, and 12 mg respectively. By contrast placebo group showed a 0.5 points improvement only, a value remarkably inferior (p<0.001) in comparison with data referred to paliperidone ER. In addition, at endpoint the percentage of patients showing some improvement in one or more PSP categories was greater in the three paliperidone ER groups (respectively 60.5%, 50.9% and 59.7%) compared with the placebo group (32.5%). In the olanzapine group, the PSP score was improved by 10.3 points with 62.7% of patients experiencing improvements in at least one category.

The third study[17] included 618 patients randomized to placebo, paliperidone ER, or olanzapine. Paliperidone ER was given at fixed doses of 3, 9 or 15 mg and olanzapine at a dose of 10 mg. Of those, 605 were included in the ITT group. The doses of 3 and 9 mg of paliperidone ER were maintained throughout the 6-week study period. In the case of the 15 mg paliperidone ER arm the full dose was instead reached after one week of treatment with 12. The change from baseline to endpoint in the PANSS total score was greater for all doses of paliperidone ER compared to placebo (p<0.001), with an average reduction of -15, -16.3 and -19.9 points in patients treated with paliperidone ER respectively at 3, 9, 15 mg and of -2.8 in whom treated with placebo. Paliperidone ER was also superior to placebo in all Marder factors (p<0.005), regardless of the dose. The difference from placebo on the PANSS total score emerged since day 4 (p≤0.003) for all three doses of paliperidone ER. The number of patients treated with paliperidone ER, showing a greater than or equal to 30% improvement in PANSS total score, was approximately as twice as the patients receiving placebo (39.8% in paliperidone ER 3 mg, 45.5% in paliperidone ER 9 mg, 52.7% in paliperidone ER 15 mg, 18.3% in placebo; p≤0.005). At endpoint a more marked improvement on the CGI-S was also observed in patients treated with paliperidone ER compared to placebo (p<0.001 for all doses of paliperidone ER): in fact, fewer patients in the paliperidone ER groups were classified as "marked" or "severely ill". As regards the changes from baseline to endpoint in the PSP scale scores, a superiority for all doses of paliperidone ER was observed compared to placebo (8.3 for paliperidone ER 3 mg; 7.6 mg for paliperidone ER 9 mg; 12.2 for paliperidone ER 15 mg; -1.5 for placebo; paliperidone ER versus placebo p<0.001). In addition, at endpoint the number of patients showing an improvement in one or more PSP categories was higher in the groups treated with paliperidone ER 3, 9 and 15 mg (respectively 50.4%, 48.3% and 63.6%) compared to the placebo group (30.3%). It should be noted that olanzapine was used only as an arm for the sensitivity analysis and a direct comparison to paliperidone ER groups was not made.

Pooled and post-hoc analyses

From these first three 6-week multicenter trials[15-17], various pooled and post-hoc analysis were conducted[23-28].

The first pooled analysis[23] included 1306 patients and compared with placebo the efficacy and safety of paliperidone ER, respectively at doses of 3, 6, 9, 12 and 15 mg. The mean scores on both the PANSS total and the five Marder factors improved from baseline to endpoint for all the doses of paliperidone ER (p<0.001). Similarly, the improvement in the CGI-S was greater for all the doses of paliperidone ER compared to placebo (p<0.001). The distribution of CGI-S scores at endpoint showed that, at all the doses, a greater number of paliperidone patients was classified as "mild", "very mild", or "not ill" compared with subjects who received placebo. Conversely, a lower percentage of patients were classified as "severe/extremely ill" among the subjects treated with paliperidone ER compared to those receiving placebo. Also, the PSP scale score showed a greater improvement in patients treated with paliperidone ER (8.3 in paliperidone ER 3 mg, 9 in paliperidone ER 6 mg, 7.8 in paliperidone ER 9 mg; 9.5 in paliperidone ER 12 mg, 12.2 in paliperidone ER 15 mg) compared to placebo (0.5; p<0.001). Moreover, at endpoint, a greater number of patients in the paliperidone ER groups across all the doses showed an improvement on at least 1 category on the PSP scale compared with those who received placebo (p<0.005).

In another pooled analysis[24], 1306 patients were included and challenged in more detail the area of personal and social functioning as it emerged from the PSP scale score. The percentage of patients achieving at least one category improvement in the PSP was higher (p<0.005) with all paliperidone ER doses (50.4% in 3 mg, 56.1% in 6 mg, 49.6% in 9 mg, 54.1% in 12 mg, 63.6% in 15 mg) compared with placebo (33.1%). Similarly, the percentage of patients with an endpoint PSP score greater than or equal to 51 was greater for all doses of paliperidone ER (63.7% in 3 mg, 58% in 6 mg, 63.3% in 9 mg, 60.5% in 12 mg, 74.8% in 15 mg) compared with placebo (44.2%; p<0.005). Raising the cut-off score greater than or equal to 71 (a value suggestive of no dysfunctions or mild difficulties in personal and social functioning), a clear distinction was observed across all doses of paliperidone ER (21.2% in 3 mg, 18.4% in 6 mg, 20.1% in 9 mg, 17.7% in 12 mg, 21.5% in 15 mg) and placebo (8.5%; p<0.05 except for the dose of 3 mg).

In a post-hoc analysis[25], was conducted on the first three double-blind, placebo-controlled, 6-week trials[13-15]. Among

the 198 patients identified and suitable for the analysis, the 142 individuals treated with paliperidone ER 3-12 mg had a history of exposure to risperidone for an average of 418.8 days at a mean dose of 4.2 mg/day while the 56 patients randomized to placebo had been previously treated with risperidone for an average of 527 days at a mean dose of 4.1 mg/day. At endpoint, paliperidone ER 3-12 mg showed a significant improvement versus placebo in the PANSS mean total score (-14.1 versus -6.4, p=0.011) although with some differences among the different paliperidone arms (17 subjects of the 3 mg arm: -3.0, p=0.592; 49 individuals of the 6 mg arm: -15, p=0.016; 35 subjects of the 9 mg arm: -12.2, p=0.11; 41 individuals of the 12 mg arm -19.2, p=0.002). Moreover, compared with placebo, paliperidone ER determined a significantly greater reduction in two Marder PANSS factors, namely respectively those related to negative symptoms (p=0.007) and conceptual disorganization (p=0.002). At endpoint, paliperidone ER resulted to be better than placebo also in relation to the CGI-S score (p=0.002) and the PSP total score (p<0.001).

A second post-hoc analysis[26] were conducted including paliperidone and placebo patients with acute schizophrenia and predominant negative symptoms. A 23% of the eligible population (270 patients) was involved: 195 patients received paliperidone ER (28 of them 3 mg, 53 of them 6 mg, 50 of them 9 mg, 64 of them 12 mg) and 75 received placebo. The definition of a predominance of negative symptoms was based on a baseline score on the PANSS negative subscale greater than or equal to 24, corresponding to 40% or more of the maximum score, and on a positive subscale score less than 27 (that is less than 40% of the maximum score). At baseline, the sample population presented mean scores of 27.4 on the PANSS negative subscale (49% of the maximum) and of 23.7 on the positive subscale (33% of the maximum). The mean paliperidone ER dose in patients with predominant negative symptoms was 8.3 mg/day. At endpoint, patients treated with paliperidone ER showed greater improvements both on the PANSS total (p<0.0001) and on the various Marder factors (p≤0.05) compared with placebo. In particular, the mean endpoint reduction in negative symptoms were -6.3, -4.2, -5.5, and -5.6 respectively for the 3, 6, 9, and 12 mg paliperidone ER doses. Paliperidone ER was also superior to placebo on the CGI-S scale and on the PSP.

In a third post-hoc analysis[27], focused not only on the data of the first three 6-week randomized trials[15-17] but also on the results of their open-label extension studies, patients were stratified by time since diagnosis (greater than or equal to 3 years compared to less than 3 years). Of the 1193 patients enrolled in double-blind phase, 259 of them (21.9%) received a diagnosis of schizophrenia from less than 3 years (32 in paliperidone ER 3 mg, 42 in paliperidone ER 6 mg, 68 in paliperidone ER 9 mg, 47 in paliperidone ER 12 mg, 70 in placebo). At endpoint patients treated with paliperidone ER showed a better response compared with the placebo group in the PANSS total (p<0.001), the CGI-S (p=0.012) and the PSP total score (p=0.018).

A fourth post-hoc analysis[28], based once again on the data from the first three 6-week, randomized, double-blind, placebo-controlled trials[15-17], evaluated the effects of paliperidone ER in schizophrenic patients with a prominent affective symptoms (as defined as a PANSS depression item score greater than 4 and/or a PANSS grandiosity score greater than 3, plus a score greater than 3 on at least one of the following PANSS items: excitement, hostility, uncooperativeness, poor impulse control). From a total of 193 patients with prominent affective symptoms, 140 received paliperidone ER and 53 received placebo. Patients treated with paliperidone ER showed greater improvement compared to placebo group both in the PANSS total score (p<0.001) and the individual Marder factors score (positive symptoms, p<0,001; negative symptoms, p<0,001; anxiety/depression, p=0.008, conceptual disorganization, p<0,001; uncontrolled hostility/excitement p<0.001). Furthermore, compared to patients who received placebo, those receiving paliperidone ER showed a greater improvement in 5 of the 6 PANSS items used as inclusion criteria (depression, p=0,016; grandiosity, p=0,244; excitement, p=0,006; hostility, p<0,001; uncooperativeness, p<0,001; poor impulse control, p=0.004). Also compared with the placebo group, the paliperidone ER group showed a higher percentage (56.4% versus 28.3%, p<0.001) of responders, lower CGI- S scores (p<0.001) and higher PSP scores (p=0.004). In this post-hoc study a subgroup analysis to verify the presence of possible differences between patients with prominent depressive symptoms and those with prominent manic symptoms was not performed.

Further study

Another 6-week, randomized, double-blind, placebo-controlled study[29] is somehow different from the previous ones. To be included in the study, patients had to have experienced an acute psychotic exacerbation for less than 4 weeks but more than 4 days, to score 4 or more on at least two among hostility or excitement or tension or uncooperativeness or poor impulse control PANSS items, to reach a global score of 17 at least for these items and to present a CGI-S score greater than 4. A 2-week monotherapy phase was followed by a 4-week period during which participants were permitted to receive other psychotropic medications, including antipsychotics. At baseline, participants discontinued all psychotropic drugs and on day 1 they were randomized, in a 2:2:1 ratio, to paliperidone ER, quetiapine or placebo. The paliperidone ER dosage was 6 mg from day 1 to day 3 with an increase to 9 mg on the fourth day and a further optional increase to 12 mg starting from day 8. Quetiapine was initiated at 50 mg and the dose was doubled on day 2, to 200 mg on day 3, to 400 mg on day 4 and to 600 mg on day 5; an optional increase to 800 mg was permitted on day 8. Efficacy was evaluated using the PANSS, CGI-S, Clinical Global Impression-Change scale (CGI-C)[20], a composite response measure consisting of the reduction in the PANSS total score of at least 30% from baseline plus a CGI-C score of 1 or 2 and the Medication Satisfactory Questionnaire (MSQ)[30,31]. Except for the MSQ, which was administered on day 14 and day 42, and for the CGI-C which is obviously not administrable at baseline, all the outcome measures were performed at baseline, on days 3, 5, 7, 9, 14, 21, 28, 42, and at endpoint. The selected population presented a clinical picture of high gravity as indicated by a mean baseline PANSS score greater than 100. The PANSS total score improvement was greater in paliperidone ER group compared to quetiapine group from the fifth day of treatment (-11.4 versus -8.2, p=0.011) to the endpoint of monotherapy phase (-23.4 versus -17.1, p<0.001). At this endpoint, the mean changes in 4 out of 5 PANSS factors (positive symptoms, negative symptoms, conceptual disorganization, hostility/excite-

ment) resulted greater with paliperidone ER compared with quetiapine or placebo (p£0,008). Paliperidone ER performed better than quetiapine (p=0.002) and placebo (p<0.001) also in CGI-S and CGI-C score changes. Similarly, the MSQ showed greater mean improvement with paliperidone ER (4.9) compared to quetiapine (4.5, p=0.006) and placebo (4.6, p=0.030). At the end of the 6-week period, that is at the end of phase in which polypharmacy was allowed, the PANSS total score improvement was greater for paliperidone ER compared to quetiapine (p=0.023) and placebo (p=0.002). Furthermore, throughout the study period, paliperidone ER has proved to be more effective than placebo and quetiapine as regards the PANSS factors related to negative symptoms, conceptual disorganization and hostility/excitement (p<0.050). At endpoint paliperidone ER was also more effective than quetiapine and placebo in improving CGI-S. Furthermore, paliperidone ER, but not quetiapine, was better than placebo on the CGI-C. As for the MSQ, the mean changes were greater with paliperidone ER (5.3) compared to quetiapine (4.8, p=0.002) and placebo (4.7, p=0.06).

In a first single-arm, open-label study[32] the efficacy of flexible-doses of paliperidone ER was evaluated in 294 adult patients. The treatment was initiated using 6 mg paliperidone ER once daily, with doses adjusted between 3-12 mg/day throughout the 6-week study. To evaluate the efficacy of the treatment, researchers used PANSS total, subscale and Marder factor scores, CGI-S and PSP. PANSS total score presented a statistically significant decrease from the first post-baseline assessment (day 2) throughout the remaining 6 weeks (p<0.0001). Similar statistically significant change was observed in all PANSS subscale scores and in each Marder factor score. Also mean CGI-S scores decreased significantly (p<0.0001). Also, the PSP functioning scores showed statistically significant improvements from baseline to the endpoint (p<0.0001). After switching to paliperidone ER, both sleep quality and daytime drowsiness showed statistically significant change (respectively an improvements in the first one at weeks 8, 13 and 26; p<0.05) with a trend at endpoint (p=0.09) and a reduction in the second one from baseline to all visits and equal to -1.4±2.9 (p<0.0001 at the endpoint).

In a 12-week, randomized, parallel-group, open-label, flexible-dose[33] study paliperidone ER was compared with risperidone. 58 Korean schizophrenic patients in monotherapy with risperidone were recruited. The patients were randomized to continue treatment with risperidone or switched to paliperidone ER. Mean doses of risperidone and paliperidone ER at baseline were 4.9±3.0 mg/day and 5.5±4.0 mg/day, respectively. The primary outcome measure was a computerized neurocognitive function test battery, while secondary efficacy measures included the PANSS, the Social and Occupational Functioning Scale (SOFAS)[21], the Calgary Depression Scale for Schizophrenia (CDSS)[34], the Beck Depression Inventory (BDI)[35], the Subjective Well-Being Under Neuroleptic Treatment-Brief Form (SWN-20)[36], the Drug Attitude Inventory (DAI)[37], and the Visual Analogue Scales (VAS) for subjective evaluation of sleep. The paliperidone-switch group showed greater changes in the trial A6 of the verbal learning tests compared to the risperidone-continuation group (p=0.042). No significant differences were found in the other neurocognitive domains. The increase in SOFAS was greater in the paliperidone ER group than in risperidone group (p=0.044). In the other efficacy measures, significant differences were not observed between the two groups.

In an open-label, prospective, non-comparative, 48-week study[38], researchers evaluated the safety and the tolerability of paliperidone ER in schizophrenic patients who had switched from risperidone or other antipsychotic (olanzapine, aripiprazole, amisulpride, ziprasidone, quetiapine, typical antipsychotic). The starting dose was generally 6 mg/day, but it was possible to start with 3-12 mg/day. Dosage adjustments were allowed within a range 3-12 mg/die. To evaluate the level of efficacy of switching to paliperidone ER, PANSS, CGI-S and PSP were used. Of 184 patients enrolled, 169 had at least one post-baseline effectiveness assessment. Researchers found a statistically significant decreased in PANSS total score from baseline to endpoint (p<0.001 both in the risperidone and in the non-risperidone group). Similar results were found also in CGI-S and PSP score (all p<0.001).

In an open-label, single-arm, multicenter, 13-week treatment study[39] researchers evaluated the efficacy of paliperidone in schizophrenic patients. In case of participation to an investigational drug trial in the 30 days before the study enrollment, patients were excluded. Neuroleptics and other psychotropic medication could be continued during the trial at a stable dose if they had been previously administered for different reasons other than schizophrenia, while benzodiazepines and anticholinergics were allowed. Symptomatic patients were switched from their current antipsychotic therapy to 6 mg once daily of paliperidone ER, within a 3-12 mg/day dose range. As efficacy criterion, the researchers evaluated PANSS total scores, PANSS subscales, CGI-S scores and a 11-point self-administered sleep evaluation scale (to check the quality of sleep and daytime drowsiness) at baseline and at weeks 2, 6, and 13. At baseline and weeks 6 and 13, PSP scale, the 30-item DAI (DAI-30)[37] and the SWN-20 were evaluated. From baseline to endpoint, the clinical response (defined as a reduction of 30% or more in PANSS total score) was evaluated. From a total of 133 enrolled patients, 132 of them entered in the intention to-treat population and 118 (88.7%) completed the 13-week study. At the primary endpoint (including 126 patients), the PANSS total score showed a significant reduction (p<0.001), that was maintained throughout the study. At every assessment PANSS subscales scores showed significant changes (p<0.0001 for each visit compared to baseline) and 51 patients (40.5%) were classified as responders. From baseline to endpoint, the mean CGI-S scores decreased significantly (p<0.0001). This change was observed at all time-points from week 2 onwards (p<0.0001). A mean significant improvement in PSP scores was observed at week 6 and at the endpoint (p<0.0001). From baseline, the mean DAI-30 scores (indicating the patients' attitudes to treatment) and the SWN-20 improved significantly at week 6 (respectively p<0.01 and p<0.0001) and at the endpoint (both p<0.0001). From baseline to endpoint, also the quality of sleep and the daytime drowsiness showed a significant improvement (respectively p<0.005 and p<0.0001).

In a subgroup analysis of patients from a previously published 6-month, international, multicenter, open-label, single-arm study[40] using flexible doses of paliperidone ER (3 to 12 mg), researchers treated patients with non-acute schizophrenia previously unsuccessfully exposed to other oral antipsychotics. The efficacy of the treatment was evaluated at baseline and at weeks 4, 8, 13 and 26 (or endpoint) with PANSS subscale, Marder factor and CGI-S scores. Patient functioning was measured using the PSP scale at baseline, at week 13 and at the endpoint. From a total of 397 enrolled patients, 396 of

them received more than 1 dose of paliperidone ER. From baseline to each visit, clinically and statistically significant improvements were observed in PANSS total, PANSS subscale and Marder factor scores between patients who were switched to paliperidone ER ($p<0.0001$ each). Changes in PANSS total and subscale scores appeared to be significant for subgroups of patients switching for lack of efficacy ($p<0.0001$), tolerability ($p\leq0.0289$) and adherence ($p\leq0.0005$), but no significant changes were observed in switching for other reasons. Similarly, the Marder factor scores appeared to be significantly changed for patients who switched for lack of efficacy ($p<0.0001$), tolerability ($p\leq0.0361$; except for the uncontrolled hostility/excitement factor, which was not significant) and adherence ($p\leq0.0039$), but no significant changes were observed for other reasons. From baseline to endpoint, also in the CGI-S it was observed a significant improvement ($p<0.001$). About the PSP, patients with a score greater than or equal to 70 ("mild degree of difficulty" or less functional impairment) doubled from 16.3% at baseline to 32.2% at endpoint.

An open-label extension (24-week) phase of a randomized, double blind, placebo-controlled, parallel group study[41] included 106 schizophrenic patients. During the open-label extension phase, the administration of oral acetaminophen, non-steroidal anti-inflammatory drugs, antihypertensives, beta-adrenergic blockers, oral benzodiazepine, and non-benzodiazepine hypnotic agents was allowed. From the total of enrolled patients, 47 of them were randomized to paliperidone ER (using a flexibly dose between 3-12 mg) and 59 to placebo. At the baseline, all patients were provided a starting dose of 6 mg (with increments or decrements of 3 mg) which was given at termination of double blind phase of the study. The efficacy was evaluated from baseline to endpoint through the changes in PANSS total score, PANSS subscale scores, PANSS factor scores, CGI-S and PSP scale. From a total of 106 patients who entered this phase (47 in paliperidone ER and 59 in placebo), 85 (80%) completed it. From the open-label extension baseline to the endpoint, in the total group the mean PANSS total score showed a decrease of -10.4±13.2, indicating an improvement in the severity of schizophrenic symptoms. The mean PANSS total score appeared greater in the placebo/paliperidone group as compared to paliperidone/paliperidone group (respectively -15.4±12.4 and -3.9±11.3). Overall, all patients showed improvement in mean PANSS subscale scores (positive subscale -3.7±5.0, negative subscale -1.5±3.7, psychopathology subscale -5.2±6.9) and PANSS factor scores (positive symptoms -3.3±4.8, negative symptoms -1.5±3.96, disorganized thoughts -2.0±3.4, uncontrolled hostility/excitement -2.1±3.7, anxiety/depression -1.4±2.6). Furthermore, the placebo/paliperidone group showed greater improvements in the mean CGI-S scores and PSP scores as compared with paliperidone/paliperidone group.

A 24-week, open, single-arm, multicenter prospective study[42] on 95 schizophrenic patients valued the improvement in social and cognitive functioning associated with paliperidone ER treatment. To evaluate the efficacy of the therapy, researchers used PANSS, CGI, PSP scale and a Chinese version[43] with high reliability and validity of the MATRICS consensus cognitive battery (MCCB)[44]. The dosage of paliperidone ER was between 3 and 12 mg/day during the 24-week study period. Assessments were performed from day 1, every 4 weeks until the conclusion of the study period. 35 patients (38.90%) were switched from risperidone, while 18 were switched from olanzapine (20.00%). During the study period, 15 participants dropped out, while 3 participants exceeded the time allowed for follow-up assessment. The full analysis set included 99 patients and the per protocol set (a subset characterized by program and good compliance as defined as greater than or equal to 80% days of proper medication) 72 patients. A significantly decrease was observed in PANSS total scores, PANSS positive symptoms scores, PANSS negative symptoms scores and PANSS general pathology ($p<0.01$) and continued to improve until the endpoint. This trend was observed also in CGI-S scores ($p<0.01$). From baseline to endpoint, a significantly improved was observed in the PSP score ($p<0.001$) and in the MCCB, more specifically in six of the nine individual subtests, six of the seven cognitive domains, and total cognitive scores improved ($p<0.05$).

LONG-TERM STUDIES

The long-term efficacy of paliperidone ER has been evaluated in several studies (Table 3).

Table 3. Long term studies: assessments and main findings.

Authors	Assessment	Main effect of treatment with paliperidone
Patrick et al.[24(*)]	Patients were assigned to Pali ER (n:123, 3 mg/die; n:234, 6mg/die; n:245, 9 mg/die; n:240, 12 mg/die; n:113, 15 mg/die) or PB (n:351)	The improvements in personal and social functioning observed during the acute treatment are maintained over the long-term
Canuso et al.[27(*)]	Effects of Pali ER compared to PB were evaluated in patients based on the time of the diagnosis in the OL population (n:188, ≤3 years; n:556, >3 years)	Patients with a more recent diagnosis presented greater improvements in PANSS TC, CGI-S and PSP
Kramer et al.[45]	Patients received open-label Pali ER (3-15 mg/die) during the run-in phase and were assigned to receive Pali ER (n:104) or PB (n:101) during the final phase	Compared to PB: longer time to recurrence and greater time to relapse; more effective as regards other secondary efficacy measures referred to symptom severity, patient functioning and quality of life
Emsley et al.[48(*)]	Regardless to the treatment in the DB phase, all patients in the OLE were treated with flexibly doses (3-15 mg/day) of Pali ER (n:628, Pali ER/Pali ER; n:249, Ola/Pali ER; n:206, PB/Pali ER)	Compared to the 6-week DB phase: further improvements in PANSS TS, Marder factors (positive and negative), CGI-S and PSP

DB: double-blind; OL: open-label; Ola: olanzapine; OLE: open-label extension; Pali ER: paliperidone ER; PB: placebo; TS: total score.
(*)These studies are analysis from the same sample, derived from (A), (B), (C).

In a randomized, double-blind, multicenter, placebo-controlled trial[45] specifically carried on to challenge in 530 schizophrenia patients the ability of the drug to prevent relapses, long-term efficacy and tolerability of paliperidone ER has been assessed. The trial had a five-phases design: a screening phase, a 8-week run-in phase (in which patients were hospitalized and received open-label paliperidone ER in a flexible dose of 3-15 mg until they were deemed clinically stable), a 6-week open-label stabilization (in which patients were discharged and the dose was maintained), a double-blind period of variable duration (in which patients were randomized in a 1:1 ratio to receive paliperidone ER or placebo) and a 52-week optional open-label extension phase. Patients were kept in the double-blind phase until the occurrence of a relapse, the withdrawal of consent or the end of the study. Time to recurrence during the double-blind phase acted as the primary efficacy measure. Secondary efficacy measures included changes in PANSS total score, Marder and Lindenmayer PANSS factors[46], CGI-S, PSP, Schizophrenia Quality-of-Life Scale (SQLS)[47] and a sleep visual analog scale. An interim analysis showed a longer time to recurrence for patients treated with paliperidone ER compared with those who received placebo (p=0.005). Furthermore, 29 patients (53%) presented a relapse in the placebo group compared to the 14 (25%) in the paliperidone ER group. The final analysis, limited to 205 patients, confirmed the data from the interim analysis and showed a greater time to relapse for paliperidone ER compared with placebo (p<0.001) as well as a higher incidence of recurrence in patients receiving placebo (52%), compared to those treated with paliperidone ER (22%). In addition, compared to placebo, treatment with paliperidone ER proved to be more effective as regards other secondary efficacy measures referred to symptom severity, patient functioning and quality of life.

The efficacy and safety of paliperidone ER in the long term has been assessed also in several 52-week, open label studies[24,27,48], which are an extension of the first three 6-week randomized trials[15-17]. In particular, a publication[48] referred to the 1083 patients included in the open-label extension studies, has reported the effectiveness of paliperidone ER administered at flexible doses of 3, 6, 9 and 15 mg. Depending on the therapy they received in the initial double-blind phase, the population included in the open-label extension phase was divided into three groups: placebo/paliperidone ER, paliperidone ER/paliperidone ER, and olanzapine/paliperidone ER. The efficacy measures included changes from baseline to endpoint in PANSS total score, Marder factors and CGI-S. A clinical response was defined as an improvement, to the completion of the extension phase, of the PANSS total score of at least 30% compared with the beginning of both the double-blind period and the open-label extension. Among the patients enrolled, 507 of them (47%) completed the open-label phase. The analysis showed that the reductions in the PANSS total score observed in the active treatment groups during the 6-week double-blind phase were maintained over the long-term. Moreover, in the first 12 weeks of the open-label phase, further significant reductions in PANSS total score occurred. At endpoint of the open-label extension, PANSS total scores improved in comparison with the double-blind phase baseline (-26.1 for placebo/paliperidone ER, -28.1 for paliperidone ER/paliperidone ER, -27.3 for olanzapine/paliperidone ER) and the beginning of the open-label phase (-16.5 for placebo/paliperidone ER, -5.3 for paliperidone ER/paliperidone ER, -4.2 for olanzapine/paliperidone ER). Among the completers of the 52-week study, a more substantial improvement from open-label extension phase baseline was observed: -27.7 for placebo/paliperidone ER; -12.2 for paliperidone/paliperidone ER; -13 for olanzapine/paliperidone ER. Although a PANSS total score improvement was observed across all treatment groups compared with the beginning of the open-label phase, the most marked reduction was observed in the placebo/paliperidone ER group. The same trend was also evident from an independent analysis of positive and negative Marder factors. At the end of the open-label phase, a PANSS total score improvement of at least 30% compared with the values observed at the beginning of the double-blind phase was achieved by 68% of patients in the placebo/paliperidone ER group, 69% of those of the paliperidone ER/paliperidone ER group and 66% of those in the paliperidone ER/olanzapine. At the end of the open-label phase an improvement of at least 30% of the total PANSS score was observed in 47% of patients in the placebo/paliperidone ER group, 35% of those in the paliperidone ER/paliperidone ER and 33 % of those of the olanzapine/paliperidone ER group. At the end of the open-label phase, the rate of patients with an improvement of at least 50% of the PANSS total score at the beginning of the double-blind phase and of the open-label phase was reached across the various treatment arms, from 43-46 % and 18-27% of patients, respectively. The percentage of patients classified as "marked", "severely" and "extremely severe" ill at the CGI-S decreased from the beginning of the double-blind phase to the endpoint of the open-label extension from 50% to 12.6%, from 57.5% to 16.4% and from 59.9% to 17.4% respectively in the placebo/paliperidone ER, paliperidone ER/paliperidone ER, and olanzapine/paliperidone ER groups. The placebo/paliperidone ER group also experienced at the endpoint a reduction of the percentage of cases who had been classified at the beginning of the open-label trial as "marked", "severely", "extremely severe" ill. Among the completers of the open label phase, the percentage of cases classified as "marked", "severely", and "extremely severe" ill at week 52 was only 3.2%, 2% and 3.7% in the placebo/paliperidone ER, paliperidone ER/paliperidone ER and olanzapine/paliperidone ER groups. At the endpoint of the open-label phase, mean changes on the PSP were of 10.3 points for placebo/paliperidone ER group, 4.4 for the paliperidone ER/paliperidone ER group and 3.6 for the olanzapine/paliperidone ER group. A more marked improvement was observed in the group of patients who completed the open-label extension phase: 16.7 points for the placebo/paliperidone ER group, 9.7 for the paliperidone ER/paliperidone ER group and 8.8 for the olanzapine/paliperidone ER group. An improvement of at least one PSP-category was registered in 58.7% of patients in the placebo/paliperidone ER group, in 47.5% of those in the paliperidone ER/paliperidone ER group and in 43.7% of patients in the olanzapine/paliperidone ER group.

Another pooled analysis[24] that also considered the open-label extensions of the first 3 double-blind 6-week studies[15-17], demonstrated that the improvements in personal and social functioning observed during the acute treatment are maintained over the long-term.

A post-hoc[27] analysis involving the three 6-week to six double-blind studies[15-17] and their open-label extensions evaluated the possible effect of the duration of the disease

on the efficacy of paliperidone ER. For this purpose, patients were stratified into two groups: those with no more than 3 of illness and those with a longer history of illness. or more than 3 years of illness. Both groups showed an improvement in all clinical and functional symptoms, even if the group having a most recent diagnosis was found to have a greater improvement. Limited to patients who completed the open label phase, the mean final PANSS total was 50.7 for the group with less than 3 years of illness and 57.4 for the group with more than 3 years, respectively. The analysis based on a mixed model for repeated-measures showed that patients with a more recent diagnosis differ from those with a longer history of illness in terms of greater improvement not only in PANSS total (p=0.002) but also in CGI-S (p=0.001) and PSP scale (p=0.004) scores.

TOLERABILITY AND TREATMENT SATISFACTION

Several studies evaluated tolerability and treatment satisfaction with paliperidone ER (Table 4).

The short-term tolerability of paliperidone has been assessed in a pooled analysis[23] centered on the 3 multicenter, double-blind, randomized, fixed-dose, placebo-controlled trials lasting 6 weeks[15-17]. The overall rates of adverse events ranged between 66-77% for paliperidone ER and 69% and 66% for olanzapine and placebo, respectively. The discontinuation rate due to adverse events was very low (2-7%) across all groups. There were no clinically significant differences in median changes from baseline to endpoint in the Barnes Akathisia Rating Scale (BARS)[49] Abnormal Involuntary Movement Scale (AIMS)[20] and Simpson-Angus Scale

Table 4. Tolerability and satisfaction: assessments and main findings.

Authors	Assessment	Main findings
Meltzer et al.[23(*)]	Patients were assigned to Pali ER (n:123, 3 mg/die; n:234, 6 mg/die; n:245, 9 mg/die; n:240, 12mg/die; n:113, 15 mg/die) or PB (n:351)	No significant differences were observed between Pali ER and PB group about extrapyramidal effect. The mean changes in body weight appeared smaller in Pali ER group than in the Ola one.
Schmauss et al.[32]	Adults hospitalized with an acute exacerbation of schizophrenia were prospectively treated with OL flexibly-dosed (3 to 12 mg/die) of Pali ER	Most TEAEs were considered mild or moderate in intensity. Improvements were observed especially in AIMS, SAS.BMI increased but not it was not considered clinically relevant.
Kim et al.[33]	26 patients continued Ris treatment and 32 patients were switched to Pali ER (3-12 mg/die)	Both Ris and Pali ER resulted well tolerated and both groups did not show significant change in EPS, in laboratory parameters, menstrual disturbance and body weight
Kim et al.[38]	Previous antipsychotic agents (n:81, Ris; n:88, non-Ris) were switched to Pali ER treatment	Improvements in DIEPSS TS (both Ris and non-Ris groups). The LUNSERS TS showed a significantly decreased in both groups. Prolactin levels changed less in the Ris group than in the non-Ris group, while all patients presented an increase in weight
Mauri et al.[39]	Symptomatic patients were switched to flexible doses (3 to 12 mg/die) of Pali ER.	Decrease in extrapyramidal symptoms. All patients presented an increase in weight and BMI
Kotler et al.[40]	Adult patients with non-acute schizophrenia who had been treated unsuccessfully with oral Ola were switched to flexible doses (3-12 mg/die) of Pali ER (n:396)	Improvement in subjective, functioning treatment satisfaction sleep quality and daytime somnolence, with a greater reduction at the ESRS in whom switched for lack of efficacy or tolerability, while who switched for lack of tolerability showed greater weight reduction
Zhang et al.[41]	Regardless to the treatment in the DB phase, all patients in the OLE were treated with flexibly doses (3-12 mg/day) of Pali ER (n:47, Pali ER/Pali ER; n:59, PB/Pali ER)	Compared to Pali ER/Pali ER group, the PB/Pali ER group showed higher incidence of TEAEs, EPS-related TEAEs and greater change in mean BMI, triglycerides and cholesterol.
Emsley et al.[48(*)]	Regardless to the treatment in the DB phase, all patients in the OLE were treated with flexibly doses (3-15 mg/day) of Pali ER (n:628, Pali ER/Pali ER; n:249, Ola/Pali ER; n:206, PB/Pali ER)	EPS-related adverse occurred in similar percentage in the Ola/Pali ER and Pali ER/Pali ER groups, while they were lower in the PB/Pali ER group. Maximun QTcLD was observed with Pali ER treatment. Irregular menstruation and erectile dysfunction were observed in PB/Pali ER group and Ola/Pali ER, respectively
Yang et al.[55]	Patients dissatisfied with previous antipsychotic medications were switched to Pali ER (n:153, 3 mg/die; n:1082, 6 mg/die; n:361, 9 mg/die; n:87, 12 mg/die) based on clinical judgment.	Improvement in treatment satisfaction

DB: double-blind; EPS: extrapyramidal syndrome; OL: open-label; Ola: olanzapine; OLE: open-label extension; Pali ER: paliperidone ER; PB: placebo; QTcLD: linear-derived QTc; Ris: risperidone; TEAEs: Treatment Emergent Adverse Events; TS: total score.
(*)These studies are analysis from the same sample, derived from (A), (B), (C).

(SAS)[50] scores between paliperidone ER and placebo. Among patients receiving paliperidone ER, the greatest increase in SAS was found in the groups treated with doses above the 6 mg/day. Patients exposed to paliperidone ER doses that exceeded 6 mg/day also had an increased incidence of EPS-related adverse events such as dystonia (1% in paliperidone ER 3 mg, 1% in paliperidone ER 6 mg, 5% in paliperidone ER 9 mg, 5% in paliperidone ER 12 mg, 2% in paliperidone ER 15 mg), dyskinesia (5% in paliperidone ER 3 mg, 3% in paliperidone ER 6 mg, 8% in paliperidone ER 9 mg, 9% in paliperidone ER 12 mg, 9% in paliperidone ER 15 mg), parkinsonism (3% in paliperidone ER 3 mg, 3% in paliperidone ER 6 mg, 7% in paliperidone ER 9 mg, 6% in paliperidone ER 12 mg, 6% in paliperidone ER 15 mg), hyperkinesia (4% in paliperidone ER 3 mg, 3% in paliperidone ER 6 mg, 8% in paliperidone ER 9 mg, 10% in paliperidone ER 12 mg, 10% in paliperidone ER 15 mg). No significant differences were observed in the incidence of EPS-related adverse events between olanzapine (dystonia 1%, dyskinesia 2%, parkinsonism 2%, hyperkinesia 2%) and placebo (dystonia 1%, dyskinesia 3%, parkinsonism 2%, hyperkinesia 4%). Only one patient included in the pooled analysis reported tardive dyskinesia, but it was not possible to identify a causal relationship between treatment with paliperidone ER 9 mg and the adverse event because the patient had a history of tardive dyskinesia. The most frequent cardiovascular adverse event was found to be tachycardia (6% in paliperidone ER, 4% in olanzapine, 3% in placebo) and sinus tachycardia (6% in all paliperidone ER, 5% in olanzapine, 4% in placebo). Syncope was reported in few patients receiving paliperidone ER (0.8%) or placebo (0.3%). No cases of sudden death, ventricular fibrillation or flutter, or torsades de pointes occurred among patients treated with paliperidone ER. The incidence of orthostatic hypotension for paliperidone ER at doses of 3 (2%), 6 (1%) and 9 mg (2%) was similar to placebo (1%). Higher values were instead observed among subjects who received paliperidone ER doses of 12 and 15 mg (respectively 4% and 3%). The mean difference in linear-derived QTc (QTcLD) values between placebo and all doses of paliperidone ER was minimal (<4 msec). None of the patients receiving paliperidone ER presented a QTcLD ≥480 msec. The mean changes in body weight at endpoint were less than 2 kg in all paliperidone treatments groups (0.6 in 3 mg, 0.6 in 6 mg, 1 in 9 mg, 1.1 in 12 mg, 1.9 in 15 mg, -0.4 in placebo). Weight gain resulted to be dose-related and smaller within the recommended dose range of 3 mg to 12 mg. The weight gain in the olanzapine group was 2 kg. Paliperidone ER was associated with elevations in serum prolactin levels. The most common adverse events, with an incidence in at least 5% of patients, were headache and insomnia. Serious adverse events were reported by only 6% of patients in the placebo or in the olanzapine group and in 5-6% of subjects receiving paliperidone ER. The most frequently reported serious adverse event was exacerbation of psychotic symptoms, for example a proxy of lack of efficacy. Excluding those related to psychiatric symptoms, the incidence of serious adverse events never resulted superior to 1%. No relevant relationship between paliperidone ER dosage and the incidence of serious adverse events has been documented. In addition, there was no report of death or neuroleptic malignant syndrome. In 10 patients assigned to paliperidone ER (1%) and in 5 patients receiving placebo (1%) a serious suicidal risk-related adverse event was observed. The rates of suicidal ideation and suicide attempts per patient/year of exposure were 14.5 and 3.6 for the placebo group and 10.3 and 1.1 for those receiving paliperidone ER. The mean changes from baseline to endpoint of glucose values were minimal (0.1 mmol/L) across all groups treated with paliperidone ER and resulted similar to those of placebo. Other potentially glucose-related adverse events were reported in 8 patients treated with paliperidone ER (1%) and in 2 of those receiving placebo (1%): among these adverse events the most common was the increase in blood glucose levels (4 patients treated with paliperidone, 1 patient receiving placebo). In two of the cases treated with paliperidone ER, the blood glucose increase was classified as serious. The changes in the levels of total cholesterol, LDL, HDL and triglycerides from baseline to endpoint were minimal (≤0.1 mmol/L) and not clinically significant. The median increase in prolactin concentration was higher among female patients (81 ng/mL) than male patients (24 ng/mL). Prolactin concentration increased with increasing doses of paliperidone ER. Prolactin-related adverse events such as impotence or other sexual dysfunction, galactorrhea, gynecomastia, amenorrhea, menstrual irregularity, were found only in 1-2% of patients who received placebo or paliperidone ER at doses of 3 to 12 mg but did not imply discontinuation of treatment. Potentially prolactin-related adverse events were observed in 4% of patients treated with paliperidone ER 15 mg.

The long-term safety and tolerability of paliperidone ER at doses of 3-15 mg has been evaluated in another pooled analysis[48] that included the data obtained in the 52-week open-label extensions of three 6-week, double- blind, placebo-controlled trials[15-17]. During the 52-week open-label phase, 76% of patients experienced some adverse event. Adverse events leading to discontinuation occurred in 1% or less of the patients and included edema, hepatitis A, cardiac or eye disease, gastrointestinal disorder, injury, poisoning, organ complications. Extrapyramidal side effects occurred in 25% of patients. A similar percentage of patients in the olanzapine/paliperidone ER and paliperidone ER/paliperidone ER groups reported EPS-related adverse events between 23 and 25%, i.e. rates lower than the 32% observed in the placebo/paliperidone ER group. The median AIMS, SAS and BARS scores were 0 at both the beginning and the endpoint of the open-label extension phase. During the open-label phase the AIMS score resulted equal or superior to 4 in 108 patients (10%): of them, 35 (32%), reported a severe degree of dyskinesia also at baseline. 11 patients (1%) reached a BARS global clinical rating of marked or severe. No patients developed movement disorders classified as serious according to SAS. During the open-label phase 11 patients (1%) treated with paliperidone ER showed a maximum linear-derived QTc (QTcLD) value between 450 and 480 msec (among these, 8 had a normal baseline QTcLD and 3 a baseline QTcLD ≥ 450 msec) and only one patient had a value exceeding 480 msec (baseline QTcLD was in the normal range). This patient belonged to the paliperidone ER/paliperidone ER group and was the only patient to reach a maximum postbaseline QTcLD >500 msec. During the double-blind and the open-label phases a weight gain from 75.6 to 77.5 kg occurred in the three groups. In the period between the beginning of the open-label extension phase and the endpoint the weight was even smaller across all groups:

1.8 kg in placebo/paliperidone ER, 1.2 kg in paliperidone ER/paliperidone ER, 0.3 kg in olanzapine/paliperidone ER. During the open-label extension phase a weight gain greater than or equal to 7% was registered in 15% of patients, and the mean change in BMI was 0.4 kg/m^2. A serious adverse event was reported by 16% of the patients, while 7% had an event resulting in withdrawal from the study and less than 1% had an event that concluded in death (suicide). Serious adverse events were observed in more than 1% of cases and included psychotic disorders (5%), schizophrenia (5%), agitation, suicidal ideation, depression, aggression and suicide attempts (1% of patients). Glucose-related adverse events (for example increased blood glucose, diabetes mellitus, glucosuria) were reported by 1% of patients, while the most common prolactin-related adverse events were amenorrhea (4% of female patients in each treatment group), irregular menstruation (5% of women in the placebo/paliperidone ER group) and erectile dysfunction (3% of male patients in the olanzapine/paliperidone ER group).

In a first single-arm, open-label study[32] the tolerability of flexible-doses of paliperidone ER was evaluated in 294 adult patients, aged more than 18 years old and with acutely exacerbated schizophrenia. During the study, vital signs did not present any relevant changes. Most Treatment Emergent Adverse Events (TEAEs) were considered mild or moderate in intensity (95.2%) and no action was taken for 90.7% of all TEAEs. Consequently to AE, 6.5% of all events required a dose adjustement, while treatment was temporary discontinued in 0.6% patients or suspended in 3.1% patients. Extrapyramidal disorders and insomnia were the most commonly TEAEs (respectively 6.1% and 5.1%), while schizophrenia was considered the most common serious TEAE. Nobody died during the study. Seven patients (2.4%) presented prolactin-related relevant TEAEs (galactorrhea, menstrual disorder, sexual dysfunction and breast swelling were observed in one patient each). 2 patients (0.7%) presented glucose-related TEAE. From baseline to the endpoint, a significant change in BMI was observed ($p<0.0001$), but it was not considered clinically relevant (0.22±0.97 kg/m^2), with a mean percentage weight change at endpoint equal to 1.0%. Overall, at endpoint 7.2% of patients presented an increased in body weight greater than 7%. Baseline values for EPS measures were low and, after 42 days of treatment, researchers observed a generally improvement in AIMS total score (-0.18±1.7), SAS global score (-0.02±0.24) and BARS global clinical rating of akathisia score (-0.03±0.5), which reached statistical significance for AIMS and SAS (respectively $p=0.0439$ and $p=0.0201$). At endpoint, patients' satisfaction with paliperidone ER tolerability was rated as "very good" (31.3%), "good" (46.3%), "reasonable" (13.1%), "moderate" (5.6%) and "poor" (3.7%).

In a 12-week, randomized, parallel-group, open-label, flexible-dose[33] study, researchers compared paliperidone ER with risperidone. During the study both risperidone and paliperidone resulted to be well tolerated (at least 10% of the patients from both groups did not report any adverse effect, except for menstruation disturbances in women). Both groups did not show significant change from baseline to endpoint about the prevalence of parkinsonism, akathisia, and tardive dyskinesia or in laboratory parameters (including cholesterol profiles, glucose, alanine transaminase and prolactin). Amenorrhea was observed in 5 patients in the paliperidone ER group (45.5%) and 4 patients in the risperidone group (44.4%), while oligomenorrhea in 4 patients in the paliperidone ER group (36.3%) and 2 patients in the risperidone group (22.2%). Menstrual disturbance was not significantly different between the two groups (respectively 9 patients in the paliperidone ER group, 81.8%, and 6 patients in the risperidone group, 66.7%; $p=0.617$). Body weight increased significantly in 4 patients (12.5%) after switching to paliperidone ER, whereas no one in the risperidone group showed clinically relevant weight gain. Anyway, the mean change in body weight did not significantly differ during the study between the risperidone-continuation group and the paliperidone ER-switch group (+0.5 and +0.9 kg, respectively).

In an open-label, prospective, non-comparative, 48 week study[38] researchers evaluated safety and tolerability of paliperidone ER among schizophrenic patients who had switched from risperidone or other antipsychotic. To evaluate the level of satisfaction and tolerability, the SNW, the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS)[51] and the Liverpool University Neuroleptic Side-Effects Rating Scale (LUNSERS)[52] were used. The total rate of AE occurrence in the risperidone group was 63.7% and 73.1% in the non-risperidone ($p=0.171$). The three most common AEs were akathisia, increased weight and muscle rigidity (respectively 16.5%, 9.9% and 9.9% in the risperidone group and 20.4%, 18.3% and 11.8% in the non-risperidone group). DIEPSS total score showed a significant improvement from baseline to endpoint ($p<0.001$ in all patients; $p<0.001$ in the risperidone group and $p=0.033$ in the non-risperidone group), while about the individual items a significant improvement was found in the ratings accorded to gait, bradykinesia, muscle rigidity, tremor and overall severity in the risperidone group and in bradykinesia and overall severity in the non-risperidone group (all $p<0.005$). The LUNSERS total score showed a significantly decreased ($p<0.001$ in all patients; $p<0.001$ in the risperidone group and $p=0.005$ in the non-risperidone group). In both groups there was a significant increase in weight ($p<0.05$) but with a similar increase. Prolactin levels changed less among women in the risperidone group than those in the non-risperidone group ($p=0.008$).

In an open-label, single-arm, multicenter, 13-week treatment study[39] in schizophrenic patients, researchers evaluated tolerability of paliperidone. Every week the researchers evaluated the safety assessments, including the report of AEs at every scheduled visit. The Extrapyramidal Symptom Rating Scale (ESRS)[53] was used to evaluate the severity of movement disorders at baseline and at weeks 2, 6 and 13, while physical examination, vital signs and assessment of body weight were performed at baseline and on weeks 6 and 13. Researchers did not find clinically relevant changes in vital signs. At least one AE was showed by 21 patients (15.9%). About the intensity of AEs, the majority of them (93.8%) were mild or moderate and only in one patient were severe. In addition, 2 patients discontinued the treatment because of tolerability issues and nobody died. The extrapyramidal symptoms decreased significantly at each postbaseline timepoint from baseline to endpoint (respectively 7.39±13.2 and 2.21±4.6, $p<0.001$). Even if both body weight and BMI presented an increase at the endpoint (respectively 0.7±3.8 kg, $p=0.05$, and 0.3±1.4, $p<0.05$), these changes were not estimat-

ed clinically significant. At the endpoint, the mean percentage of weight change was 0.7% (p=0.05) but no patients experienced a change in body weight of at least 7%.

In the subgroup analysis of patients from a previously published 6-month, international, multicenter, open-label, single-arm study[40] using flexible doses of paliperidone ER (3 to 12 mg/d), researchers compared the treatment satisfaction and the tolerability between olanzapine and paliperidone ER. To evaluate the treatment satisfaction with oral olanzapine and paliperidone ER, researchers used a 5-point categorical scale (ranging from "very good" to "very poor"), a sleep quality and daytime drowsiness, an 11-point scale for both sleep quality (from "slept very badly" to "slept very well") and daytime drowsiness (from "not at all" to "all the time") respectively at the baseline and at the endpoint. Extrapyramidal symptoms were measured by ESRS total scores. The researchers found out that paliperidone ER was generally well tolerated, with an improvement in subjective and functioning treatment satisfaction, even if a statistically significant and clinically relevant improvements in extrapyramidal symptoms was observed switching from olanzapine at each assessment and at the endpoint for the entire population (p<0.0001). About the ESRS, Parkinsonism (-0.7±2.7; p<0.0001), hypokinesia (-0.5±1.9; p<0.0001) and dystonia/dyskinesia/akathisia (-0.5±2.2; p<0.0001) were the domain with the largest change. From baseline to endpoint, patients switching for lack of efficacy or tolerability showed the most significant change in total ESRS scores (respectively ranging from -0.7±2.7 to -1.1±3.3, p<0.0001 and from -0.5±3.2 to -1.1±3.9, p≤0.0276), while in case of switching for lack of adherence or for other reasons, changes were not statistically significant (respectively ranging from -0.3±1.7 to 1.6±6.0 and from -1.0±2.2 to -0.4±2.6). About body weight, patients presented an average decrease of almost 1 kg during the study (mean weight at baseline 83.4±16.9 kg, with decreased equal to -0.5±3.9 kg at week 13, -1.0±5.5 kg at week 26 and -0.8±5.2 kg at endpoint; p≤0.0053), especially in whom switched for lack of tolerability. From baseline to endpoint, weight loss until 4 kg occurred in 100 patients (27.7%), while more than 4 kg occurred in 61 patients (16.9%). Conversely, a total of 38 patients (10.5%) gained more than 4kg and 29 patients (8.0%) showed a clinically relevant weight gain from baseline to endpoint. Patients switching from olanzapine for lack of tolerability showed the most important weight reduction (p≤0.0005), while who switched for lack of efficacy or lack of adherence or other reasons did not. Furthermore, switching from olanzapine to paliperidone ER presented a significant improvement in sleep quality (p<0.05) and reduced daytime somnolence (p<0.0001). In the end, treatment satisfaction appeared to be superior with paliperidone ER than olanzapine (respectively "good" to "very good" 65.3% versus 20.5% of patients, "moderate" 15.1% versus 46.7% and "poor" to "very poor" 19.6% versus 32.7%).

In an open-label extension (24-week) phase[41] safety was evaluated through AIMS, BARS, SAS, Columbia Suicide Severity Rating Scale[54] and clinical laboratory parameters, ECGs, weight, vital signs, physical examinations. From a total of 106 patients, TEAEs were experienced by 35 of them (33%) and their incidence was higher in the placebo/Paliperidone group (37.3%) than the paliperidone/paliperidone group (27.7%). Akathisia, somnolence, nasopharyngitis, and constipation were the most common TEAEs (3.8% each). One patient from paliperidone/paliperidone group committed suicide during the open-label extension phase. Two patients from paliperidone/paliperidone group (4.3%) experienced serious TEAEs (completed suicide and worsening of schizophrenia). By the way, TEAEs did not lead to a permanent discontinuation of the study drug. EPS-related TEAEs were experienced by 8 patients (7.5%) and the incidence was higher in the placebo/paliperidone group than in the paliperidone/paliperidone group (respectively 11.9% and 2.1%). Hyperkinesia (5.7%), akathisia (3.8%) and restlessness (1.9%) were the most common. Increased prolactin levels was more pronounced in women compared to men (respectively 83% versus 76% in placebo/paliperidone group and 19% versus 5% in paliperidone/paliperidone group), but generally it was not commonly associated with TEAEs (except for the presence of galactorrhea in a patient from the paliperidone/paliperidone group). The 99% of patients presented a Columbia Suicide Severity Rating Scale score equal to 0 (no suicidal ideation), while 1% of them had a score equal to 1 (wish to be dead). From open-label extension baseline to endpoint, patients from the placebo/paliperidone group showed greater change in mean BMI, triglycerides and cholesterol than the one in paliperidone/paliperidone group (respectively 0.39±1.6 kg/m^2, 0.42±0.8 mmol/L and 0.12±0.8 mmol/L versus 0.23±1.2 kg/m^2, 0.13±0.7 mmol/L and -0.03±0.7 mmol/L), while no clinically relevant changes in vital signs (for example fasting glucose values), ECG recordings or other clinical laboratory parameters were observed.

In a nonrandomized, open-label, single-arm, phase-4, multicenter, prospective, 8-week study[55] the treatment satisfaction with paliperidone extended release tablets was evaluated in 1,693 patients dissatisfied with previous antipsychotic treatment. The patients were subgrouped based on reasons for switching (dissatisfaction with social functioning, dissatisfaction with efficacy and dissatisfaction with safety), antipsychotic drug use at baseline (chlorpromazine, olanzapine, ziprasidone, aripiprazole, quetiapine, risperidone or others) and severities of the disease (evaluated through MSQ, CGI-S and PSP scores). Finally, according to the CGI-S score at baseline, patients were divided into 3 categories: a mild subgroup (borderline mentally ill and mildly ill), a moderate subgroup (moderately ill and markedly ill) and a severe subgroup (severely ill and extremely ill). Enrolled patients were treated with paliperidone ER dose ranging from 3 mg/d to 12 mg/d. Patients treated with risperidone had been directly switched to paliperidone ER, while patients treated with other antipsychotics needed a titration period (1-week in case of haloperidol, ziprasidone or amisulpride and 2-week in case of chlorpromazine, olanzapine or quetiapine). In patients previously treated with more antipsychotics, the primary antipsychotic was switched to paliperidone ER within 1 month. In this study, after 8 weeks, an important decrease in disease severity was observed in paliperidone ER treatment group. The researchers observed a reduction in CGI-S scores by 2.37±1.20 (p<0.0001), with a remission of the schizophrenic symptoms in about 83% patients; 95% of patients expressed treatment satisfaction for paliperidone ER: after the switch, mean MSQ score improved 2.99±1.05 points (p<0.0001) and a significant improvement was present in the PSP score (mean change equal to 25.5±15.03; p<0.0001), with up to 56% patients achieving the PSP score at the endpoint.

CONCLUSIONS

Considering the above-mentioned randomized double-blind studies, we can assume that paliperidone ER is a therapeutic option strongly indicated in the short-term treatment of schizophrenia: data on the changes induced by treatment, in particular on PANSS, CGI-S, CGI-C and PSP scores, are unequivocal. As regards the long-term use, the available data, which are mainly derived from open-label extension studies of short-term controlled trials suggest that paliperidone ER not only permits to maintain the improvement observed in the acute phases of treatment, but it is also able to induce further improvements both in the symptoms picture and in personal and social functioning. With respect to tolerability, the short-and long-term studies indicate that paliperidone ER has a very favorable profile, as documented by a reduced incidence of serious adverse events. Furthermore, it is worth noting that the extrapyramidal side effects are rare, the impact on body weight is minimal and that there are no clinically significant metabolic index changes. It should also be noted that, although increases in prolactin levels were observed, only few patients reported adverse events. Finally, as regards the cardiovascular profile, only 1% of patients treated with paliperidone ER has in the long-term show post-baseline QTc values exceeding 450 msec and only 1 patient had a post-baseline value greater than 480 msec, which suggests a low potential of adverse events related to QT lengthening. The main limitations of the present review lie in its narrative structure: its findings cannot be considered conclusive as those of a systematic or meta-analytical review, which could yield with greater methodological precision a complete analysis of all evidences concerning the short and long terms use of paliperidone ER in the treatment of schizophrenia. Therefore, it's possible that a number of studies on this subject have not been considered for inclusion. However, such structure would require more definite and strict study objective and design, which does not meet the broader, more narrative aims of the present work. Instead, this paper aims to provide a descriptive overview of various aspects that are of significant clinical relevance. In conclusion, taking into account the tolerability and efficacy data, together with the use of innovative sustained-release formulation based on the OROS system that ensures a steady release over 24 hours and allows a single daily administration, paliperidone can be considered a valid option for the short and long-term treatment of schizophrenia.

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