Symptomatic Remission with Paliperidone Palmitate 3-Monthly Formulation in Schizophrenia Patients in a Clinical Practice Setting: REMISSIO

Maria Paz Garcia-Portilla[1], Pierre-Michel Llorca[2*], Giuseppe Maina[3], Vasilis P Bozikas[4], Halise Devrimci-Ozguven[5], Kim Sung Wan[6], Paul Bergmans[7], Irina Usankova[8], Pierre Cherubin[9], Katalin Pungor[10]

*[1]University of Oviedo, CIBERSAM, Spain; [2]CMP B, CHU Clermont-Ferrand, Clermont Auvergne University, France; [3]SCDU Psichiatria, AOU San Luigi Gonzaga, Università degli Studi di Torino, Italy; [4]Second Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Greece; [5]Department of Psychiatry, School of Medicine, Ankara University, Turkey; [6]Chonnam National University Medical School, Gwangju, South Korea; [7]Janssen Cilag, Biostatistics & Programming, Breda, The Netherlands; [8]Johnson & Johnson, EMEA Medical Affairs Organization, Moscow, Russia; [9]Janssen Cilag, EMEA Medical Affairs, Issy-les-Moulineaux, France; [10]Janssen Cilag, EMEA Medical Affairs, Dusseldorf, Germany; *Presenting author*

INTRODUCTION

- In patients with schizophrenia, achievement of symptomatic remission (SR; defined as low levels of selected symptoms maintained for ≥6 months[1]) predicts improvement in psychosocial functioning and quality of life[2]
- Long-acting injectable paliperidone palmitate 3-month formulation (PP3M), administered four times a year, is approved for use in the USA, Canada, the EU and several Asian countries as maintenance treatment for patients with schizophrenia whose symptoms have been stabilized with paliperidone palmitate 1-month formulation (PP1M)[3]
- In two pivotal randomized controlled trials, PP3M demonstrated favourable efficacy and tolerability in schizophrenia[4,5]; in the non-inferiority trial comparing PP3M and PP1M, >50% of patients achieved SR in the final 6 months of the double-blind treatment phase[2]
- However, due to the selective nature of randomized clinical trials, results from the populations studied may not be entirely representative of the diverse population of schizophrenia patients in real life

OBJECTIVE

- To assess the impact of the transition from PP1M to PP3M in patients with clinically stable schizophrenia in a real-world setting, with a primary objective of assessing the percentage of patients achieving SR at study endpoint

METHODS

Study design

- An international prospective Phase 3b, single-arm, non-randomized, open-label, 52-week study conducted in a diverse population of patients with schizophrenia seen in clinical practice (REMISSIO study; ClinicalTrials.gov identifier NCT02713282)
- In patients previously stabilized on PP1M treatment, PP3M was administered from Day 1 to Day 360, with the last injection of PP3M at Month 9
- The initial dose of PP3M and subsequent dose changes (possible at clinicians' discretion) were made according to the product label[5]

Patients

- Patients aged 18–50 years with a confirmed diagnosis of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*)
- Adequate treatment with PP1M for ≥4 months (the last two doses of PP1M being the same)
- A baseline Positive and Negative Syndrome Scale (PANSS) total score <70

Assessments

- Assessments were made at 3-monthly intervals during the treatment period
- A follow-up call for safety assessments was made 3 months after Month 12 or at 3 months after early study discontinuation

Outcomes

- The primary outcome was the number of patients who achieved SR (score ≤3 on PANSS items P1, P2, P3, N1, N4, N6, G5, and G9, maintained for ≥6 months[1]) at the last observation carried forward (LOCF) endpoint (Month 12 or early discontinuation)
- Main secondary outcomes included changes in PANSS total and subscores, PANSS Marder factors, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C) and adverse events (AEs)
- The primary analysis set for efficacy and safety comprised all patients who provided written informed consent and received at least one dose of PP3M during the treatment phase and who had at least one post-baseline efficacy assessment (modified intent-to-treat [mITT] population)

RESULTS

Patient disposition

- A total of 312 patients were screened at 57 study sites across Europe, Asia and the Middle East
- The mITT population comprised 305 patients; however, two patients withdrew at Month 3 without any post-baseline data
- The primary set for efficacy and safety analysis therefore included 303 patients
- A total of 291 (95.4%) patients completed the 12-month study

Demographics

- Baseline characteristics are presented in **Table 1**

Table 1. Baseline characteristics (modified ITT population)

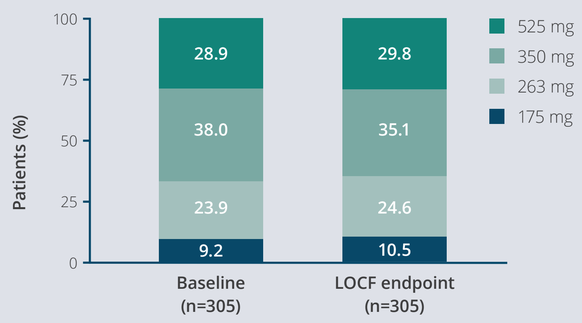
Characteristic	Total group (N=305)
Age, years	n=305
Mean (SD)	36.5 (8.0)
Median (range)	36 (20–51)
Males, n (%)	200 (65.6)
Years from schizophrenia diagnosis to study baseline	n=304
Mean (SD)	9.2 (7.3)
Median (range)	7 (0–35)
Last PP1M dose category, n (%)	n=305
50 mg	27 (8.9)
75 mg	74 (24.3)
100 mg	114 (37.4)
150 mg	90 (29.5)
Therapy prior to PP1M switch, n (%)	n=305*
Risperidone	149 (48.9)
Paliperidone	63 (20.7)
Olanzapine	24 (7.9)
Aripiprazole	9 (3.0)
Duration of previous PP1M treatment, n (%)	n=305†
4–6 months	57 (18.7)
>6 months	235 (77.0)
Patients switched from PP1M monotherapy, n (%)	253 (83.0)

**14 patients who reported to have switched from PP1M, but who withdrew early from the study, are not presented in the table. †13 patients used PP1M for at least 4 months, but the exact duration was not known. ITT: intent-to-treat; PP1M: paliperidone palmitate 1-month formulation; SD: standard deviation.*

Treatment exposure

- Mean (SD) follow-up was 352.7 (52.30) days and duration of exposure was 263.0 (42.49) days
- Doses of PP3M received remained stable during the treatment period **(Figure 1)**
  - A total of 15 patients (4.9%) had ≥1 dose decrease. Reported reasons were: tolerability concerns (n=5), improved condition (n=2), good health/stable (n=3), adverse events (n=1), persistent amenorrhoea (n=1), excessive sedation (n=1), worsening of extrapyramidal symptoms (n=1), and investigator choice (n=1)
  - A total of 11 patients (3.6%) had ≥1 dose increase. Reported reasons were: worsening of schizophrenia/psychotic symptoms (n=4), efficacy not within expectations (n=3), mistaken administration of a higher dose (n=1), deficiency effect in order to control residual symptoms (n=1) and investigator opinion that the patient's condition could be improved (n=1)

Figure 1. First and last PP3M doses

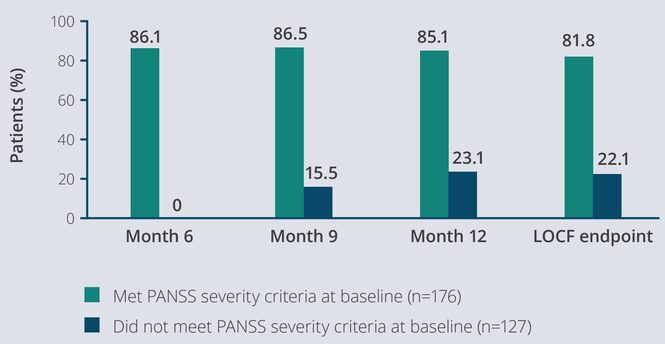


LOCF: last observation carried forward; PP3M: paliperidone palmitate 3-month formulation

Efficacy outcomes

- At LOCF endpoint, 172 of 303 patients (56.8%; 95% confidence interval [CI] 51.0–62.4) had achieved SR
- During the 12-month study period a total of 184 patients achieved SR
  - Five patients who had met the SR at Month 6 lost SR at Month 9, and 7 who achieved SR at Month 9 lost it at Month 12
- The Kaplan–Meier estimate of median time to achievement of SR was 247 days (95% CI 189–275)
- At baseline, 176 patients (58.1%) met the PANSS severity criterion
  - The number of these patients who achieved SR remained higher than those who did not fulfil this criterion during the study period **(Figure 2)**

Figure 2. Achievement of symptomatic remission in patients who met the PANSS severity criterion for remission at baseline and in patients who did not meet the PANSS severity criterion for remission at baseline



PANSS: Positive and Negative Syndrome Scale

- Mean PANSS total score decreased by 3.1 points from baseline to LOCF endpoint **(Table 2)**
  - Maintained efficacy was demonstrated by means of a statistically significant Schuirmann non-inferiority test (p-value <0.0001) with the non-inferiority margin set at 5 points

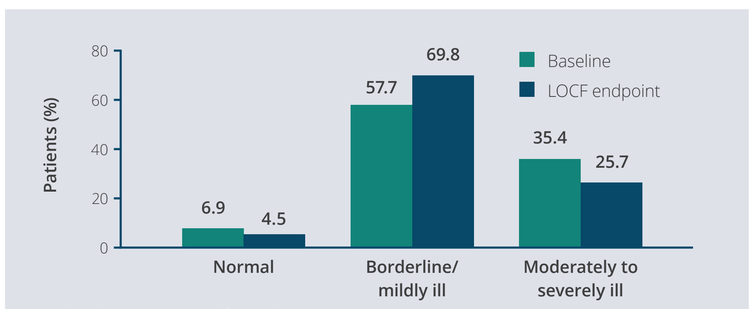
Table 2. PANSS scores at baseline and LOCF endpoint

	Baseline (n=302)	LOCF endpoint (n=302)	Mean change from baseline (95% CI)
PANSS total	52.4 (10.6)	49.4 (12.3)	**-3.1 (-4.1, -2.0)**
PANSS positive subscale	10.7 (3.2)	10.0 (3.5)	**-0.8 (-1.1, -0.4)**
PANSS negative subscale	16.2 (5.4)	15.1 (5.1)	**-1.1 (-1.5, -0.7)**
PANSS general subscale	25.6 (5.2)	24.4 (5.9)	**-1.2 (-1.8, -0.6)**
PANSS Marder positive symptoms	13.8 (4.0)	13.0 (4.3)	**-0.8 (-1.2, -0.5)**
PANSS Marder negative symptoms	15.5 (5.6)	14.3 (5.1)	**-1.3 (-1.7, -0.9)**
PANSS Marder disorganized thoughts	12.2 (3.3)	11.8 (3.7)	**-0.4 (-0.7, -0.1)**
PANSS Marder uncontrolled hostility	4.9 (1.4)	4.8 (1.5)	**-0.1 (-0.3, 0.1)**
PANSS Marder anxiety/depression	6.1 (2.1)	5.7 (2.0)	**-0.4 (-0.7, -0.2)**

Values are mean (standard deviation) unless otherwise indicated. CI: confidence interval; LOCF: last observation carried forward; PANSS: Positive and Negative Syndrome Scale

- The mean (SD) CGI-S score was 3.2 (1.0) at baseline and remained stable at LOCF endpoint (3.0 [1.0])
- The number of patients in the categories of normal, borderline and mildly ill increased from 64.6% at baseline to 74.2% at LOCF endpoint **(Figure 3)**

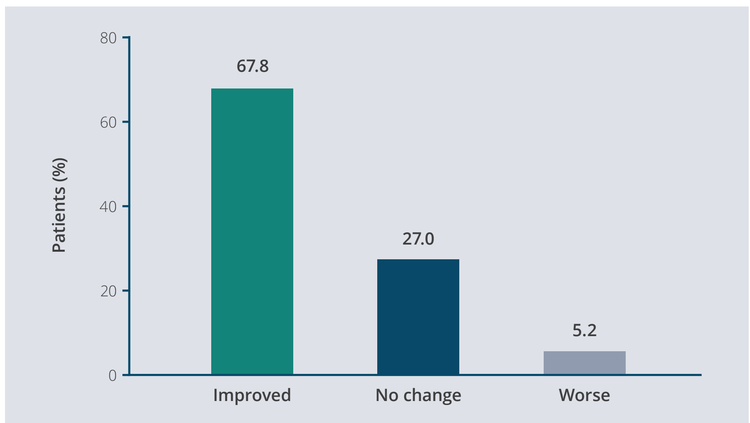
Figure 3. Clinical Global Impression of Severity at baseline and LOCF endpoint



LOCF: last observation carried forward

- At LOCF endpoint, 67.8% of patients were considered to have improved, according to the CGI-C **(Figure 4)**

Figure 4. Clinical Global Impression of Change at LOCF endpoint



Safety

- A total of 161 patients in the mITT (53.1%) reported at least one treatment-emergent adverse event (TEAE)
  - 91 (30.0%) patients reported a TEAE that was at least possibly related to study medication
  - 18 (5.9%) patients experienced a serious TEAE (5 were psychiatric disorders) and 4 (1.3%) patients withdrew from the study due to TEAEs

Table 3. Treatment-emergent adverse events experienced by ≥3% of patients

Adverse event, n (%)	Total group (N=303)
Injection site pain	18 (5.9)
Weight increased	26 (8.6)
Akathisia	11 (3.6)
Viral upper respiratory tract infection	11 (3.6)
Insomnia	11 (3.6)
Schizophrenia	10 (3.3)
Weight decreased	10 (3.3)

- 14 patients (4.6%) experienced ≥1 possibly prolactin-related TEAEs (no laboratory testing was required by the study protocol)
  - Menstrual disturbance (n=8); sexual or erectile dysfunction (n=3); galactorrhoea (n=1); hyperprolactinaemia (n=2)
- A weight increase of >7% from baseline was observed in 11 patients (10.4%) with a baseline body mass index (BMI) <25 kg/m^2, 13 patients (11.6%) with a baseline BMI 25 to <30 kg/m^2, and 7 patients (9.3%) with a baseline BMI ≥30 kg/m^2

CONCLUSIONS

- For the majority of clinically stable patients with schizophrenia, converting from PP1M in a naturalistic setting, PP3M achieved SR and maintained symptom stability
- In this patient population of mild/moderate symptomatology around 68% of the participants showed improvement according to the CGI-C
- The completion rate of 95.4% is one of the highest ever observed for a 1-year study in schizophrenia, with a low number of discontinuations due to AEs (4 participants; 1.3%)
- PP3M was generally well tolerated
- Results from this naturalistic study were similar to those observed in randomized clinical trials for PP3M, and underline the importance of continuous treatment in patients with schizophrenia

REFERENCES

1. Andreasen NC, et al. Am J Psychiatry 2005;162:441–9; 2. Savitz AJ, et al. Int Clin Psychopharmacol 2017;32:329–36; 3. TREVICTA. Summary of Product Characteristics. June 2018; 4. Berwaerts J, et al. JAMA Psychiatry 2015;72: 830–9; 5. Savitz AJ, et al. Int J Neuropsychopharmacol 2016;19:1–14.

DISCLOSURES

This study was sponsored by Janssen. Writing and editorial assistance were provided by Michelle Preston, Cello Health MedErgy, and were funded by Janssen. P-M Llorca has received speaker and consultation fees from Janssen, EISAI, Lundbeck, Otsuka, and Bouchara-Recordatti. I Usankova, P Cherubin, and K Pungor are full-time employees of Janssen. P Bergmans is a full-time employee of Janssen and a stockholder of Johnson & Johnson. M P Garcia-Portilla has been a consultant to and/or has received honoraria/grants from Angelini, CIBERSAM, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer. G Maina, V Bozikas, H Devrimci-Özgüven, and SW Kim have no conflicts of interest to disclose.

This poster was first presented at the 31st Congress of the European College of Neuropschopharmacology, 6-9 October 2018, Barcelona, Spain

48° Congresso Nazionale Società Italiana di Psichiatria, 13-17 Ottobre 2018, Torino, Italia