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Stable patients with schizophrenia switched to paliperidone palmitate 3-monthly formulation in a naturalistic setting: impact of patient age and disease duration on outcomes

Katalin Pungor, Vasilis P. Bozikas, Robin Emsley, Pierre-Michel Llorca, Srihari Gopal, Maju Mathews, Annette Wooller and Paul Bergmans

Abstract

Background: Paliperidone palmitate 3-monthly (PP3M) is a second-generation, long-acting injectable antipsychotic formulation indicated for the maintenance treatment of adults with schizophrenia first stabilized with paliperidone palmitate 1-monthly (PP1M). This exploratory *post hoc* subgroup analysis of the 52-week, phase 3b REMISSIO study analysed outcomes according to patient age and disease duration in a naturalistic clinical setting.

Methods: Outcomes of patients with schizophrenia were analysed according to age [<35 years (n = 123) *versus* ⩾35 years (n = 182)] and disease duration [⩽3 years (n = 72) *versus* >3 years (n = 233)]. The primary efficacy outcome was the proportion of patients achieving symptomatic remission according to the Andreasen criteria. Adverse events were monitored throughout the study.

Results: At endpoint (last observation carried forward), 60.7% (95% CI: 51.4%, 69.4%) of younger patients and 54.1% of older patients (95% CI: 46.6%, 61.6%) achieved symptomatic remission. The proportions for patients with disease duration ⩽3 years and >3 years were similar: 57.8% (45.4%, 69.4%) *versus* 56.5% (49.8%, 62.9%). Functional remission was reached by 45.4% (36.2%, 54.8%) of patients aged <35 years and 36% (28.9%, 43.6%) of patients aged ⩾35 years with a similar pattern when analysed by disease duration. PP3M had a favourable safety profile and was generally well tolerated in both age groups.

Conclusion: Patients with schizophrenia, previously stabilized on PP1M, may benefit from PP3M treatment with some additional potential improvements if started early in the disease course.

Clinical trials.gov: NCT02713282

Keywords: disease duration, functional remission, paliperidone palmitate 1-monthly formulation, paliperidone palmitate 3-monthly formulation, patient age, *post hoc* analysis, schizophrenia, symptomatic remission

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Correspondence to:
Katalin Pungor
Janssen, EMEA Medical Affairs, Johnson & Johnson Platz 1, Neuss, 41470, Germany
kpungor@its.jnj.com

Vasilis P. Bozikas
Second Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Greece

Robin Emsley
Stellenbosch University, Cape Town, South Africa

Pierre-Michel Llorca
CMP B, CRU Clermont-Ferrand, Clermont Auvergne University, France

Srihari Gopal
Maju Mathews
Department of Neuroscience, Janssen Research and Development, LLC, NJ, USA

Annette Wooller
Janssen, EMEA Medical Affairs, High Wycombe, UK

Paul Bergmans
Janssen Cilag, Biostatistics, Breda, The Netherlands

Introduction

Schizophrenia is a chronic, severe and disabling illness[1,2] affecting over 20 million people globally.[3] Antipsychotics are the cornerstone of pharmacological treatment for schizophrenia,[4] and maintenance treatment with oral antipsychotics can lead to improved outcomes such as symptom control and lower relapse rates.[5–7] However, suboptimal adherence to daily oral antipsychotic medication is common and associated with more frequent relapse, hospitalization and a longer time to remission.[8,9]

Long-acting injectable antipsychotic treatments (LATs) offer advantages in schizophrenia treatment; for example, removing the burden of daily oral antipsychotic medication[10] may improve adherence.[11] Compared with daily oral antipsychotics, LAT use

has been associated with fewer relapses and less carer burden as well as improvements in functioning, quality of life and mortality rates in patients with schizophrenia.[12,13] A meta-analysis of 42 cohort studies reported that LATs are superior to oral medication with regard to the rate, but not risk, of hospitalization.[14] Second-generation LATs (SG-LATs) combine the improved tolerability of oral second-generation antipsychotics with the convenience and adherence of LATs.[15]

Paliperidone palmitate 3-monthly (PP3M) is an SG-LAT indicated for the maintenance treatment of adult patients with schizophrenia who have been stabilized with paliperidone palmitate 1-monthly (PP1M).[16,17] It is currently the only SG-LAT with a 3-monthly regimen.[18] Two randomized controlled trials (RCTs) demonstrated that PP3M has a favourable efficacy and safety profile in schizophrenia treatment. Berwaerts *et al.* showed that PP3M significantly delayed time to first relapse compared with placebo [hazard ratio: 3.45; 95% confidence interval (CI): 1.73; 6.88; $p < 0.001$].[19] Subsequently, Savitz *et al.* reported that PP3M and PP1M relapse rates (8% *versus* 9%) and symptomatic remission rates (58% *versus* 59%) were similar.[20] However, as with most RCTs, these studies incorporated stringent eligibility criteria, excluding many patients encountered in routine clinical practice.[21]

REMISSIO was a 52-week, phase 3b study designed to complement RCTs by evaluating the efficacy and safety of transitioning patients with schizophrenia previously stabilized [Positive and Negative Syndrome Scale (PANSS) total score <70] with PP1M to PP3M in a naturalistic clinical setting.[22] The authors reported that 56.8% of patients achieved symptomatic remission [two-fold criteria as defined by the Remission in Schizophrenia Working Group: (1) symptom control based on PANSS eight core items,[23] (2) maintained for a minimum of 6 consecutive months], and 31.8% achieved both symptomatic and 'functional remission' [Personal and Social Performance (PSP) total score >70] at last observation carried forward (LOCF) endpoint. Patients who achieved symptomatic remission tended to be younger and had a shorter disease duration than those who did not achieve symptomatic remission.[22]

Here we report results from exploratory *post hoc* subgroup analyses of the REMISSIO dataset, which assessed outcomes in younger (<35 years) *versus* older (⩾35 years) patients with schizophrenia treated with PP3M, and in those with duration of disease ⩽3 years *versus* >3 years.

Methods

REMISSIO study design and PP3M treatment

REMISSIO (ClinicalTrials.gov: NCT02713282; EudraCT: 2015-004835-10) was a single-arm, open-label, 52-week, phase 3b study designed to evaluate the efficacy and safety of converting adult patients with schizophrenia stabilized with PP1M for ⩾4 months (the last two doses the same) to PP3M in a naturalistic clinical setting. Patients in the study had baseline PANSS total score <70 and were considered by the physician likely to benefit from switching. The study design (supplemental material Figure 1), patient eligibility criteria, and PP3M treatment and dosing were described in the primary publication.[22] The study protocol and amendments were reviewed by an independent ethics committee or institutional review board, as appropriate, for each study site. The study was conducted in compliance with the Declaration of Helsinki and was consistent with Good Clinical Practice and applicable regulatory requirements. Written informed consent was obtained from all patients before enrollment.

Efficacy and safety endpoints

The primary efficacy endpoint was the proportion of patients achieving symptomatic remission (according to the two-fold Andreasen criteria[23]) at LOCF endpoint.[22] Secondary efficacy endpoints[22] included: symptomatic remission at Months 6, 9, 12; time to symptomatic remission; change from baseline in PANSS (total and subscales) and the five Marder factors, Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Change (CGI-C) scores; PSP total and subscale scores; functional remission; patient satisfaction with medication; and health care resource utilization. Other secondary endpoints and safety evaluations are described more fully in the primary manuscript.[22]

Statistical analysis

The modified intention-to-treat efficacy and safety analysis sets comprised all patients who provided written consent, received at least one dose of PP3M during the 52-week treatment

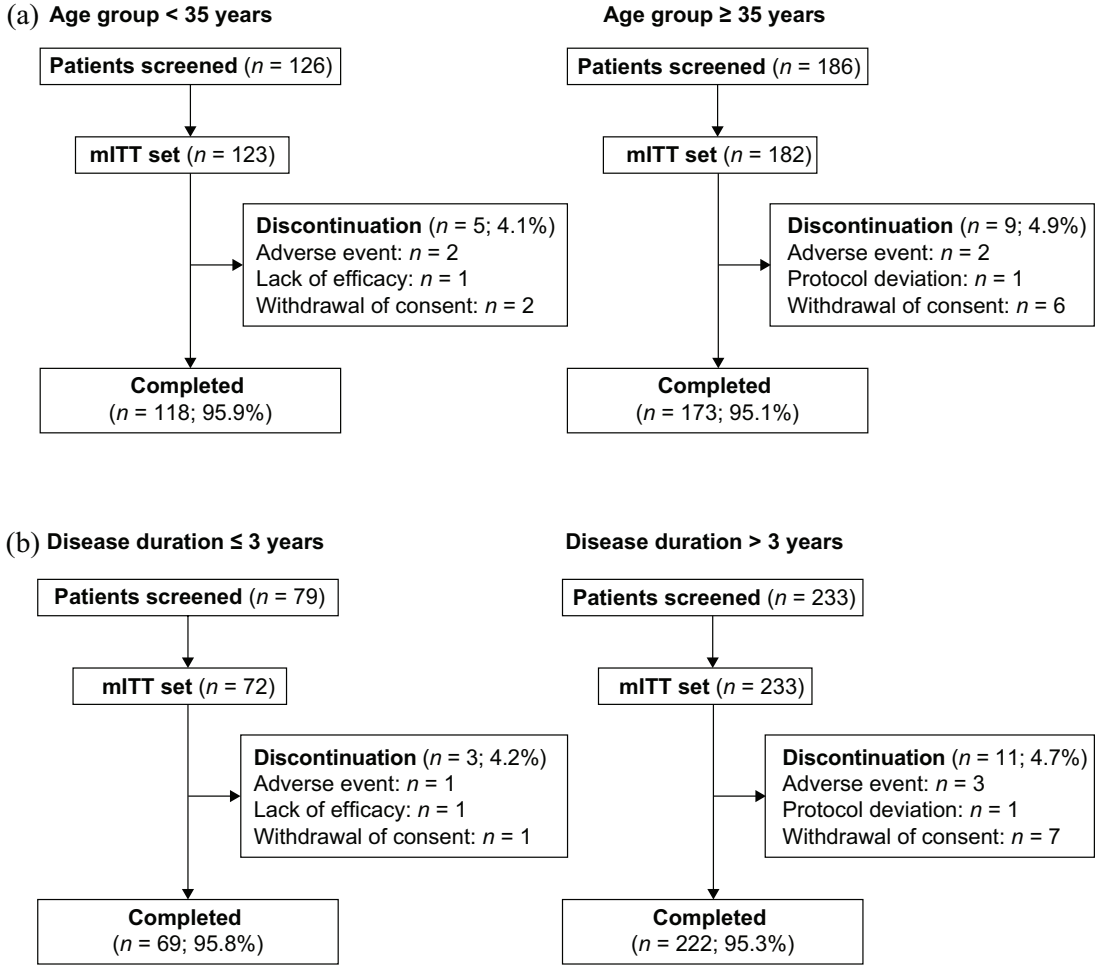

Figure 1. Patient disposition (mITT analysis set) when analysed by (a) age; and (b) disease duration.
mITT, modified intention-to-treat.

period, and had at least one post-baseline efficacy or safety assessment, respectively.[22]

Exploratory *post hoc* subgroup analyses assessed the impact of patient age and disease duration on efficacy and safety endpoints. Endpoint analysis using the LOCF method was performed in addition to observed-case analysis. Efficacy (including 95% CIs) and safety results were analysed descriptively.

Results

Patients

In total, 305 patients were included in the subgroup analysis: 123 in the younger (<35 years) group and 182 in the older (≥35 years) group. Study completion rates were high in both age groups (younger: 95.9%; older: 95.1%) (Figure 1). There were 72 patients in the ≤3 years disease duration and 233 in the >3 years group. The mean (standard deviation; SD) disease duration in each group was 1.7 (1.1) years and 11.6 (6.8) years, respectively.

Baseline demographics and clinical characteristics

The mean (SD) age of the younger group was 28.5 (3.8) years *versus* 41.9 (4.9) years in the older group. There was a higher proportion of males in the younger group (75.6% *versus* 58.8%). As expected, disease duration was lower in the younger group: mean (SD) time from schizophrenia diagnosis to baseline visit in the two groups was 5.4 (4.2) years *versus* 11.9 (7.8) years (Table 1). The overall frequency of comorbidities at baseline was lower in the younger age group: 27.6% *versus* 36.3%.

Table 1. Demographic and baseline clinical characteristics (mITT analysis set).

Patient demographics/disease characteristics	Patient age group		Disease duration group	
	<35 years (*n* = 123)	⩾35 years (*n* = 182)	⩽3 years (*n* = 72)	>3 years (*n* = 233)
Age, years	28.5 (3.8)	41.9 (4.9)	31.7 (7.4)	37.9 (7.6)
Sex, male, *n* (%)	73 (75.6)	107 (58.8)	49 (68.1)	151 (64.8)
BMI (kg/m^2)	26.7 (5.5)	27.9 (4.9)	26.4 (5.3)	27.8 (5.1)
Therapy prior to PP1M switch, *n* (%)				
Risperidone	55 (45.8)	94 (55)	35 (49.3)	114 (51.8)
Paliperidone	27 (22.5)	36 (21.1)	19 (26.8)	44 (20)
Age at first onset of psychotic symptoms	21.3 (4.5)	27.4 (7.1)	26.2 (5.4)	24.5 (6.8)
Years since schizophrenia diagnosis*	5.4 (4.2)	11.9 (7.8)	1.7 (1.1)	11.6 (6.8)
Years since first antipsychotic use*	6.1 (4.4)	13.1 (7.3)	3.6 (3.5)	12.3 (6.8)
Patient previously hospitalized for psychiatric reasons, *n* (%)	103 (83.7)	152 (84.0)	56 (78.9)	199 (85.4)
Total number of psychiatric hospitalizations*	2.5 (2.4)	3.8 (4.5)	1.9 (1.6)	3.6 (4.1)
Years since first hospitalization*	5.3 (4.2)	11.4 (7.9)	2.8 (3.0)	10.7 (7.2)
Suicide attempts since diagnosis*, *n* (%)	9.0 (7.3)	14 (7.7)	2 (2.8)	21 (9)

Values are mean (standard deviation) unless otherwise stated.
*To baseline visit.
BMI, body mass index; mITT, modified intention-to-treat; PP1M, paliperidone palmitate 1-month.

Baseline demographics and clinical characteristics for the two disease duration groups are presented in Table 1. When comparing age groups, the rate of prior hospitalization and suicide attempts are similar, but there were fewer suicide attempts in those with a shorter than a longer duration of disease (2.8% *versus* 9.0%).

PP3M exposure and dose

The mean duration of PP3M exposure, mean dose of PP3M and distribution of PP3M dose categories were similar in the two age (Table 2) and the two disease duration groups. The proportion of patients who required dose modification was low overall: 12.2% (⩾1 dose decrease/increase: 7.3%/4.9%) *versus* 6.0% (⩾1 dose decrease/increase 3.3%/2.7%), in younger *versus* older patients, respectively. Similarly, in shorter *versus* longer disease duration, respectively: 18.0% (⩾1 dose decrease/increase: 11.1%/6.9%) *versus* 5.6% (⩾1 dose decrease/increase 3.0%/2.6%).

Concomitant medication

The proportions of patients requiring concomitant medication at baseline and during PP3M treatment were similar in the two age groups. At baseline, 43.1% of younger *versus* 42.3% of older patients required ongoing psychotropic medication. After starting PP3M, 31.7% *versus* 29.1% of younger compared with older patients initiated treatment with a new psychotropic medication. At baseline, over one-third (36.1%) of shorter disease duration patients continued to use at least one psychotropic medication that was initiated prior to the start of treatment with PP3M, while 37.5% of shorter disease duration patients initiated treatment with a new psychotropic medication after starting PP3M.

For those with disease duration of >3 years, 44.6% continued to use at least one psychotropic medication initiated prior to starting PP3M and 27.9% initiated treatment with a new psychotropic medication after starting PP3M.

Table 2. PP3M exposure and dosing (mITT analysis set).

Parameter	Patient group			
	<35 years (*n* = 123)	⩾35 years (*n* = 182)	Disease duration ⩽3 years (*n* = 72)	Disease duration >3 years (*n* = 233)
Completed follow-up, *n* (%)	118 (95.9)	173 (95.1)	69 (95.8)	223 (95.7)
Exposure duration, days	262.8 (42.2)	263.1 (42.8)	264.0 (47.0)	262.6 (41.1)
Follow-up duration, days	352.4 (56.9)	352.8 (49.1)	352.7 (64.7)	352.6 (48.0)
Average dose during follow-up, mg eq.	364.6 (111.6)	363.2 (119.2)	360.0 (113.7)	365.0 (116.9)
Distribution of dose categories, *n* (%)				
First dose – Day 1				
175 mg eq.	9 (7.3)	19 (10.4)	6 (8.3)	22 (9.4)
263 mg eq.	29 (23.6)	44 (24.2)	18 (25.0)	55 (23.6)
350 mg eq.	52 (42.3)	64 (35.2)	29 (40.3)	87 (37.3)
525 mg eq.	33 (26.8)	55 (30.2)	19 (26.4)	69 (29.6)
Last dose				
175 mg eq.	12 (9.8)	20 (11.0)	9 (12.5)	23 (9.9)
263 mg eq.	30 (24.4)	45 (24.7)	19 (26.4)	56 (24.0)
350 mg eq.	46 (37.4)	61 (33.5)	23 (31.9)	84 (36.1)
525 mg eq.	35 (28.5)	56 (30.8)	21 (29.2)	70 (30.0)

Values are mean (standard deviation) unless otherwise stated.
Time between the first and last PP3M administration.
eq., equivalent; mITT, modified intention-to-treat; PP3M, paliperidone palmitate 3-monthly.

Primary efficacy endpoint

At LOCF endpoint, 60.7% (95% CI: 51.4%, 69.4%) of younger patients and 54.1% of older patients (95% CI: 46.6%, 61.6%) achieved symptomatic remission (Figure 2a).

When analysed by shorter or longer disease duration, similar proportions (95% CI) of patients achieved symptomatic remission at LOCF endpoint: 57.8% (45.4%, 69.4%) *versus* 56.5% (49.8%, 62.9%), respectively (Figure 2b).

Secondary efficacy endpoints

The Kaplan–Meier estimate of median (95% CI) time to symptomatic remission was numerically, though non-significantly shorter for younger patients, 189 (184, 262) days *versus* 273 (191, 364) days with overlapping CIs. There was a similar non-significant trend by disease duration. The median (95% CI) time to symptomatic remission was 190.5 (185.0, 274.0) days for those with shorter disease duration compared with 268.0 (189.0, 342.0) days for those with longer disease duration. The proportion of patients achieving symptomatic remission from Month 6 to 12 increased in both groups (Figure 2).

PANSS total and subscales. At baseline, mean (95% CI) PANSS total scores were similar: 51.2 (49.1, 53.2) *versus* 53.3 (51.8, 54.7), indicating mild/moderate disease severity in both age groups. At LOCF endpoint, mean (95% CI) PANSS total score was 49.0 (46.8, 51.2) in the younger and 49.7 (47.8, 51.5) in the older group, equating to a mean (95% CI) change from baseline to LOCF endpoint of −2.2 (−3.7, −0.8) *versus* −3.6 (−5.1, −2.2) (Figure 3a). Improvements from baseline to LOCF endpoint were observed in all three PANSS subscales (positive, negative, general) for both age groups (Table 3).

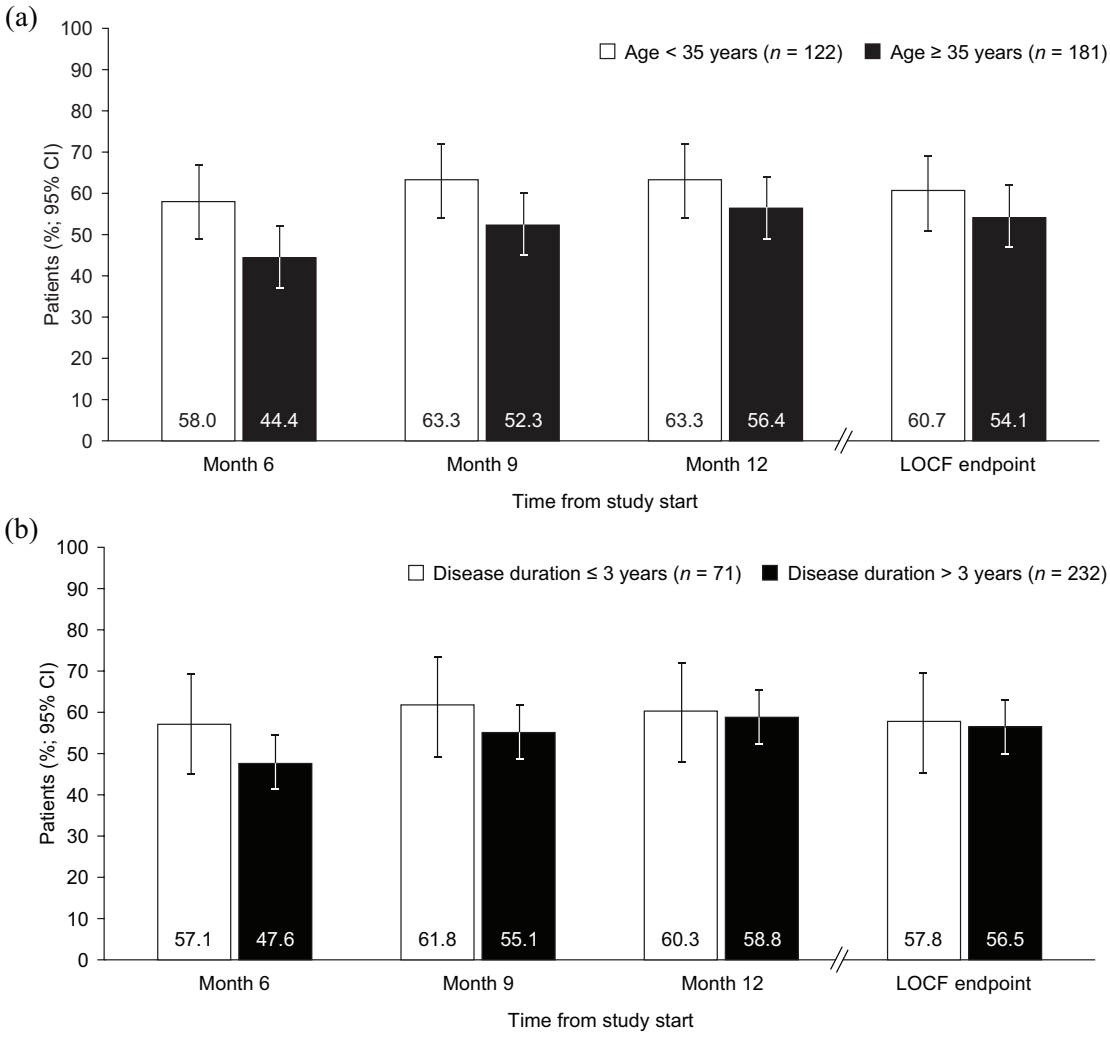

Figure 2. Symptomatic remission during follow-up and at LOCF endpoint (mITT efficacy set) by (a) patient age; and (b) disease duration.
CI, confidence interval; LOCF, last observation carried forward; mITT, modified intention-to-treat.

Mean (95% CI) PANSS total scores were similar in patients with disease duration of ⩽3 years [52.5 (49.9, 55.1)] and of >3 years [52.4 (51.1, 53.8)] at baseline, and indicated mild/moderate disease severity. Mean (95% CI) PANSS total score change from baseline to LOCF endpoint was −2.8 (−4.9, −0.7) and −3.2 (−4.3, −2.0) for the ⩽3 year and >3 year groups, respectively (Figure 3b).

Clinical Global Impression. Mean (95% CI) CGI-S scores at baseline and LOCF were similar in both age groups. The proportion of patients with CGI-C scores indicating improvements at LOCF endpoint were slightly higher in the younger group: 70.4% *versus* 66.1% (Figure 4a). A similar pattern was seen when analysed by duration of disease. Change from baseline to LOCF endpoint (95% CI) was −2.8 (−4.9, −0.7) and −3.2 (−4.3, −2.0) for the shorter and longer disease duration groups, respectively (Figure 4b).

Personal and Social Performance. There was a trend suggesting that more patients in the younger age group achieved functional remission, PSP score 71–100 (95% CI) both at baseline [43.7% (34.6, 53.1) *versus* 34.9% (27.8, 42.4)] and LOCF endpoint [45.4% (36.2, 54.8) *versus* 36.0% (28.9, 43.6)], but as the confidence intervals overlapped the difference was not statistically significant (Figure 5a). There was a 10.5% increase in the proportion of patients achieving functional remission from baseline to LOCF endpoint in the shorter disease duration group (37.3% to 47.8%); those

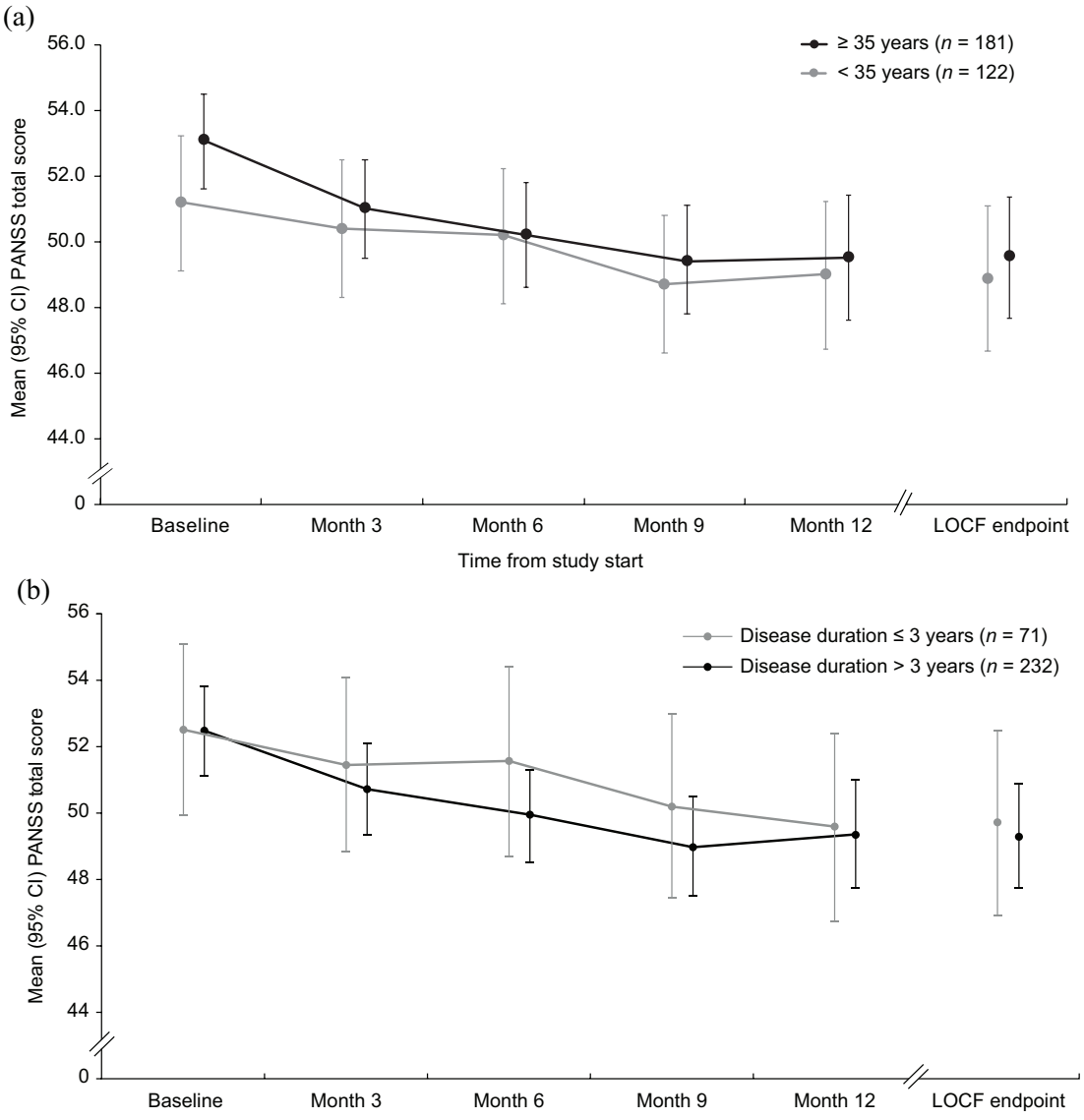

Figure 3. Mean PANSS total score: from baseline to LOCF endpoint (mITT efficacy set) by (a) patient age; and (b) disease duration.
CI, confidence interval; LOCF, last observation carried forward; mITT, modified intention-to-treat; PANSS, Positive and Negative Syndrome Scale.

achieving functional remission remained similar between baseline and LOCF endpoint in the longer disease duration group (38.8% to 37.4%) (Figure 5b). Moreover, 35.9% (95% CI: 27.2, 45.3) of younger patients and 29.1% (95% CI: 22.4, 36.5) of older patients achieved the composite endpoint of symptomatic and functional remission at LOCF endpoint (Figure 6a) with a similar pattern seen when analysed by disease duration (Figure 6b).

Satisfaction with medication. Patient satisfaction with medication was high in both age groups at baseline and LOCF endpoint. The proportion of younger/older patients who were very or extremely satisfied was 57.5%/61.1% at baseline and 63.4%/60.4% at LOCF endpoint, respectively. The proportion of physicians reporting that they were very or extremely satisfied with the medication given to younger/older patients was 64.7%/69.0% at baseline and 78.2%/73.6% at LOCF endpoint, respectively.

The proportion of recently diagnosed/chronic patients who were very or extremely satisfied was 58.6%/60.0% at baseline and 60.0%/62.1% at LOCF endpoint, respectively. The proportions of

Table 3. PANSS subscale scores: change from baseline to LOCF endpoint (mITT efficacy set).

	PANSS positive subscale	PANSS negative subscale	PANSS general subscale
Patient age group			
<35 years (*n* = 122)			
Baseline	10.6 (10.0, 11.2)	15.6 (14.5, 16.6)	25.0 (24.1, 26.0)
LOCF endpoint	10.1 (9.4, 10.8)	14.7 (13.8, 15.6)	24.2 (23.2, 25.2)
Change from baseline	−0.5 (−1.1, 0.1)	−0.9 (−1.5, −0.3)	−0.9 (−1.7, −0.1)
⩾35 years (*n* = 181)			
Baseline	10.8 (10.3, 11.2)	16.6 (15.9, 17.3)	25.9 (25.1, 26.6)
LOCF endpoint	9.8 (9.4, 10.3)	15.3 (14.6, 16.1)	24.5 (23.6, 25.4)
Change from baseline	−0.9 (−1.3, −0.6)	−1.3 (−1.8, −0.7)	−1.4 (−2.3, −0.6)
Disease duration group			
⩽3 years (*n* = 72)			
Baseline	10.2 (9.4, 11.0)	16.6 (15.3, 17.9)	25.7 (24.4, 26.9)
LOCF endpoint	9.4 (8.8, 10.1)	15.6 (14.4, 16.7)	24.7 (23.3, 26.1)
Change from baseline	−0.8 (−1.4, −0.3)	−1.0 (−2.0, −0.1)	−0.9 (−2.1, 0.2)
>3 years (*n* = 232)			
Baseline	10.9 (10.5, 11.3)	16.1 (15.4, 16.7)	25.5 (24.8, 26.2)
LOCF endpoint	10.1 (9.6, 10.6)	14.9 (14.3, 15.6)	24.2 (23.5, 25.0)
Change from baseline	−0.8 (−1.1, −0.4)	−1.1 (−1.6, −0.7)	−1.3 (−2.0, −0.6)

Data are mean (95% CI). Only patients with baseline and ⩾1 post-baseline assessments were included in the analysis.
CI, confidence interval; LOCF, last observation carried forward; mITT, modified intention-to-treat; PANSS, Positive and Negative Syndrome Scale.

physicians who reported being very or extremely satisfied with the medication given to recently diagnosed/chronic patients was 65.6%/67.7% at baseline and 71.6%/76.6% at LOCF endpoint, respectively.

Carer burden. The overall carer burden, as assessed by mean (95% CI) Involvement Evaluation Questionnaire (IEQ) total score, decreased from 22.0 (19.7, 24.4) at baseline to 19.5 (17.2, 21.8) at LOCF endpoint in younger patients and from 25.1 (22.1, 28.1) to 20.0 (17.5, 22.5) in older patients, equating to changes from baseline of −2.6 (−4.9, −0.2) and −5.1 (−8.0, −2.3), respectively. There were similar reductions in the IEQ total score in patients with both shorter and longer duration of disease.

Healthcare resource utilization. The proportion of patients requiring hospitalization for psychiatric reasons in the younger group was 16.4% in the 12 months prior to baseline and 4.9% during the PP3M treatment period. Corresponding rates in the older group were 9.4% and 1.1%, respectively (Figure 7a). Mean (SD) total number of days spent in hospital for psychiatric reasons were 33.6 (22.9) in the 12 months prior to baseline and 13.8 (10.3) during the PP3M treatment period in younger patients, and 32.7 (22.6) and 16.1 (11.7) in older patients, respectively. When analysed by duration of disease, the proportion of patients requiring hospitalization for psychiatric reasons in the shorter disease duration group was 23.9% in the 12 months before PP3M initiation and 4.2% during PP3M treatment. In the more

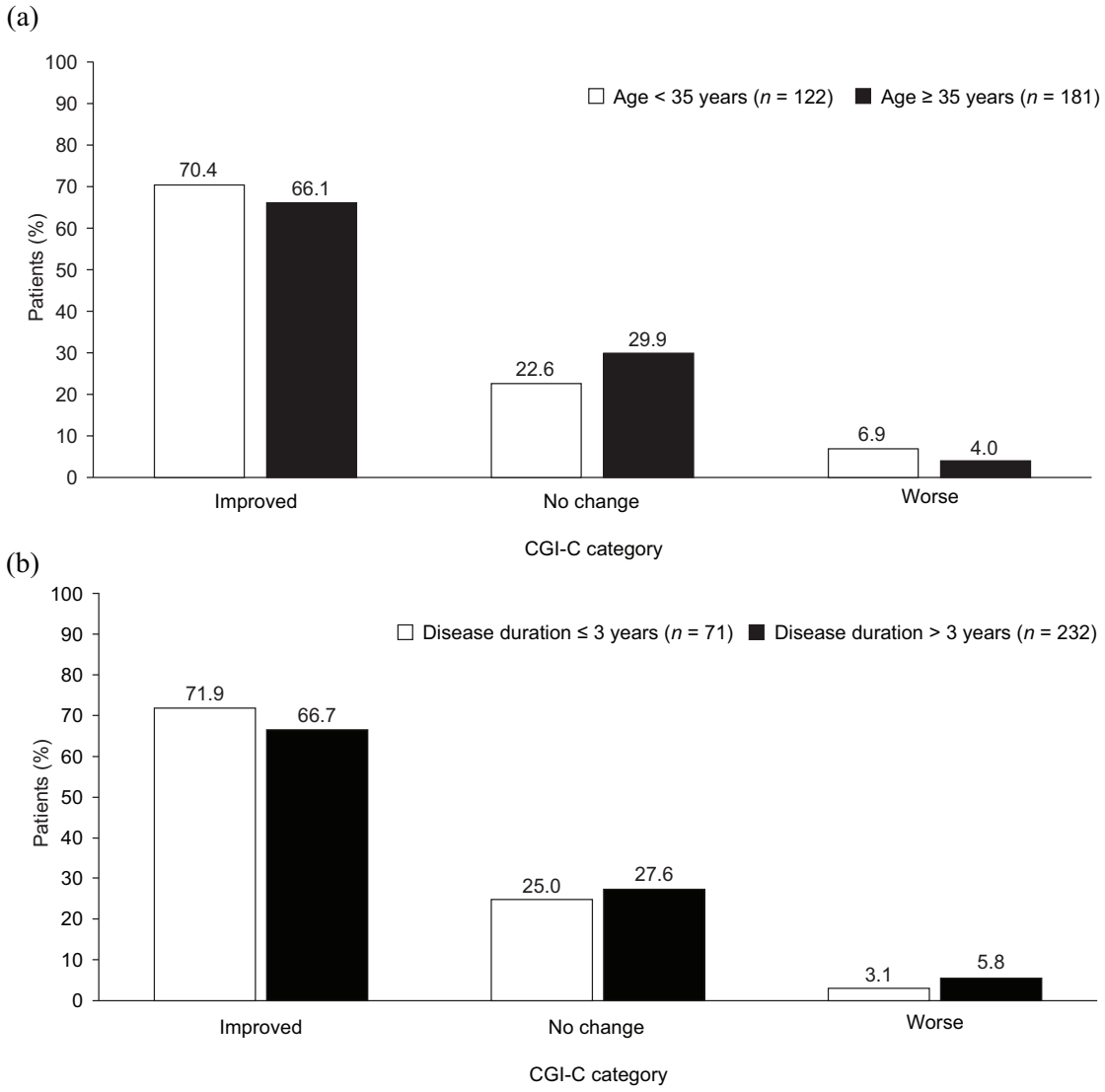

Figure 4. CGI-C: frequency distribution score categories at LOCF endpoint (mITT efficacy set) by (a) patient age; and (b) disease duration.
'Improved' is a composite of the categories 'very much improved', 'much improved' and 'minimally improved'.
CGI-C, Clinical Global Impression-Change; LOCF, last observation carried forward; mITT, modified intention-to-treat.

chronic group, the proportions were 8.6% and 2.2%, respectively (Figure 7b).

Relationship between disease duration and patient age. To investigate the influence of patient age, the disease duration groups were stratified according to age (<35 years and ⩾35 years). As expected, psychiatric history was most extensive in older patients with chronic disease (duration >3 years, age ⩾35 years).

Selected efficacy endpoints for this analysis are presented in Supplemental Table 1. Symptomatic remission rates at LOCF endpoint improved by a comparable amount across all four groups. Generally, patients in the older group and those with more chronic disease tended to achieve lower effectiveness responses among the four groups.

Safety

Overall, the safety data were similar in the two age groups and in those with disease of shorter and longer disease duration, with a possible indication of more frequent adverse effects in those with a shorter disease duration compared with a

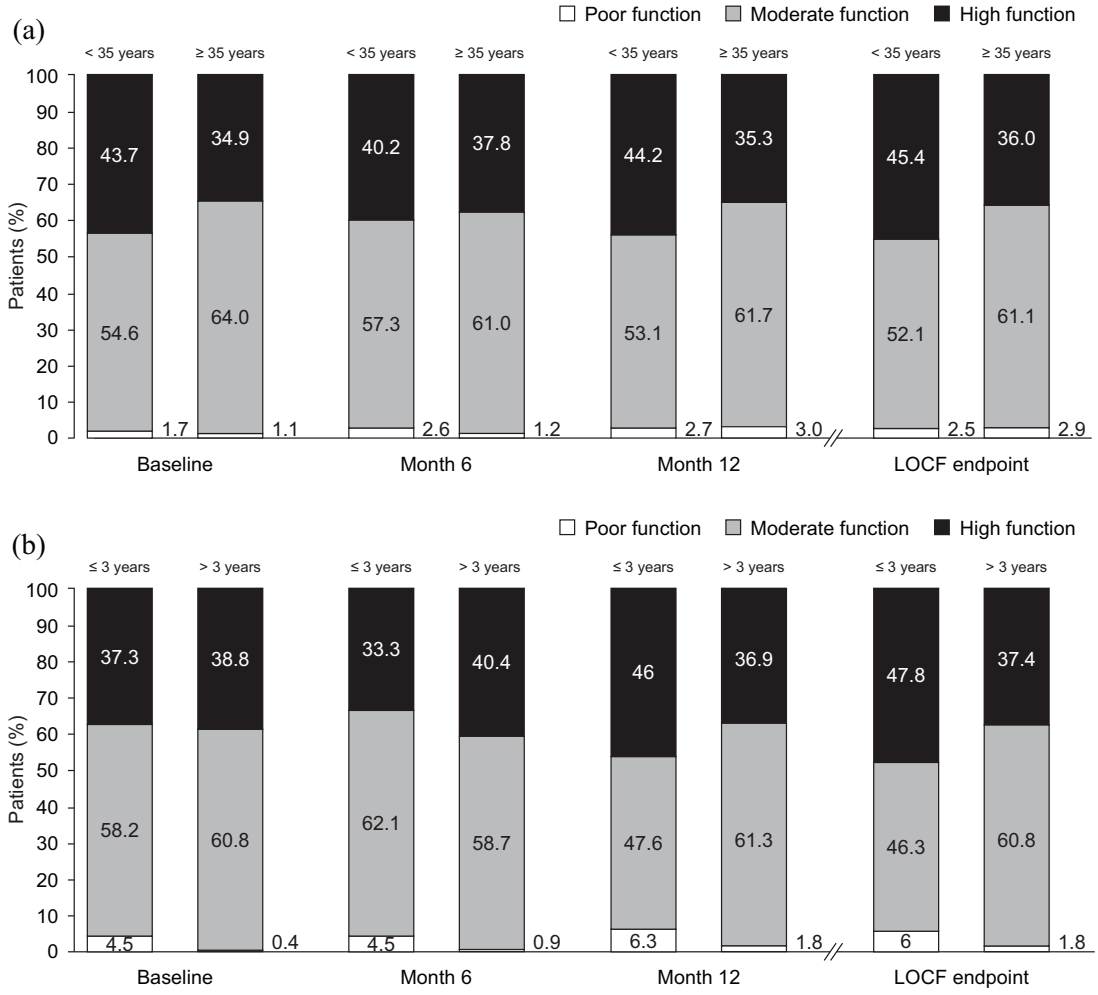

Figure 5. PSP frequency distribution score categories* from baseline to LOCF endpoint (mITT efficacy set) by (a) patient age; and (b) disease duration.
*PSP score: 1–30, poor function; 31–70, moderate function; 71–100, high function.
LOCF, last observation carried forward; mITT, modified intention-to-treat; PSP, Personal and Social Performance.

longer duration (Table 4). The proportions of younger *versus* older patients reporting at least one treatment-emergent adverse event (TEAE) was 53.3% *versus* 53.0%, and at least one serious TEAE was 6.6% *versus* 5.5%. The proportions of patients in the ⩽3 years duration and >3 years duration groups reported to have at least one TEAE were 60.6% and 50.9%, respectively, while the proportion with at least one serious TEAE was 7.0% *versus* 5.6%, respectively. The number of patients with at least one TEAE leading to study discontinuation was low and similar in the ⩽3 years duration (1.4%) and >3 years duration (1.3%) groups.

The proportion of TEAEs leading to study discontinuation was low and similar in both age groups (1.6% *versus* 1.1%). The number of TEAEs leading to treatment/study withdrawal was also low in the two disease duration groups: 1.4% compared with 1.3% in those with disease duration of ⩽3 years and >3 years respectively.

There was a slightly higher proportion of younger patients with possible/probable/very likely drug-related TEAEs (32.8% *versus* 28.2%). The proportion of patients with possible, probable or very likely drug-related TEAEs was also higher (38.0%) in the ⩽3 years disease duration group than in those with disease >3 years duration (27.6%).

The most common drug-related TEAEs were injection site pain (6.6% *versus* 5.5% in younger

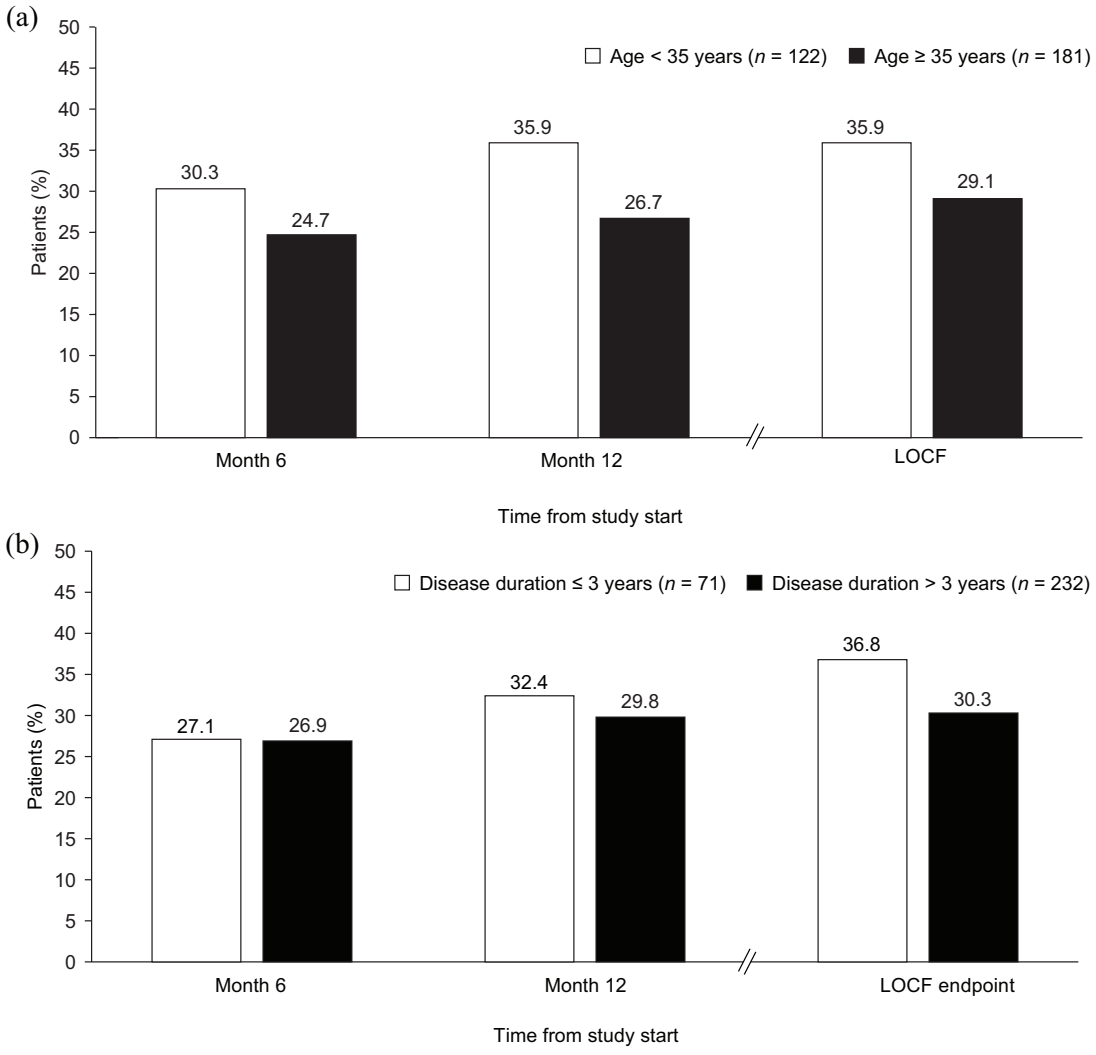

Figure 6. Composite symptomatic and functional remission* during follow-up and at LOCF endpoint (mITT efficacy set)† by (a) patient age; and (b) disease duration.
*A composite endpoint consisting of symptomatic remission and functional remission (Personal and Social Performance total score >70).
†Month 9 data are not available, PSP assessments were performed at Month 6 and 12 only.
LOCF, last observation carried forward; mITT, modified intention-to-treat.

versus older, and 5.6% and 6.0% in shorter disease duration *versus* longer duration patients); increased weight (6.6% *versus* 7.2% in younger versus older patients and 11.3% *versus* 7.8% in shorter disease duration versus longer duration patients) and prolactin-related TEAEs (4.9% *versus* 4.4% in the younger and older age groups, and 8.5% versus 3.4% in shorter disease duration and longer duration patients respectively). Mean (95% CI) Extrapyramidal Symptom Rating Scale (ESRS) scores at baseline were low for both age groups and both disease duration groups and change from baseline to LOCF endpoint in ESRS scores were also similar (Supplementary Figure S2).

Discussion

This *post hoc* subgroup analysis of the REMISSIO study assessed the impact of patient age (<35 years and ⩾35 years) and disease duration (⩽3 years and >3 years) on efficacy and safety outcomes in patients with stable schizophrenia who were switched from PP1M to PP3M in a naturalistic clinical setting.[22] Effective treatment of schizophrenia at an early age and/or with shorter disease duration may be critical for positive long-term prognosis,[24] and the findings presented here suggest that patients with schizophrenia may benefit from PP3M treatment in general with some additional potential improvements if started earlier in the disease course.

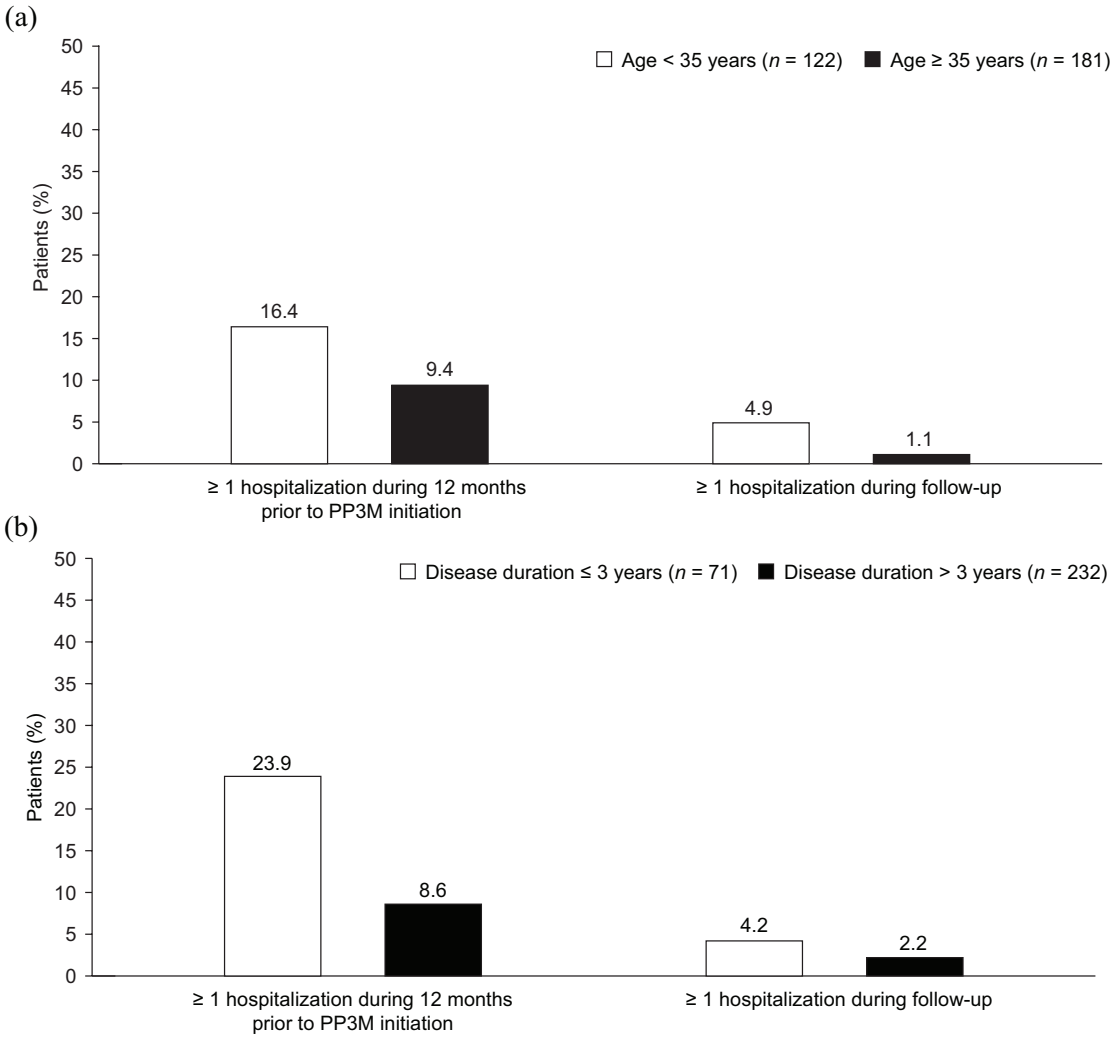

Figure 7. Hospitalizations for psychiatric reasons: prior to PP3M initiation and during follow-up (mITT efficacy set) by (a) patient age; and (b) disease duration.
mITT, modified intention-to-treat; PP3M, paliperidone palmitate 3-monthly.

The early phase of psychosis is a critical window for treatment – the aggressive nature of schizophrenia, the intensity of symptoms and functional deterioration occur in the first years after diagnosis.[25,26] Earlier LAT use is associated with favourable clinical outcomes, and LATs are increasingly recognized as an earlier treatment option for younger adult patients.[13,27]

Several factors determined the age cut-off point of 35 years. Firstly, various psychosis early-intervention programmes set the upper limit of age entry as 35 years.[24,28] Secondly, studies often define the upper age limit for younger patients at 35–40 years.[29–31] Lastly, results of a recent multinational incidence study reported that most patients – 68% of men and 51% of women – present to mental health services before 35 years of age.[32]

The duration cut-off at 3 years is based on the 'critical period hypothesis'. This suggests that the psychosocial function of patients with schizophreniform illnesses declines within the first 3 years after onset and then tends to level out. The authors suggested that intensive treatment, including antipsychotic medication, in the first 3 years of illness could improve long-term outcomes.[25,26]

Achieving and maintaining symptomatic remission is an important treatment goal associated with significant functioning and quality of life, and may reduce healthcare resource utilization.[33,34] Despite such

Table 4. Summary of TEAEs (mITT safety set).

Characteristic, *n* (%)	Patient age group		Disease duration group	
	<35 years (*n* = 122)	⩾35 years (*n* = 181)	⩽3 years (*n* = 71)	>3 years (*n* = 232)
Patients with ⩾1 TEAE	65 (53.3)	96 (53.0)	43 (60.6)	118 (50.9)
Serious TEAEs	8 (6.6)	10 (5.5)	5 (7.0)	13 (5.6)
Treatment-related (possible, probable or very likely) TEAEs	40 (32.8)	51 (28.2)	27 (38)	64 (27.6)
TEAEs leading to treatment/study withdrawal	2 (1.6)	2 (1.1)	1 (1.4)	3 (1.3)
Treatment-related AEs experienced by ⩾5% of patients in either group				
Injection site pain	8 (6.6)	10 (5.5)	4 (5.6)	14 (6.0)
Weight increased	8 (6.6)	13 (7.2)	8 (11.3)	18 (7.8)
Akathisia	6 (4.9)	5 (2.8)	5 (7.0)	6 (2.6)
Schizophrenia	7 (5.7)	3 (1.7)	5 (7.0)	5 (2.2)
Potentially prolactin-related TEAEs*	6 (4.9)	8 (4.4)	6 (8.5)	8 (3.4)
Amenorrhoea/menstruation irregular	4 (3.3)	4 (2.3)	5 (7.0)	3 (1.3)
Sexual/erectile dysfunction	1 (0.8)	2 (1.1)	0	3 (1.3)
Hyperprolactinaemia/blood prolactin increased	3 (2.5)	5 (2.8)	5 (7.0)	3 (1.3)

*Events occurring >1% in either group shown.
AE, adverse event; mITT, modified intention-to-treat; TEAE, treatment-emergent adverse event.

improvements, patients may not attain the same level of functioning that they had before the episode/relapse, and symptom remission should be considered 'a necessary, but not sufficient step towards recovery'.[23]

The most important finding in this *post hoc* analysis is that treatment with PP3M for 1 year was associated with the achievement of symptomatic remission (score of ⩽3 for the eight core PANSS items, maintained for ⩾6 months)[23] in most patients in both age groups throughout follow-up [60.7% of younger and 54.1% of older patients (LOCF endpoint)]. In an open-label study of young patients (aged 16–43 years) with newly diagnosed schizophreniform disorder or schizophrenia receiving LATs, symptomatic remission was achieved by 64% of patients,[35] a figure similar to that reported for the younger group of patients in the current analysis.

Patient age is, of course, correlated with disease duration, and in the current analysis, mean disease duration in the younger group was less than half that of the older group. It is possible that disease duration rather than age *per se* was the important determining factor in achieving symptomatic remission. Thus, the primary endpoint was also analysed according to disease duration (⩽3 years *versus* >3 years; mean duration, 1.7 *versus* 11.6 years). We found that symptomatic remission rates were similar in the two disease duration groups. These results are consistent with a *post hoc* analysis of long-acting risperidone treatment (Dubois *et al.*), which reported comparable symptomatic remission rates in disease duration groups of ⩽3 years and >3 years.[36] However, in another *post hoc* analysis of a non-inferiority study of PP1M and PP3M treatment in patients with schizophrenia (Brown *et al.*),[37] symptomatic remission was maintained for ⩾12 months more in patients with a shorter disease duration (⩽5 years, 42.4%) than in those with a longer disease duration (>10 years, 33.1%).[37] The discordance may be due to the substantially higher discontinuation rate in the Brown study (26% *versus* <5%). The relatively small size of the recent onset group ($n = 72$) may also have reduced the statistical power to detect a difference.

As a complement to symptomatic remission, functional remission is a valuable goal for patients with schizophrenia. It is associated with real-world outcomes, such as ability to work and live independently.[38–41] The functional remission data in this analysis indicated that younger patients had higher baseline functioning, and this was maintained to LOCF endpoint. This is supportive evidence for use of LATs in younger patients in early disease, and is consistent with a retrospective review of medical records of adult patients with newly diagnosed schizophrenia which found improvements in functional remission in young patients (mean age: 24.1 years) receiving treatment with PP1M for ⩾12 months in a naturalistic clinical setting.[41]

In the present analysis, somewhat higher proportions of younger than older patients and shorter than longer disease duration achieved both symptomatic and functional remission (although CIs overlapped, indicating a non-significant trend). This is in line with an observational study of a cohort of young patients with schizophrenia (<35 years) treated with LATs, which found that clinical remission correlated strongly with functional remission. The authors proposed that clinical remission 'facilitated' functional remission, particularly during the early phase of the illness.[42]

PANSS total and subscale scores indicated a reduction in disease severity during the 1-year follow-up period in both age groups. Improvements were seen in both negative symptoms and other non-psychotic symptoms. The improvement in disease severity indicated by PANSS scores was corroborated by the high proportion of patients with CGI-C improvements in both age groups. Various studies have demonstrated improvements in PANSS in patients with early schizophrenia treated with LATs.[13] For example, in an open-label trial of 382 patients who had been diagnosed with schizophrenia for a mean of 1.5 years and who had received a LAT for 6 months, significant ($p \leqslant 0.0001$) improvements were seen in PANSS total and all its subscale scores.[43] Also, in a 6-month, naturalistic, non-interventional study, 242 patients initially treated with an oral antipsychotic were then treated with the LAT formulation. While improvements in CGI-S were noted in all patients, significantly higher differences were noted in the younger (⩽35 years) compared with the older (>35 years) patients.[44]

The rates and number of days of hospitalizations for psychiatric reasons decreased during the year after PP3M initiation in both age groups. This is consistent with both the primary REMISSIO study and other studies that have demonstrated a reduction in rehospitalization rates for patients treated with LATs.[19,22,45] For example, an electronic healthcare database study involving veterans with schizophrenia who were transitioned from PP1M to PP3M demonstrated a significant reduction in mean total healthcare costs (from $27,745 to $23,772).[46] A cost-effectiveness analysis in the Netherlands reported that PP3M performed better than PP1M, risperidone LAT, haloperidol LAT and oral olanzapine in relation to hospitalization rates (0.11, 0.46, 0.40, 0.56 and 0.57, respectively).[45] A separate analysis in Spain found patients treated with PP3M to have a lower hospitalization rate than those treated with PP1M (0.034 and 0.065, respectively).[47]

As in the primary study,[22] patient and physician satisfaction with PP3M therapy was high, in line with the high study completion rates (>95% in both age groups). Mean PP3M dose and duration of exposure were similar for both age groups. Overall low frequency of dose changes (which were permitted after first PP3M administration) during the study confirms the real-world pragmatic applicability of the dose-switching regimen in the prescribing information.[16,17] Frequency of dose adjustments, albeit low, was about twice that in the younger (12.2%) than the older age group (6.0%). While this could suggest that a proportion of younger patients – possibly those with the lowest duration of disease – may not have been adequately stabilized on PP1M prior to switching to PP3M, there are several other reasons why such dose adjustments may have occurred. For example, high levels of patient functioning, weight gain and problematic alcohol use have been shown to be predictors of dose modification or discontinuation in patients with schizophrenia.[35] Ringen *et al.* found that a statistically significant reduction in antipsychotic dosages over the first 12 months of treatment was associated with early medication-related weight increase in first-episode schizophrenia. Of note, in this analysis a slightly higher proportion of younger than older patients experienced weight increase (10.7% and 7.2%) while in the current study the difference was limited (6.6% *versus* 7.2%).[48]

PP3M generally exhibited a favourable safety profile and was well tolerated in both age and duration groups. The proportion of patients with possible/probable or very likely drug-related TEAEs was slightly higher in the younger *versus* the older group and was also higher in the shorter versus longer duration group. The number of patients with at least one TEAE leading to study

discontinuation was low and similar across all subgroups (1.1–1.6%). There was a low incidence of potentially prolactin-related TEAEs in both age and both duration groups, and extrapyramidal symptoms, as indicated by ESRS scores, were generally low at baseline. Observed improvements in ESRS scores were greater for younger than older patients and for those with a shorter rather than a longer disease duration. The safety findings, including the low incidence of extrapyramidal symptoms and prolactin-related TEAEs, were in line with the safety results reported in the two previous RCTs involving PP3M.[19,20]

The primary limitations of this analysis are those inherent to *post hoc* subgroup analyses. In brief, the primary REMISSIO study was not designed to evaluate outcomes according to age and/or disease duration, therefore, the results of such an analysis are subject to bias and could have occurred by chance. Furthermore, REMISSIO was an open-label analysis, patients were not randomized and there was no control group, so no conclusion on comparative treatment can be drawn. Thus, the current analysis should be viewed as exploratory or hypothesis-generating and may provide further insights into the potential benefits of PP3M in younger patients, earlier in the disease course. The potential gender differences have not been explored and are targets of further analyses.

Conclusion

The results from this exploratory *post hoc* analysis support switching from PP1M to PP3M treatment in both younger (<35 years) and older (≥35 years) patients with schizophrenia, regardless of disease duration. While improvements in disease severity and symptom control were noted in both younger and older patients, PP3M treatment may be of greater benefit in younger patients with a shorter disease duration. Overall the data are consistent with previous studies, suggesting that SG-LAT use is associated with better clinical outcomes, particularly in younger patients with a shorter disease duration. The safety and tolerability profiles after 52 weeks of PP3M treatment were favourable and comparable in the two age groups. Further long-term studies examining the impact of patient age and disease duration on the efficacy and safety of PP3M in schizophrenia are warranted.

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Conflict of interest statement

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ORCID iDs

Katalin Pungor https://orcid.org/0000-0003-4679-2050

Pierre-Michel Llorca https://orcid.org/0000-0001-7438-8990

Data sharing statement

Access to anonymized individual participant-level data will not be provided for this trial as it meets one or more of the exceptions described on https://yoda.yale.edu/ under "Data Use Agreement - Janssen Pharmaceuticals DUA".

Supplemental material

Supplemental material for this article is available online.

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