

Efficacy and tolerability of paliperidone ER in patients with unsatisfactorily controlled schizophrenia by other antipsychotics: a flexible-dose approach

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This study evaluates the effectiveness of paliperidone ER in patients with symptomatic but not highly acute schizophrenia in terms of efficacy, safety, and patients' perception of their social functioning and well-being. This is a multicenter, open-label prospective study with a flexible-dose approach; 133 patients were enrolled and followed for 13 weeks after switching to paliperidone ER. Outcome efficacy measures were as follows: the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression-Severity (CGI-S) scale, and the Personal and Social Performance (PSP) scale; in addition, the Subjective Well-being under Neuroleptics (SWN-20) scale, the Drug Attitude Inventory (DAI-30), and the sleep evaluation scale were used. Symptom Rating Scale (ESRS), adverse events, and subjective side effects were recorded. 118/133(88.7%) patients completed the study. The mean PANSS score decreased (88.98 ± 10.09 to 66.52 ± 16.29 ; $P < 0.001$); 40.5% of the patients achieved improvement of at least 30%. PSP and CGI-S scores as well as DAI-30 and SWN-20 decreased ($P < 0.001$). ESRS ($P < 0.001$) decreased significantly from the baseline. Throughout the trial, no deaths occurred and

only one serious adverse event was reported. Paliperidone ER has proved to be efficacious, safe, and well tolerated also with this approach more closely resembling actual clinical practice. Patient-relevant outcome parameters such as social functioning and quality of life improved, which is crucial for treatment adherence in clinical practice. *Int Clin Psychopharmacol* 30:329–337 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Schizophrenia is a debilitating condition that is classified among the 20 most important causes of disability worldwide (Leucht *et al.*, 2010). Deficits in social functioning can be observed throughout the course of schizophrenia as in the early stages, both during the acute exacerbation periods and over the long-term maintenance treatment (Huang *et al.*, 2012). Patients' objectives and expectations from treatment widened with the availability of new medications. Improvement in health-related quality of life and social functioning are important indices of treatment success although research on schizophrenia treatments has focused predominantly on symptom improvement (Schaub *et al.*, 2011).

Several studies have been carried out to better establish the efficacy and safety of the available antipsychotic drugs. Daily oral paliperidone ER has been approved for the treatment of schizophrenia and schizoaffective disorder by the European Medicine Agency and the US Food and Drug Administration. On the basis of pre-clinical and clinical investigations, paliperidone ER is an effective and safe antipsychotic. It has been shown to

improve symptoms and functioning significantly in patients with schizophrenia irrespective of time since diagnosis (Davidson *et al.*, 2007; Kane *et al.*, 2007; Marder *et al.*, 2007; Canuso *et al.*, 2010a, 2010b). Phase III efficacy and safety, placebo-controlled, pivotal studies were carried out using randomly fixed doses of paliperidone ER (Davidson *et al.*, 2007; Kane *et al.*, 2007; Marder *et al.*, 2007). It is well known that placebo-controlled, randomized studies enroll more restricted patient samples that do not fully reflect typical clinical practices, comprise a defined homogenous group of patients with schizophrenia, and also include an initial wash-out.

Daily clinical practice, however, usually focuses on an individual patient's needs and aims to optimize patients' personal therapy, therefore applying flexible dosing in an attempt to achieve the best balance between efficacy and tolerability in that particular patient. Flexible-dose studies therefore enable gathering of more information on the day-to-day use of medication. To date, some studies have been carried out in a flexible-dose design (Huang *et al.*, 2012; Kim *et al.*, 2012; Schmauss *et al.*, 2012; Na *et al.*, 2013; Kim *et al.*, 2013; Gattaz *et al.*, 2014; Schreiner

et al., 2014), but only two of them (Kim *et al.*, 2013; Schreiner *et al.*, 2014) also used general measures of psychopathology, functioning, and well-being for a direct transition from a variety of oral antipsychotics to flexibly dosed paliperidone ER.

The aim of this study is to investigate flexible dosing of paliperidone ER in a representative population of patients with symptomatic, but not highly acute schizophrenia, within 10 years from diagnosis, followed as outpatients in psychiatric structures (a routine care setting) using less stringent inclusion and exclusion criteria and allowing a direct transition from any previous oral antipsychotic other than clozapine. This patient population is particularly interesting because it is important to treat symptomatic patients as soon as they start presenting symptoms to avoid an acute relapse and consequently improve their prognosis. This prevention is one of the aims of the outpatient follow-up in outpatient services.

In addition, there is overwhelming evidence that non-compliant patients are more likely to relapse than medication compliers and that the psychological response to neuroleptic treatment is a significant predictor of treatment outcome. The assessment of the subjective effects of antipsychotics is particularly useful to evaluate both the benefits and the burdens of drug therapy and it is an indirect measure of patients' quality of life.

The Subjective Well-being under Neuroleptics (SWN-20) and the Drug Attitude Inventory (DAI-30) self-rating scale have been used to evaluate the subjective effects of neuroleptics and patients' perspective of the drug therapy, respectively.

Methods

The study (R076477-SCH-3037) was carried out in accordance with the ethical principles in the Declaration of Helsinki and in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol. Twenty-eight sites in Italy were involved in the study, which was carried out between January 2009 and March 2010. The study protocol was reviewed and approved by the independent ethics committee of each investigational site.

Patients

Participants were men or women, between 18 and 45 years of age, and fulfilled the DSM-IV criteria for schizophrenia. A disease duration lasting less than 10 years was an inclusion criterion. At baseline, patients were experiencing psychotic symptoms, with a Positive and Negative Syndrome Scale (PANSS) total score between 70 and 100. All participants were followed as outpatients and were switched to paliperidone ER from previous antipsychotics because of unsatisfactory control because of poor efficacy and/or tolerability. Patients

signed an informed consent document indicating that they understood the study purpose and procedures, they were willing to participate in the study, and able to fill out self-administered questionnaires.

The main exclusion criteria included a diagnosis of substance dependence (current or within the previous 6 months); medical condition affecting absorption, metabolism, or excretion of the study drug including inability to swallow the pill; history of tardive dyskinesia or neuroleptic malignant syndrome; being at significant risk of suicide or violent behavior; female patients who were pregnant or breast-feeding; patients receiving clozapine or a depot antipsychotic within 3 months. Patients were also excluded if they had severe and unstable physical illness and if they had participated in an investigational drug trial in the 30 days before the study enrollment. A history of drug sensitivity or allergy, including hypersensitivity to risperidone or paliperidone, also resulted in exclusion from the study.

Study design

This was an open-label, single-arm, multicenter, 13-week treatment study in patients with schizophrenia.

Patients were assessed at day 0 (baseline) and at weeks 2 (visit 2), 6 (visit 3), and 13 (visit 4).

Symptomatic patients were switched from their current antipsychotic therapy to flexible doses of paliperidone ER, within a 3–12 mg/day dose range, according to the clinical judgment of each research psychiatrist. Generally, the recommended paliperidone ER dose was 6 mg once daily, although some patients benefited from lower or higher doses in the recommended dose range.

At each visit, patients received the amount of medication required until the next visit. Patients receiving any oral antipsychotic medication could be switched to an effective dose of paliperidone ER without the need for titration.

Dosing was flexible throughout the study period according to the investigators' discretion on the basis of individual patients' clinical response to and tolerability of the study drug.

Neuroleptics other than paliperidone ER for the treatment of schizophrenia were not allowed during this trial. However, neuroleptics and other psychotropic medication that had been administered before the trial and prescribed for different reasons other than the disorder itself (e.g. sleep induction or sedation) could be continued during the trial at a stable dose.

Benzodiazepines were allowed as rescue medication during the trial if the use did not exceed 10 consecutive days.

Biperidene (up to 4 mg/day) or trihexyphenidyl (up to 10 mg/day) or other available anticholinergics could be

used for the treatment of extrapyramidal symptoms. The investigator had to continuously re-evaluate the need for anticholinergic medication during the study.

Efficacy and safety scales, reports of adverse events (AEs), and treatment information were recorded at each preplanned clinic visit. Patients could withdraw from this study at any time; the reasons for withdrawal or loss of follow-up were recorded.

Efficacy measures

Total PANSS scores, PANSS subscales (Positive, Negative, and General Psychopathology Symptoms scores), and Clinical Global Impression-Severity (CGI-S) scores were assessed at baseline, and weeks 2 (V2), 6 (V3), and 13 (V4). The primary efficacy criterion was the change in the total PANSS score measured at the end of the study (week 13 or the last postbaseline evaluation) versus baseline.

Personal and social functioning, determined using the Personal and Social Performance (PSP) scale, was assessed at baseline and weeks 6 (V3) and 13 (V4). This scale is based on the DSM-IV (American Psychiatric Association, 1994) Social and Occupational Functioning Assessment scale (Morosini *et al.*, 2000), and provides a clinician rating of personal and social functioning on a 100-point scale, with a score of 1–10 representing lack of autonomy in basic functioning and 91 to 100 reflecting excellent functioning. The ratings are mainly based on the assessment of a patient's functioning in four main areas: (a) socially useful activities, including work and study; (b) personal and social relationship; (c) self-care; and (d) disturbing and aggressive behaviors.

Other efficacy endpoints included determination of clinical response (patients with $\geq 30\%$ reduction in PANSS total score from baseline to endpoint), the 30-item DAI-30 (Rossi *et al.*, 2001), and the Subjective Well-Being under Neuroleptic Treatment Scale-short version (SWN-20) (Naber *et al.*, 2001), which were assessed at baseline and weeks 6 (V3) and 13 (V4).

The DAI-30 is a widely used self-report inventory that measures subjective response to medication as well as attitude toward pharmacological treatment, illness, and health in an effort to gain a more complete understanding of factors influencing medication compliance. We computed the score on the 25 items that mostly contribute toward an increase in the score's internal consistency (Rossi *et al.*, 2001): accordingly, the score ranges from a minimum of 25 (negative attitude) to a maximum of 50 (the higher the score, the more positive the attitude).

The SWN-20 is the most widely used self-report scale assessing the well-being of patients receiving anti-psychotic medication. The SWN-20 scale contains five subscales consisting of four items each: mental functioning, self-control, emotional regulation, social

integration, and physical functioning. The total score ranges from a minimum of 20 (poor subjective experience) to a maximum of 120 (excellent subjective experience).

Quality of sleep and daytime drowsiness were evaluated at baseline and weeks 2, 6, and 13 using an 11-point sleep evaluation scale. This self-administered scale rates sleep quality and daytime drowsiness. Patients are asked to rate on an 11-point scale (from 0 to 10) how well they slept in the previous 7 days ('very badly' to 'very well') and how often they felt drowsy within the previous 7 days ('not at all' to 'all the time'). On the sleep evaluation scale, score '0' corresponds to 'very badly' and score '10' to 'very well'. On the daytime drowsiness scale, score '0' corresponds to 'not at all' and score '10' to 'all the time'.

Safety measures

Safety assessments were performed at least weekly and included the reporting of AEs at every scheduled visit. Treatment-emergent adverse events (TEAEs) were defined using the WHO Adverse Reaction Terminology preferred terms. The Medical Dictionary for Regulatory Activities (MeDRA) AE dictionary was used to map AEs to preferred terms and system organ class. The severity of movement disorders was evaluated using the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005) at baseline and weeks 2, 6, and 13. Vital signs, physical examination, and assessment of body weight were also performed at baseline and weeks 6 and 13.

Statistical analysis

A sample size of 102 patients was considered to have 90% power to detect a difference in the total PANSS score means of 6.8 from baseline to endpoint, assuming a SD of differences of 20.9. Considering a dropout rate of 20%, the necessary sample size was at least 128 patients.

All patients who received at least one dose of paliperidone ER were included in the efficacy analysis (intention-to-treat population). The last available data after baseline were used for missing data of patients who dropped out, in accordance with the Last Observation Carried Forward method. For all efficacy parameters, comparisons between measures recorded at the end of the study (week 13 or the last postbaseline visit) and at the baseline were used to characterize the treatment response in all patients.

For the primary efficacy criterion, the one-sample *t*-test was used to determine whether the total PANSS mean response changed from 'pre' and 'post' study treatment (paired difference *t*-test). The *t*-test was carried out using SAS [Version 8.2 software (SAS Institute Inc., Cary, NC, USA)] Proc. MEANS.

For the secondary efficacy criteria, changes from baseline to the end of the study (week 13 or the last postbaseline

evaluation), the one-sample *t*-test (or a nonparametric analog Wilcoxon signed rank test if the data were not normally distributed) was used to determine whether the total mean response of the scales changed from 'pre' and 'post' study treatment.

Pearson's correlation coefficients were calculated to establish the association between the efficacy evaluation scales (PANSS, CGI-S, PSP, DAI-30, and SWN-20).

All tests were two sided, with a significance level fixed at the classical level of 5%.

Statistical analysis and data listings were produced using the SAS version 8.2 package. Other efficacy endpoints included the evaluation of responder rates defined as the number of patients with at least a 30% reduction in the PANSS total score from baseline to endpoint. Evaluation of safety was performed on the safety population (all patients who received at least one dose of study medication) and was based on the frequency of AEs.

Safety data were summarized by appropriate descriptive statistics. Vital signs, body weight, and BMI were summarized as central tendency and dispersion, and descriptive statistics of comparisons with baseline values were reported at each scheduled time point. Descriptive statistics were also provided for ESRS total and subscales scores.

Results

Patients' characteristics and disposition

A total of 133 patients were enrolled, with the intention-to-treat population consisting of 132 individuals. Overall, a total of 118 patients (88.7%) completed the 13-week study, whereas 15 patients (11.3%) discontinued the trial.

The reasons for study discontinuation were as follows: AE ($n=1$), lack of efficacy ($n=3$), lost to follow-up ($n=2$), study medication noncompliance ($n=1$), and patient choice ($n=8$). Among the patients, 68.9% were men ($n=91$) and predominantly diagnosed with paranoid schizophrenia (Table 1). The mean time between diagnosis and enrollment was 4.9 years (SD 3.33). The mean total number of reported previous psychiatric hospitalizations was 2.3 (SD 1.86) and 53.8% of the patients ($n=71$) had never been hospitalized before. The mean age at diagnosis of schizophrenia was 30.5 years (SD 6.24).

Patients switched from their previous treatment to paliperidone ER because of lack of efficacy (86.4%), lack of tolerability (13.6%), or both (8.3%). The majority of patients switched from one antipsychotic medication ($N=118$, 89.4%), risperidone (32.7%), olanzapine (23.8%), and haloperidol (15.6%) being the most common.

Figure 1 shows patients' disposition.

Table 1 Baseline characteristics (intention-to-treat) of the population

Characteristics	<i>N</i> = 132
Age (years)	
Mean (SD)	35.3 (6.76)
Median	35.7
Range	20.5–49.2
Sex [<i>n</i> (%)]	
Male	91 (68.9)
Female	41 (31.1)
Race [<i>n</i> (%)]	
White	130 (98.5)
Asian	1 (0.8)
Arabic	1 (0.8)
Schizophrenia subtype [<i>n</i> (%)]	
Paranoid	86 (65.2)
Disorganized	7 (5.3)
Undifferentiated	26 (19.7)
Residual	7 (5.3)
Catatonic	3 (2.3)
Other	3 (2.3)
Duration since first diagnosis (years)	
Mean (SD)	4.9 (3.33)
Median	5
Range	0.0–15.0
Number of previous psychiatric hospitalizations over the previous 12 months	
Mean (SD)	0.2 (0.47)
Median	0.0
Range	0.0–2.0

At baseline, the mean daily dose of paliperidone ER prescribed was 5.32 mg (SD 2.0) and the mean daily dose at the end of the study was 6.91 mg (SD 2.4). Sixty-eight patients never changed the dose from the beginning to the end of the study and the majority of these patients (63.2%) received a daily dose of 6 mg. Figure 2 represents the frequencies of patients for each daily paliperidone ER dose and changes over the study.

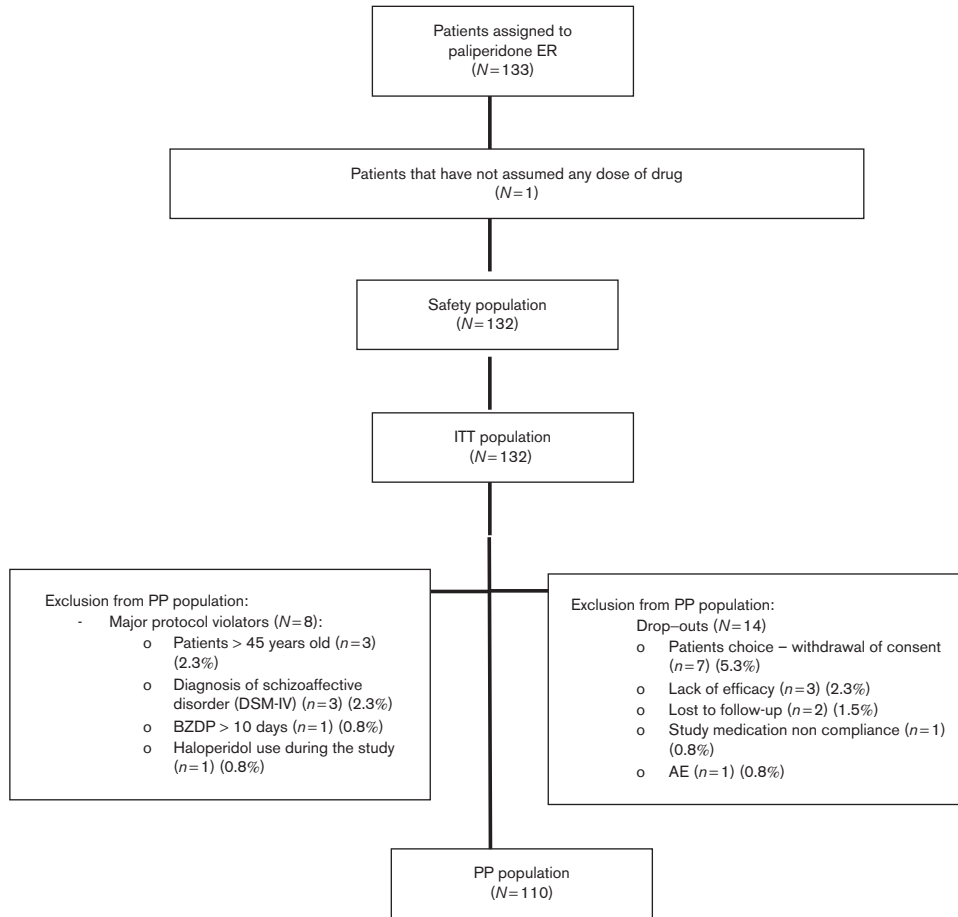
The mean duration of paliperidone ER exposure was 86.7 (SD 18.7) days. Concomitant medications other than antipsychotics were reported for 77 patients (58.3%) whereas concomitant antipsychotic medications were reported for 43 (32.6%) patients during the study. Sixteen patients (12.1%) were on anticholinergic medications during the trial. The number of patients without 'any medical condition' was 86 (65.2%) at the screening. However, the most frequent currently active diseases at screening were endocrine/metabolic ($n=10$, 7.6%).

Efficacy

The primary endpoint was evaluated in 126 patients and a significant reduction in the total PANSS score was observed from the baseline to the endpoint (Fig. 3, Table 2, $P < 0.001$). It is worth noting that a statistically significant improvement was achieved by week 2 and maintained throughout the study (Fig. 3).

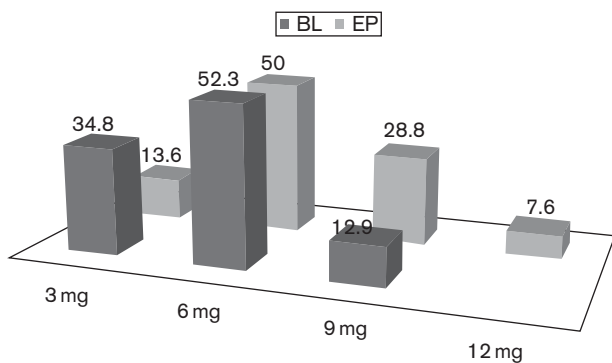
The mean improvement from baseline was statistically significant for the PANSS Positive, Negative, and General Psychopathology Subscales scores at every assessment ($P < 0.0001$ for each visit vs. baseline, Fig. 3). Fifty-one patients (40.5%) were classified as responders.

Fig. 1



Patient disposition. AE, adverse events; ITT, intention-to-treat.

Fig. 2



Paliperidone ER daily dose during the study (frequency of patients taking the reported dosages). BL, baseline; EP, endpoint.

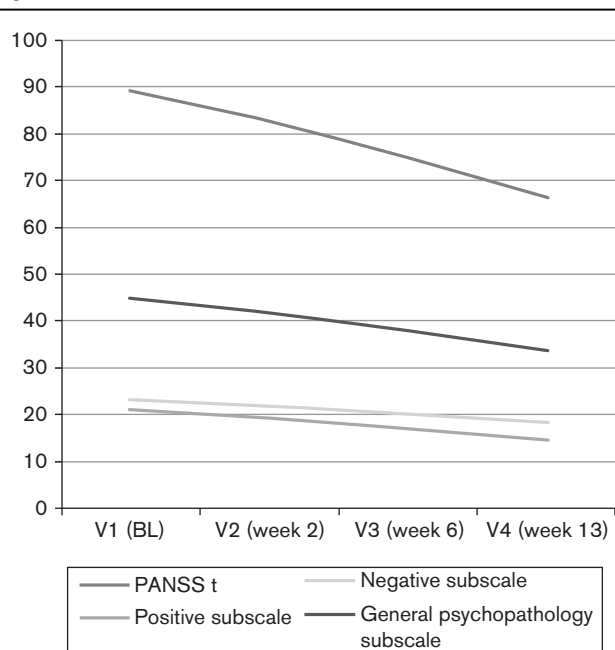
The mean CGI-S scores decreased significantly, indicating an improvement in the overall severity of patients' psychopathological condition from baseline to endpoint ($P < 0.0001$) (Table 2). This improvement was observed

at all time-points from week 2 onwards ($P < 0.0001$). Changes in CGI severity distribution are shown in Fig. 4.

The psychosocial functioning was assessed using the PSP scale and a mean improvement in PSP scores from baseline was statistically significant at week 6 and at endpoint ($P < 0.0001$) (Table 2). The frequency of patients with PSP total score of at least 71 (indicating a mild functioning deficit) increased from 8 (6.1%) at baseline to 38 (31.9%) at endpoint.

Patients' attitudes to treatment, evaluated by the mean DAI-30 scores, improved significantly from baseline to endpoint [change from baseline: 2.0 ± 5.4 (SD), $P < 0.0001$] (Table 2) and was significant at week 6 ($P < 0.01$). The SWN-20 improved significantly from baseline at week 6 ($P < 0.0001$) and endpoint [change from baseline: 6.9 ± 12.8 (SD), $P < 0.0001$] (Table 2). Quality of sleep improved significantly from baseline to endpoint ($P < 0.005$) and daytime drowsiness decreased significantly from baseline to endpoint ($P < 0.0001$) (Table 2).

Fig. 3



Mean Positive and Negative Syndrome Scale (PANSS) scores throughout treatment: mean PANSS total scores and mean PANSS subscale scores. Improvements from baseline were statistically significant at all visits for PANSS total (PANSS t) and subscales scores ($P < 0.001$) (V1–V4, $t = 14.6$, $d.f. = 125$, $P < 0.001$). BL, baseline.

Correlation analysis

At baseline, the PANSS correlated positively with CGI-S ($r = 0.44$, $P < 0.01$) and correlated negatively both with PSP ($r = -0.40$, $P < 0.01$) and with quality of sleep ($r = -0.19$, $P < 0.05$). The DAI-30 and SWN-20 were positively correlated ($r = 0.37$, $P < 0.01$). PSP was negatively correlated with CGI-S ($r = -0.50$, $P < 0.01$) and positively correlated with SWN-20 ($r = 0.17$, $P < 0.05$). At the endpoint, we could verify the maintenance of the correlation between PANSS and CGI-S ($r = 0.66$, $P < 0.01$), PANSS and PSP ($r = -0.60$, $P < 0.01$), DAI-30 and SWN-20 ($r = 0.20$, $P < 0.05$), and PSP and CGI-S ($r = -0.59$, $P < 0.01$). The SWN-20 was also negatively correlated with the PANSS ($r = -0.20$, $P < 0.05$) and positively correlated with the quality of sleep ($r = 0.39$, $P < 0.01$) at the endpoint.

Tolerability and safety

Tolerability and safety assessments were available for all 132 patients. Changes in vital signs were small and not clinically relevant. No laboratory tests were required for this study, as per protocol. Twenty-one patients (15.9%) presented at least one AE; the majority of AEs (93.8%) were mild or moderate in intensity (Table 3); only one SAE occurred. In addition, only 2/132 patients discontinued the treatment because of tolerability issues, and no deaths occurred.

The extrapyramidal symptoms, evaluated by ESRS, decreased significantly from baseline (7.39 ± 13.2) to endpoint (2.21 ± 4.6) and at each postbaseline time-point ($P < 0.001$).

Body weight and BMI were increased at the endpoint (0.7 ± 3.8 kg, $P = 0.05$, and 0.3 ± 1.4 , $P < 0.05$, respectively). However, these changes were not considered clinically relevant. The mean percentage weight change at endpoint was 0.7% (95% confidence interval, 0.00–1.38, $P = 0.05$). Overall, no patients experienced a change in body weight of at least 7% at the endpoint.

Discussion

This was an open-label, multicentric, 13-week study carried out in a setting of Italian outpatients designed to evaluate the daily clinical practice in a normal psychiatric environment. The main results of this study go beyond the expected efficacy on symptoms and do consist of a significant improvement in the functioning and well-being life aspects among those symptomatic patients affected by schizophrenia since 5 years of diagnosis on average. An excellent tolerability with paliperidone ER also emerged as a mainstream result in this population during the entire study duration.

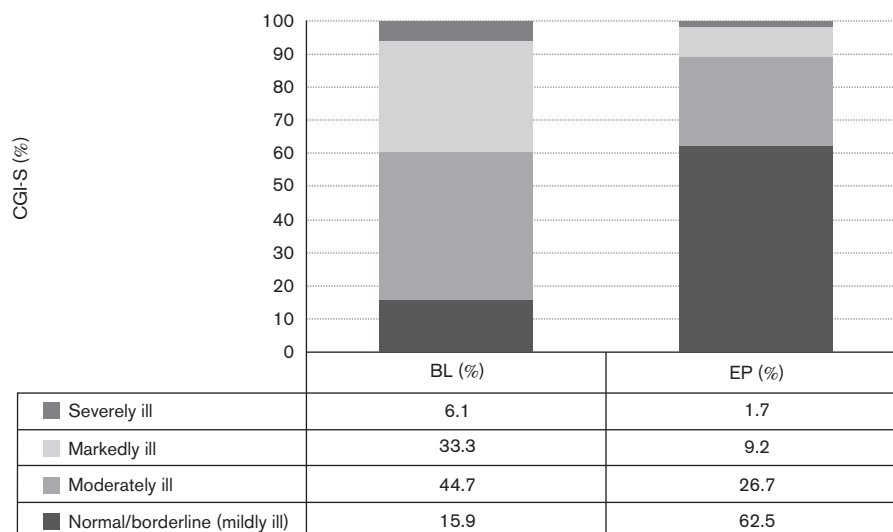
As expected, our data confirm the efficacy of paliperidone ER from the pivotal trials (Davidson *et al.*, 2007; Kane *et al.*, 2007; Marder *et al.*, 2007) by its fixed and flexible doses (Amtanick *et al.*, 2013), independent of the setting (Schmauss *et al.*, 2012). It is worth noting that the sample included patients who did not achieve satisfactory control using other treatments before starting paliperidone ER, thus showing its efficacy in this population. Our data have shown a significant improvement in the total PANSS scores, its subscales,

Table 2 Changes in the outcome measures from baseline to endpoint

	N	Baseline	Endpoint	T or Z	P-value
PANSS total score [mean (SD)]	126	88.98 (10.09)	66.52 (16.29)	14.59	<0.001
PSP score [mean (SD)]	123	56.54 (12.47)	65.70 (11.75)	-9.57	<0.0001
SWN-20 score [mean (SD)]	90	73.81 (15.4)	80.67 (16.13)	-5.08	<0.0001
CGI-S [median (range)]	127	4 (2–6)	3 (1–6)	-7.53	<0.0001
DAI-30 [mean (SD)]	123	41.20 (5.36)	43.26 (4.55)	-4.16	<0.0001
Quality of sleep score [mean (SD)]	126	6.22 (2.5)	7.08 (2.09)	-3.14	<0.01
Daytime drowsiness score [mean (SD)]	126	4.09 (2.4)	3.30 (2.52)	-3.62	<0.0001

CGI-S, Clinical Global Impression-Severity; DAI-30, Drug Attitude Inventory; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SWN-20, Subjective Well-being under Neuroleptics.

Fig. 4



Clinical Global Impression-Severity (CGI-S) throughout the study. BL, baseline; EP, endpoint.

Table 3 Treatment-emergent adverse events

TEAE	N=132
Any TEAE [n (%)]	32 (24.2)
Common TEAEs (occurring in $\geq 2\%$ of patients) [n (%)]	
Weight increase	4 (3.0)
Extrapyramidal symptoms	3 (2.3)
Insomnia	4 (3.0)
Severity of TEAEs, on the basis of the number of TEAEs [n (%)]	
Mild	15 (46.9)
Moderate	15 (46.9)
Severe	2 (6.3)

TEAE, treatment-emergent adverse events.

and severity of the symptoms by the CGI-S as well. At the same time, our data are in agreement with recent open-label studies on flexible doses of paliperidone ER in terms of symptomatological and functioning efficacy, safety, and tolerability (Huang *et al.*, 2012; Kim *et al.*, 2012; Schmauss *et al.*, 2012; Na *et al.*, 2013; Kim *et al.*, 2013; Gattaz *et al.*, 2014; Schreiner *et al.*, 2014). Furthermore, we showed that our patients experienced a significant improvement in functioning, moving from the baseline category of 'difficulty that interferes on their roles and necessity of support' (range 51–60, PSP) to an end-point category in which they presented with a difficulty not interfering with their roles (range 61–70, PSP). Furthermore, a significant improvement in well-being shown by the changes in SWN-20 total score and its subscales (mental functioning, self-control, emotional regulation, social integration, and physical functioning) might indicate an improvement in patients' quality of life as SWN-20 scores seem to be correlated to an objective evaluation of the psychopathology, quality of life, and mood control domains (Naber *et al.*, 2001).

Kim *et al.* (2012) used a flexible-dose approach in a Korean population switched from risperidone to paliperidone ER and found a significant improvement in the attitude to the treatment (by the DAI-30), the personal and social functioning (by the PSP), and well-being (by the SWN-20 and its social integration and self-control subscales). The authors made a theoretical association between social functioning/quality of life (verified by the PSP and the social integration SWN subscale) and pharmacoeconomic aspects, highlighting the usefulness of SWN-20 as an appropriate instrument to predict compliance to antipsychotics. To this extent, the SWN-20 is hypothesized by the authors as a contributing factor to physicians' and patients' shared decision, consequently improving treatment adherence. Our data provided an objective measure to support this idea by the significant correlation between SWN-20 and DAI-30 both at baseline and at endpoint. The findings of Kim *et al.* (2012) from a restricted sample of patients are confirmed by our results and further expanded as we included less restrictive criteria with a wider switching modality, thus allowing a more representative sample closer to patients accessing clinical practice.

In the same way, Huang *et al.* (2012), using a flexible study design, found a significant improvement in the efficacy and severity of overall symptoms, safety, and tolerability. The authors recommend further studies to carry out a correlation analysis between psychopathology and functioning. Hence, we carried out this analysis and observed, as expected, a negative correlation between PANSS and PSP, both at baseline and at endpoint. Thus, at the end of the study, a reduction in the psychopathology, followed by the treatment with paliperidone

ER was associated with better functioning status. Schaub *et al.* (2011) also found a negative correlation between the PANSS and PSP in a sample of chronic schizophrenic patients and reported that their data showed a close relationship between social functioning and psychopathology, thus providing strong evidence of the applicability of the PSP scale with real-world functioning. Finally, given that their work is based on a cross-sectional analysis, Schaub *et al.* (2011) underline that further studies must better evaluate the impact that clinical change in psychopathological symptoms has on psychosocial functioning or social outcomes during the treatment.

To such a degree, the present study differs from the others, being the only prospective, flexible-dose approach, study carried out in a day-to-day clinical practice (patients' profile was less homogeneous including comorbidities and concomitant medications that are usually not allowed in randomized, controlled trials) that uses patient-centered outcomes such as personal and social functioning (PSP) and subjective measures of well-being related to the treatment (SWN-20), thus showing the quality of life of these patients (Schaub *et al.*, 2011). Na *et al.* (2013) used the SCL-90 instrument as a subjective measure of psychopathology. The SWN-20 is highly supported by the scientific literature as a subjective instrument for the evaluation of therapy and disease among psychotic patients, showing good validity and sensitivity properties (Naber *et al.*, 2001). Recently, Kim *et al.* (2013) evaluated changes in SWN-20 in a cohort of patients switching to paliperidone ER in a flexible-dose design approach very close to our study, but they focused on the differences in outcomes between patients who switched from risperidone and patients who were on other antipsychotics. The authors found an improvement in SWN-20 only in those patients who switched from risperidone, but not in the other group. In this study, we did not aim to consider differences in outcomes on the basis of previous antipsychotic(s) and our findings indicate a general improvement in SWN-20, indicating better quality of life. Our findings are in agreement with the study of Schreiner *et al.* (2014), in which quality of life was assessed more directly using SF36 in a group of patients taking paliperidone ER in a flexible dose. These authors found a significant improvement in quality of life after 6 months of treatment. Paliperidone ER has proved to be efficacious, safe, and well tolerated in the range of recommended dose (3–12 mg), being mainly prescribed at doses of 6 and 9 mg in a real-world representative sample, that is with concomitant drugs and endocrine/metabolic comorbid diseases. Such data are particularly interesting considering that schizophrenic patients very often present with increased indexes of hepatic diseases, which in turn are exacerbated by their life style, with scarce access to medical care, sexual hazardous behavior, and a high prevalence of a dual diagnosis. As paliperidone ER has a pharmacokinetic profile of low hepatic

metabolism and therefore a low potential for pharmacological interactions, it has been shown to be a safe drug in this group of patients treated in real life. It must be underlined that we did not monitor plasma concentration primarily because it has been investigated in previous studies (see Citrome, 2012 for a review) and we did not expect different results in a flexible-dose approach. Furthermore, we aimed to keep the routine visits similar to the control visits that patients would have had if they had not been enrolled in a study.

This study is limited by the use of an open-label design and by the lack of a comparator. However, the use of an open-label design with a flexible-dose approach more closely reflects actual clinical practice. It should also be noted that in comparison with some recent studies (Gattaz *et al.*, 2014; Kim *et al.*, 2014; Schreiner *et al.*, 2014), the present study evaluates a smaller sample and the duration of follow-up is shorter, which could limit generalization of the findings. However, it must be taken into account that this is a national study, therefore reflecting a relatively small Italian patient population, and that particular attention has been paid to outcome parameters. Further studies are needed to confirm the stability of the results over time.

Increased attention to and improvement in patient-relevant outcome parameters such as social functioning and quality of life (indirectly assessed in this study through the SWN-20) were equally verified during this study with paliperidone ER. These results constitute the mainstreams of the current trial, besides clinical efficacy and excellent tolerability.

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Conflicts of interest

M.A. is a full-time employee of the Janssen-CilagSpA. For the remaining authors there are no conflicts of interest.

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