Janssen Research & Development, LLC

Annex 1: Supportive Data for the Application to Add Paliperidone Palmitate 3-Month Long-Acting Injection for the Treatment of Adults With Schizophrenia to the Essential Medicine List of the World Health Organization

(Paliperidone palmitate)

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[Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

APA	American Psychiatric Association
BMI	body mass index
CGI-S	clinical global impression – severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COVID-19	coronavirus disease 2019
DB	double blind
ER	extended release
FOIA	Freedom of Information Act
GCP	good clinical practice
HRU	healthcare resource utilization
IDMC	independent data monitoring committee
IM	intramuscular
ITT [DB]	intent to treat for double-blind phase
K-M	Kaplan-Meier
LAI	long-acting injectable
LOCF	last observation carried forward
LS	least squares
mITT	modified intent-to-treat
OR	odds ratio
PANSS	positive and negative syndrome scale for schizophrenia
PDC	proportion of days covered
PK	pharmacokinetic
PP	per protocol
PP1M	paliperidone palmitate 1-month injection
PP3M	paliperidone palmitate 3-month injection
PSP	personal and social performance scale
VHA	Veterans Health Administration
WHO	World Health Organization

PROPOSAL AND RATIONALE FOR INCLUSION OF PALIPERIDONE PALMITATE 3-MONTH INJECTABLE

Janssen Research & Development LLC., hereafter referred to as the Company, proposes to include paliperidone palmitate 3-month long-acting injection (PP3M) to the World Health Organization (WHO) model list of essential medicines for the maintenance treatment of schizophrenia in adults. The medicine is to be evaluated for addition on the core list as an individual medicine. The rationale to add paliperidone palmitate 3-month (PP3M) to the WHO Model List of Essential Medicines is summarized below:

- Schizophrenia is a chronic condition characterized by lifelong pharmacological treatment and lapses of medication compliance. It is estimated that two-thirds of schizophrenia patients are partially or fully non-compliant with their antipsychotic medication regimen (Oehl 2000). Poor treatment compliance results in poor outcomes, including increased hospitalizations, increased relapse risk, poorer prognosis, and increased risk of harm to self and others.
- Paliperidone palmitate 1-month injection (PP1M) and paliperidone palmitate 3-month injection (PP3M) are closely related products with similar efficacies. Patients are stabilized for at least 4 months on PP1M before switching to PP3M for greater treatment convenience and compliance.
- Long-acting formulations are designed to achieve continuous drug delivery over extended periods of time. Paliperidone palmitate 3-month injectable is commercially available as a prefilled syringe not requiring refrigeration and provides treatment advantages of longer cycle duration, longer half-life, and greater protection from relapse after sudden discontinuation. Clinical data suggests that PP3M, on average, protects patients from relapse for a median time of 274 days after a single dose.
- Paliperidone palmitate 3-month injectable assists disadvantaged patients such as those who have limited access to psychiatric care, those who cannot coordinate frequent travel, and those who are homeless or from underserved populations. In addition, PPM3 offers less frequent visits to the pharmacy, and fewer injections.
- During the current coronavirus disease (COVID-19) pandemic, PP3M treatment supports implementation of guidances from the World Health Organization and the Inter-Agency Standing Committee on the minimization of face-to-face appointments to reduce the risk of disease transmission. The frequency of face-to-face appointments needed for drug administration is lower than that of other LAI medications.

Proposed PP3M Dosage and Treatment Regimen

The PP3M dosage and treatment regimen is described below, and it is in the line with the information included in the US PI and EU SmPC. A link to the EU SmPC is provided for the reference:

https://www.ema.europa.eu/documents/product-information/trevicta-epar-product-information_en.pdf

Section 5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate pediatric dose forms/strengths (if appropriate):

Paliperidone palmitate 3-month long-acting: prolonged release suspension for injection 175 mg, 263 mg, 350 mg, 525 mg.

Section 7. Treatment details (requirements for diagnosis, treatment and monitoring):

Paliperidone palmitate 3-month long-acting injection *for the maintenance treatment of schizophrenia and related chronic psychoses in adults, with a dose regimen comprised between 175 mg and 525 mg every 3 months (±2 weeks).*

1. INTRODUCTION

1.1. Information on Disease Burden and Available Treatments

Schizophrenia is a chronic, severe, and debilitating form of mental illness, affecting, on average, approximately 0.45% of the worldwide population with a median lifetime prevalence of 4.0 per 1,000 persons (Saha 2005;.Tandon 2008).The high prevalence of schizophrenia is attributed to the fact that it is a lifelong illness that typically has an onset in young adulthood (Hafner 1994). The long-term outcome of schizophrenia varies along a continuum of reasonable recovery to total incapacitation (Rabinowitz 2007). Antipsychotic medications are the cornerstone of treatment for schizophrenia, and effective management of schizophrenia requires long-term treatment to maintain symptom control and prevent relapse (APA 2010; Robinson 1999). Adherence to antipsychotic therapy is essential for the continuous effective drug exposure needed for optimizing therapeutic benefit with respect to preventing or delaying relapse and/or rehospitalization; however, patients with schizophrenia exhibit various levels of medication compliance behavior. Continuation of antipsychotics in patients with first episode schizophrenia has been shown to increase the chance of survival (Tiihonen 2018). Nonadherence to currently available oral antipsychotic drugs among patients with schizophrenia is widespread, with the frequency estimated to be about 50% (Bhanji 2004; Lacro 2002). Partial adherence is even more prevalent, affecting up to 90% of patients with schizophrenia (Leucht 2006; Marder 2003; Weiden 2004). Numerous studies have shown that nonadherence to antipsychotic therapy has a negative impact on the course of schizophrenia, and the link between medication nonadherence (or partial adherence) and relapse, rehospitalization, and attempted suicide is well established (Higashi 2013; Morken 2008). The consequences of nonadherence contribute to the high economic burden associated with schizophrenia (Knapp 2004; Sun 2007). Results from Emsley (2012) suggest that relapse is associated with an increase in treatment resistance. A review of clinical trials investigating relapse of symptoms following effective treatment of first-episode psychosis estimated the risk of relapse within the first year following medication discontinuation to be approximately 77% compared to a 1-year risk of relapse of 3% with continued antipsychotic therapy (Zipursky 2014).

In addition to the economic consequences of nonadherence and relapse, the re-emergence of psychotic and other disease symptoms results in functional, social, and physiological declines. With each successive relapse in schizophrenia, the patient continues to deteriorate, recovery is slower and less complete, and the level of functioning to which the patient returns upon remission from a given episode is progressively lower (Doering 1998; Wiersma 1998).

Improving adherence to antipsychotic medication, therefore, has the potential to reduce psychiatric morbidity and costs of care in the long-term management of schizophrenia. The use of LAI antipsychotics offers the greatest opportunity for facilitating medication adherence (McEvoy 2006). Because LAI antipsychotics are administered by a health care provider, these drugs offer transparency with respect to medication adherence, alerting healthcare professionals to the occurrence of nonadherence, and ensure that patients with chronic psychotic illness receive a known quantity of medication at appropriate dosing intervals. Importantly, the long apparent elimination half-life of these drugs also provides a wider and more clinically convenient window

than that with oral antipsychotics for health care professionals to intervene appropriately before plasma drug levels drop below therapeutic thresholds. A post hoc analysis of a prospective, matched cohort study of outpatients at risk for poor adherence with oral antipsychotics showed that those switched to a LAI antipsychotic remained on medication longer and were less likely to discontinue their medication than those on an oral agent (Brnabic 2011). The benefits of reliable drug delivery with LAI antipsychotics have been shown to translate into improved clinical outcomes among patients with schizophrenia, including a reduced risk of relapse and hospitalization and an improved quality of life (Berra 2013; Kaplan 2013; Lloyd 2010; Offord 2013; Ren 2011), and lower mortality rates (Taipale 2018).

The initial LAI antipsychotics were formulations of conventional or first-generation antipsychotics that had the same limitations as their oral counterparts or were oil-based formulations that were often associated with pain after injection (Bloch 2001; McEvoy 2006). Paliperidone is the major active metabolite of risperidone. The PP1M formulation was developed as an aqueous suspension LAI for once-monthly dosing, aimed at achieving an appropriate duration of exposure of paliperidone in plasma within the therapeutic range. Data with PP1M from over 3,800 subjects in 9 well-designed and adequately controlled Phase 2 and Phase 3 studies, supported by results of a long-term, open-label, multiple-dose Phase 1 safety study, showed that relatively constant plasma paliperidone concentrations over the 1-month dosing interval result in sustained efficacy and good tolerability. Data from a placebo-controlled, long-term, randomized withdrawal study (R092670-PSY-3001, hereafter referred to as PSY-3001) (Hough 2010) indicated that the risk of relapse for subjects receiving placebo was 3.6 times higher than for subjects who remained on PP1M after randomization, and an indirect comparison of data from this study with a similarly designed study for paliperidone extended release (ER) (Kramer 2007) indicated that treatment with PP1M can further delay relapse after randomization to placebo beyond what is observed with oral therapy.

Using the same technology as used for PP1M, Janssen has developed PP3M, a paliperidone palmitate formulation that allows for dosing of an effective and well-tolerated antipsychotic once every 3 months. Options for the maintenance treatment of schizophrenia are currently limited to shorter-acting LAI formulations. The at least 3-fold longer dosing interval for PP3M relative to currently available LAI formulations is expected to confer advantages with respect to adherence to the antipsychotic medication and ease of use.

Additionally, PP3M is supplied in prefilled syringes that do not require reconstitution or refrigeration thus, facilitating transportation, storage and handling in less well-equipped medical settings. These characteristics make PP3M a promising treatment option for patients who prefer less frequent injections as well as those who will benefit from less frequent injections, such as patients with limited access to healthcare, who live in underserved rural or inner-city settings, or who simply cannot coordinate once-monthly transportation for injection visits.

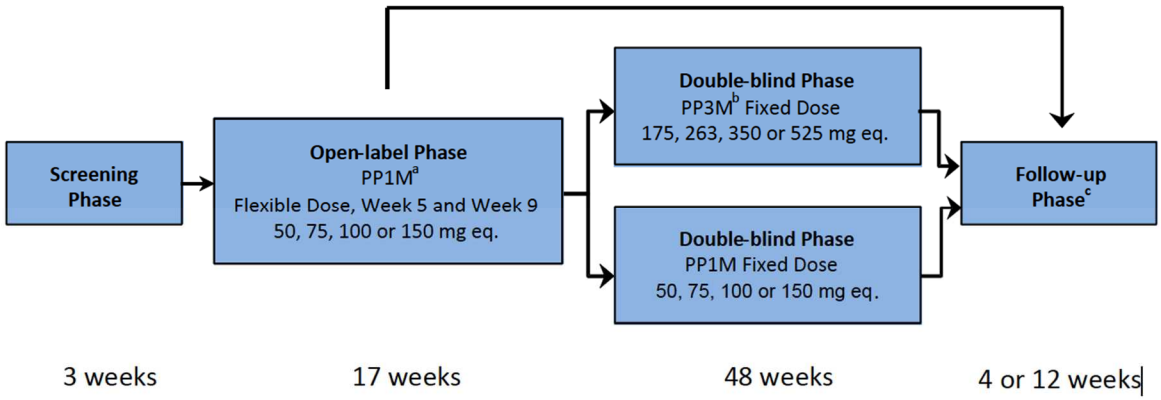
2. CLINICAL DEVELOPMENT PROGRAM

The PP3M formulation has been developed for use in the maintenance treatment of schizophrenia in adults who have shown an adequate therapeutic effect with PP1M and the ability to tolerate this LAI antipsychotic over a period of at least 4 months. PP3M is not intended to be used for the initiation of treatment without prior exposure to PP1M.

Considering the extensive clinical efficacy and safety data available with the PP1M formulation, the Committee for Medicinal Products for Human Use (CHMP) indicated that the demonstration of non-inferiority for PP3M relative to PP1M in Study PSY-3011 was acceptable to form the basis of the efficacy claims for PP3M and to support its marketing authorization. Data from the placebo-controlled, long-term, randomized withdrawal, Phase 3 Study PSY-3012 provides valuable additional support, including assay sensitivity, for the efficacy of PP3M in delaying the time to relapse of symptoms of schizophrenia among adult subjects who had achieved satisfactory symptom control with PP1M.

R092670-PSY-3011 was a randomized, double-blind (DB), parallel group, multicenter study, designed to determine if the efficacy of PP3M was non-inferior to the efficacy of PP1M as maintenance treatment in adults with schizophrenia who had already been treated with PP1M for an acute exacerbation. The study consisted of several phases, as shown in Figure 1. The design of PSY-3011 is consistent with CHMP recommendations for demonstrating the non-inferiority of a new antipsychotic formulation to a currently approved formulation (EMA 2012) and is consistent with scientific advice received by CHMP prior to its initiation.

Figure 1: Design of Phase 3 Non-inferiority Study PSY-3011



[a] PP1M doses: 50, 75, 100, or 150 mg eq.; All subjects were to receive the first PP1M injection of 150 mg eq. (234 mg) on Day 1 and the second injection of 100 mg eq. (156 mg) on Day 8, both in the deltoid muscle.

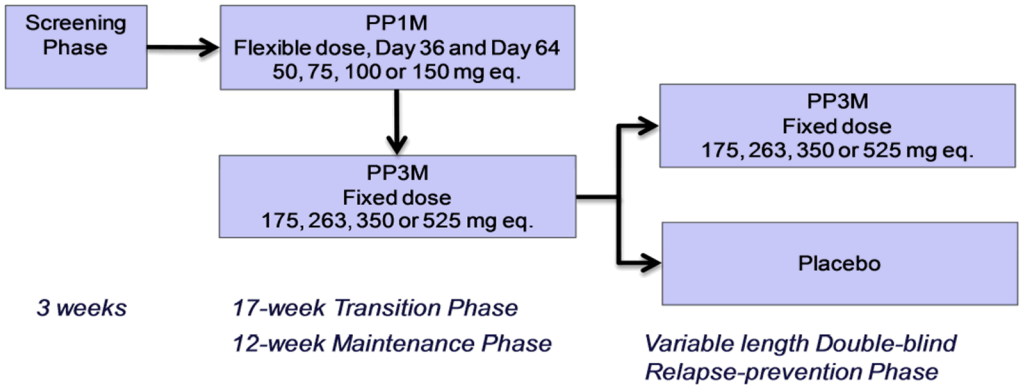
[b] See Table 1 for details of conversion between PP1M and PP3M doses.

[c] A follow-up visit was conducted 4 weeks after the EOS for subjects who withdrew early from the Open-label phase, 4 weeks after the last visit for subjects who completed the DB phase without a relapse, or 12 weeks after the last visit of the DB phase for those subjects who experience a relapse or withdraw early. The follow-up visit was added to the protocol based on a request from the Japanese Pharmaceuticals and Medical Devices Agency. During the follow-up period, study drugs were not continued, and subjects were switched to another available antipsychotic.

Key: DB=double-blind; EOS=end-of-study; mg eq. =milligram equivalent; PP1M=paliperidone palmitate 1-month formulation; PP3M=paliperidone palmitate 3-month formulation.

Study PSY-3012 was a multicenter, DB, placebo-controlled, long-term, randomized withdrawal study of PP3M in subjects with schizophrenia (Berwaerts 2015), which consisted of 4 phases as shown in Figure 2. The randomized withdrawal design used in this study was intended to evaluate the treatment effects of PP3M and, in particular, to assess whether, after symptom stabilization with PP1M and continuation with PP3M, a difference in the course of the disease was engendered by discontinuation of treatment with PP3M. The randomized withdrawal design has been stated as appropriate for demonstrating maintenance of efficacy with longer term use (EMA 2012). Moreover, this design has been accepted as evidence of efficacy for several antipsychotic drugs in schizophrenia (Beasley 2003; Kane 2012), including oral paliperidone ER and PP1M (Hough 2010; Kramer 2007).

Figure 2: Design of Phase 3 Long-term, Randomized Withdrawal Study R092670-PSY-3012



Key: mg eq.=milligram equivalent; PP1M=paliperidone palmitate 1-month formulation; PP3M=paliperidone palmitate 3-month formulation.

Neither Study PSY-3011 nor Study PSY-3012 was designed to evaluate the efficacy of distinct doses of PP3M. Rather, consistent with the anticipated use of PP3M in clinical practice, the selection of the PP3M dose for individual subjects in these 2 studies was based on the dose of PP1M optimized for treatment response and tolerability during an open-label treatment phase.

Upon entry into the DB phase of Study PSY-3011, subjects randomly assigned to the PP1M group continued to receive the same dose of PP1M as administered at Week 13, while those randomly assigned to the PP3M group had their dose of PP1M converted to the corresponding dose of PP3M using the pharmacokinetic (PK)-based conversion ratio of 1:3.5 (see Table 1). Similarly, in Study PSY-3012, subjects received a single injection of PP3M in the Maintenance phase (Week 17), using the 1:3.5 conversion ratio to the PP1M dose given on Week 13. Subjects assigned to the PP3M treatment group in Study PSY-3012 continued to receive the same dose of PP3M as given during the Maintenance phase. Dose adjustment was not permitted during the DB phases for Studies PSY-3011 or PSY-3012.

Table 1: Conversion Between PP1M and PP3M Doses, Using a 1:3.5 Fixed Ratio

PP1M mg eq. paliperidone	PP3M mg eq. paliperidone
50 mg eq.	175 mg eq.
75 mg eq.	263 mg eq.
100 mg eq.	350 mg eq.
150 mg eq.	525 mg eq.

Key: mg eq.=milligram equivalent; PP1M=paliperidone palmitate 1-month injection; PP3M=paliperidone palmitate 3 month injection.
There is no PP3M dose corresponding to the 25 mg eq. dose of PP1M.

Dose selection for PP3M uses a 3.5-fold multiplier of the PP1M doses ranging from 50 to 150 mg eq. The rationale for the 3.5-fold conversion was agreed to by CHMP in their follow-up advice. Within this advice, the CHMP also accepted the dose range for PP1M (50, 75, 100, 150 mg eq.) and PP3M (175, 263, 350, and 525 mg eq.) evaluated in the Phase 3 studies (PSY-3011, PSY-3012).

The primary efficacy endpoint in Study PSY-3011 was the percentage of subjects who had not relapsed at the end of the DB phase based on the Kaplan-Meier (K-M) 48-week cumulative estimate of survival. In Study PSY-3012, the primary endpoint was the time to relapse during the DB phase. The criteria for determining relapse were identical in both Phase 3 studies and were identical to the criteria that have been used previously in clinical studies to support approval of PP1M (ie, Study PSY-3001) (Hough 2010).

Protocol-specified relapse criteria in Studies PSY-3011 and PSY-3012 involved 1 or more of the following: sustained worsening in the positive and negative syndrome scale for schizophrenia (PANSS) total score (an increase from randomization of 25% if the score at randomization was >40 or by 10 points if the score was ≤40 on 2 consecutive visits separated by 3 to 7 days); clinically significant, overt symptomatology manifested by psychiatric hospitalization, suicidal/homicidal ideation or aggressive behavior, or deliberate self-injury and/or violent behavior resulting in injury; or sustained worsening of individual PANSS items of delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, or uncooperativeness (score of ≥5 if maximum score at randomization was ≤3, or score of ≥6 if maximum score at randomization was 4, on 2 consecutive visits separated by 3 to 7 days). The date of relapse for an individual subject was defined as the date of the first positive findings from a PANSS assessment for symptoms of relapse, rather than the date of confirmation.

3. EFFICACY

3.1. Efficacy Results: PSY-3011

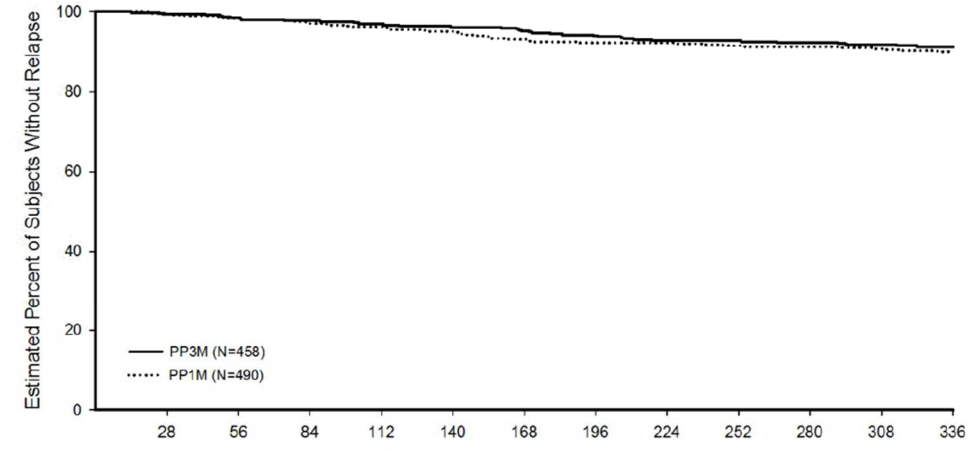
Study PSY-3011 was adequately powered (90% at the 1-sided significance level of 0.025) to demonstrate that PP3M was no worse than PP1M by a non-inferiority margin of 15% with regard to the percentage of subjects who remained relapse free at the end of the 48-week DB phase. The prespecified non-inferiority margin of 15% was selected based on available evidence with PP1M, from a meta-analysis of placebo-controlled relapse studies, and expert advice, and took into consideration the CHMP guideline on the choice of non-inferiority margin

(CPMP/EWP/49/01/2003). While a margin of 10% was proposed, CHMP agreed that the available evidence supported the clinical importance of a 15% non-inferiority margin. The lower bound of the 95% confidence interval (CI) (-2.7%) was larger than the CHMP-suggested noninferiority margin of -10%, demonstrating PP3M was non-inferior to PP1M.

The K-M method was used to estimate the 48-week cumulative estimate of survival (ie, primary endpoint of percentage of subjects who remained relapse free). Standard error estimates were based upon Greenwood's formula. Non-inferiority of PP3M to PP1M was concluded if the lower limit of the 2-sided 95% CI of the difference in relapse-free rates between the 2 treatment groups exceeded –15%. The estimate of the hazard ratio and its 95% CI were provided based on the Cox proportional hazards model with treatment as the only factor.

The primary analysis for efficacy in the per protocol (PP) analysis set for Study PSY-3011 (N=458 PP3M; N=490 PP1M) demonstrated that PP3M was non-inferior to PP1M as measured by the proportion of subjects who remained relapse free after 48 weeks based on the K-M estimate. Overall, there was a low rate of relapse during the DB phase (Figure 3), with 37 (8.1%) relapses on PP3M and 45 (9.2%) relapses on PP1M. The estimated difference (95% CI) between the 2 groups (PP3M-PP1M) in the percentage of subjects who remained relapse free was 1.2% (-2.7%, 5.1%). As the lower bound of the 95% CI (-2.7%) is larger than the prespecified noninferiority margin of -15%, it can be concluded that PP3M is non-inferior to PP1M. The lower bound of the 95% CI was also larger than the CHMP-suggested non-inferiority margin of -10%. The median time to relapse was not estimable for either the PP3M or PP1M groups due to the low number of relapses in the 2 groups. The most common reason for relapse were increases in PANSS total score (PP3M: 6%, PP1M: 5%) and psychiatric hospitalization (PP3M: 3%, PP1M: 4%). Of note, in subjects treated with PP3M, there was no clustering of relapse events at visits that would be expected to correspond to trough median plasma concentrations of paliperidone (ie, Weeks 12, 24, 36, and 48 of DB phase). Results of the Cox proportional hazards analysis further indicated that there was no loss of efficacy when switching from PP1M to PP3M. The risk (hazard) of relapse when switching from PP1M to PP3M versus the risk when remaining on PP1M was 0.87 (95% CI: 0.56, 1.34).

Figure 3: Kaplan-Meier Plot of Time to Relapse During Double-blind Phase (Study R092670-PSY-3011: Per-protocol Analysis Set)



Number of Subjects Left

Time	0	28	56	84	112	140	168	196	224	252	280	308	336
PP3M	458	454	441	425	419	406	394	386	372	368	361	353	244
PP1M	490	483	470	454	442	432	416	405	397	384	376	367	223

Paralleling the confirmed non-inferiority for PP3M to PP1M seen for relapse-free rates, analyses showed that results were similar for PP3M and PP1M for all secondary efficacy endpoints.

Specifically:

- The 95% CI for the least squares (LS) means difference between the 2 treatment groups (PP3M-PP1M) in change scores from DB baseline at DB end point in the modified intent-to-treat (mITT) (DB) analysis set for the PANSS scores (total, subscale, and factor), clinical global impression (CGI) score, and personal and social performance scale (PSP) total score all contained zero (see Table 2), indicating that the mean difference between the 2 treatment groups was not statistically significant.
- The observed mean PANSS total scores over time during the DB phase in the PP3M and PP1M groups decreased with an almost identical gradient from the DB baseline to end point (Figure 4), and there was no indication of a different pattern of results at visits that would be expected to correspond to trough median plasma concentrations of paliperidone (ie, at DB Weeks 12, 24, 36, and 48) for subjects randomized to PP3M.

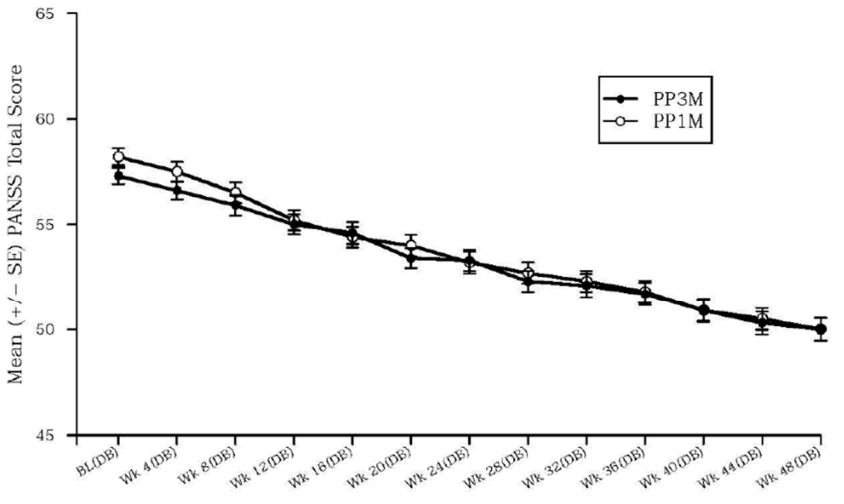
Table 2: Secondary Efficacy Endpoints: Change from Baseline (DB) to End Point (DB) (Study R092670-PSY-3011: mITT [DB] Analysis Set)

Secondary Endpoint	Mean (SD) Change: DB Baseline to End Point PP3M (N=483)	PP1M (N=512)	Difference in LS Means (95% CI)
PANSS Total Score	-3.5 (12.50)	-4.3 (11.78)	0.9 (-0.61, 2.34)
PANSS Factor Scores			
Positive symptoms	-1.1 (4.61)	-1.4 (4.16)	0.3 (-0.21, 0.84)
Negative symptom	-1.4 (3.57)	-1.3 (3.80)	-0.0 (-0.48, 0.40)
Disorganized thoughts	-1.2 (3.36)	-1.2 (3.24)	0.0 (-0.35, 0.43)
Uncontrolled hostility/excitement	0.2 (2.31)	-0.2 (2.21)	0.2 (-0.03, 0.50)
Anxiety/depression	-0.0 (2.69)	-0.2 (2.43)	0.1 (-0.15, 0.44)
PANSS Subscale Scores			
Positive	-0.6 (4.31)	-0.9 (3.7)	0.2 (-0.24, 0.72)
Negative	-1.4 (3.63)	-1.4 (3.67)	-0.0 (-0.43, 0.43)
General psychopathology	-1.4 (6.77)	-2.0 (6.57)	0.5 (-0.31, 1.29)
CGI-S Score	-0.1 (0.84)	-0.1 (0.75)	0.0 (-0.05, 0.13)
PSP Total Score	1.3 (10.22)	1.9 (9.21)	-0.5 (-1.73, 0.64)

Based on ANCOVA model with treatment (PP1M vs PP3M) and country as factors, and baseline value as a covariate. Difference is for change from baseline, PP3M - PP1M.

Key: ANCOVA=analysis of covariance; CGI-S=clinical global impression – severity; CI=confidence interval; DB=double blind; LS=least squares; mITT= modified intent-to-treat; PANSS= positive and negative syndrome scale for schizophrenia; PP1M=paliperidone palmitate 1-month formulation; PP3M=paliperidone palmitate 3-month formulation; PSP= personal and social performance scale.

Figure 4: Mean (± SE) in PANSS Total Scores (Observed Case) Over Time During the Double-blind Phase (Study R092670-PSY-3011: mITT [DB] Analysis Set)



Number of Subjects:

PP3M	483	479	463	449	441	426	419	407	400	389	383	375	364
PP1M	512	502	484	472	453	442	425	418	408	398	389	379	371

Key: DB=double blind; mITT= modified intent-to-treat; PANSS= positive and negative syndrome scale for schizophrenia; SE=standard error; PP1M=paliperidone palmitate 1-month formulation; PP3M=paliperidone palmitate 3-month formulation.

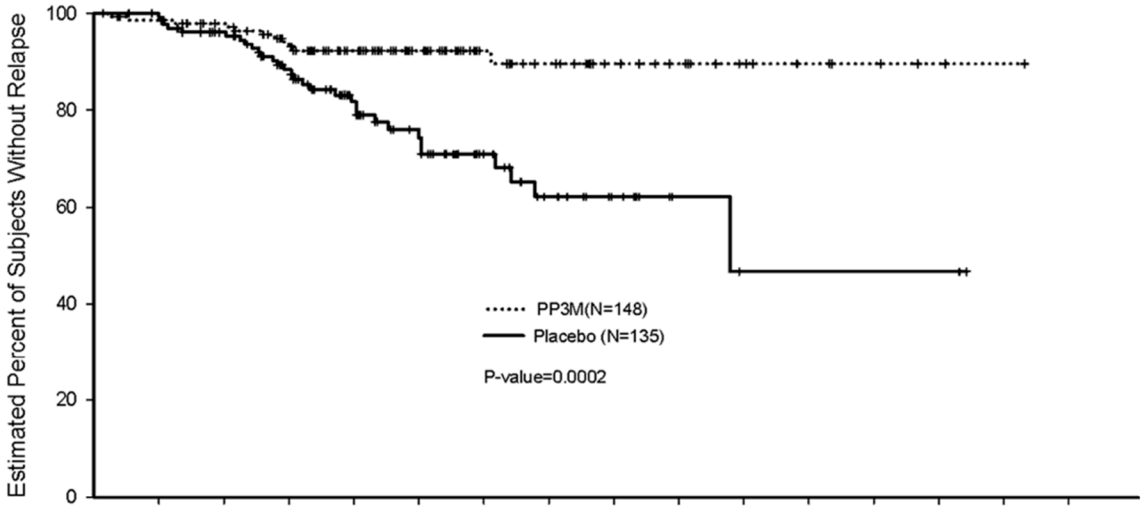
3.2. Efficacy Results: PSY-3012

Study PSY-3012 was adequately powered (90% power at the 2-sided significance level of 0.05) to detect a 20% difference in the 12-month relapse rates for PP3M and placebo, or equivalently, a relative risk of 0.44. A 2-stage group sequential design was utilized in Study PSY-3012 with 1 interim analysis for efficacy; the study design allowed for early termination of the study if significant evidence of efficacy was obtained based on the preplanned interim analysis. The interim analysis conducted by an independent data monitoring committee (IDMC), was planned when 60% of the projected relapse events (ie, 42) were observed in the DB phase. The O'Brien-Fleming boundary (corresponding to the Wang and Tsiatis power boundary with shape parameter 0) was used for sequential monitoring. The interim analysis was performed at a significance level of 0.0101 and the final analysis was to be performed at the 0.0464 significance level if the study did not stop at the interim analysis. Based upon demonstration of a statistically significant difference in favor of PP3M in delaying time to relapse compared with placebo, the study was terminated per the IDMC recommendation.

The fixed dose regimen of PP3M in Study PSY-3012 during the open-label Maintenance phase and DB phase was based upon conversion from the dose of PP1M adjusted to clinical effect during the 17-week Transition phase. As in Study PSY-3011, most subjects in PSY-3012 were on the highest doses of study medication. At the last scheduled dose of the Transition phase (ie, Week 13), the most common PP1M dose levels were 100 mg eq. and 150 mg eq. (46% and 42% of subjects, respectively). Accordingly, most subjects received a PP3M dose of 350 or 525 mg eq. (49% and 39%, respectively) at the single injection during the Maintenance phase (ie, Week 17); 2% of subjects received a PP3M dose level of 175 mg eq. and 9% received a dose level of 263 mg eq. Dose level adjustment for PP3M was not permitted during the DB phase. The median (range) duration of the DB phase was 169 days (8, 463 days) in the PP3M group and 146 days (16, 426 days) in the placebo group.

Comparison of the PANSS total and clinical global impression – severity (CGI-S) scores at randomization to the DB phase confirmed that symptoms of schizophrenia had been stabilized. Following randomization, PP3M was superior to placebo in preventing relapse of symptoms of schizophrenia. Based on the preplanned interim analysis conducted by the IDMC after 42 relapse events had occurred, 31 (23.0%) of 135 subjects randomly switched from open-label PP3M to DB placebo experienced a relapse event compared with 11 (7.4%) of 148 subjects randomized to remain on PP3M. Subjects who continued treatment on PP3M during the DB phase experienced relapse significantly later than those who were switched to placebo ($p<0.001$, based on log rank test) (Figure 5). The median time to first relapse, based on K-M estimation, was 274 days in the placebo group and was not estimable in the PP3M group.

Figure 5 Kaplan-Meier Plot of Time to Relapse during the Double-blind Phase – Interim Analysis (Study R092670-PSY-3012: ITT [DB] Analysis Set)



Number of Subjects Left

Time	0	28	56	84	112	140	168	196	224	252	280	308	336	364	392	420
PP3M	148	143	133	104	81	59	35	28	19	15	9	6	4	2	1	0
Placebo	135	131	116	91	61	44	27	18	12	4	2	2	2	0	0	0

Key: DB=double-blind; ITT=intent-to-treat; PP3M=paliperidone palmitate 3-month formulation.

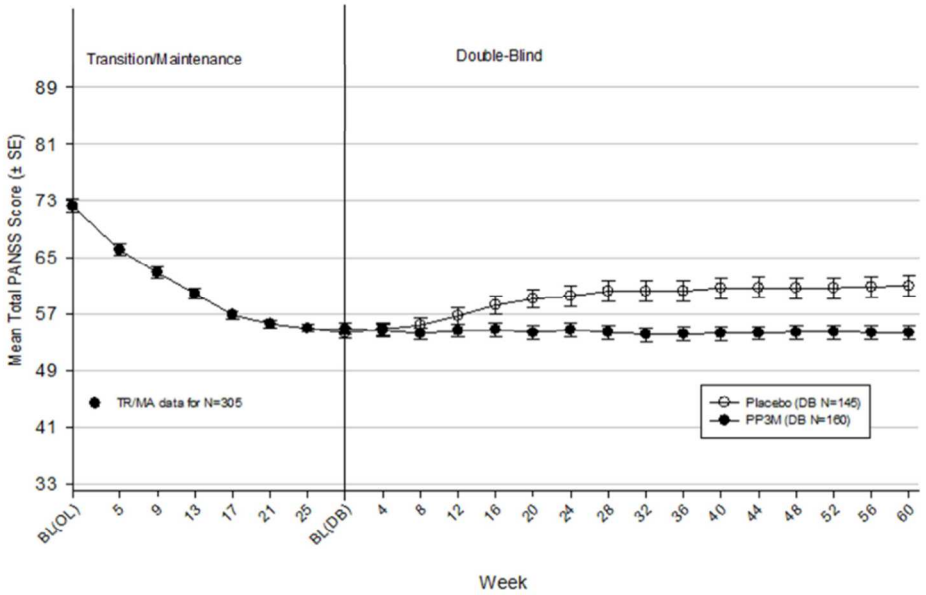
Based on these positive findings, Study PSY-3012 was terminated as per the recommendations of the IDMC. Results of the final analysis that included data from the 305 subjects in the intent to treat for double-blind phase (ITT [DB]) analysis set through the time of study termination, and conducted on a dataset with 56 relapses, confirmed results of the interim analysis. For the final analysis, 29.0% (N=42) of the 145 subjects in the placebo group, compared with 8.8% (N=14) of the 160 subjects in the PP3M group, experienced a relapse event, and there was a significant difference in the time to relapse favoring PP3M ($p<0.001$ based on log rank test). The median time to the first relapse event, based on K-M estimation, was 395 days for the placebo group and was not estimable in the PP3M group. Results of the Cox proportional hazards regression analysis of the effect of treatment on the time to relapse revealed that the instantaneous risk (hazard ratio) of relapse of schizophrenia symptoms was 3.45 (95% CI: 1.73, 6.88; $p=0.0004$) times higher for a subject switched to placebo than for a subject continuing to receive PP3M (interim analysis). Results were similar for the final analysis.

Overall, the efficacy of PP3M with respect to the proportion of subjects experiencing a relapse event was consistent among the subgroups (sex, age, body mass index [BMI], geographic region, race, and prior antipsychotic formulation [oral vs LAI]), with no noticeable differential effect of PP3M relative to placebo across any of the subgroups. The instantaneous risk (hazard [95% CI]) of relapse was 5.83 (2.40, 14.18) times higher in the placebo group than in the PP3M group in Europe (largest regional subgroup). Additional evidence for the effectiveness of PP3M in maintaining symptom control was provided by results of a post hoc analysis of the maintenance of remitter status following a single dose of PP3M during the Maintenance phase (using same definition as for Study PSY-3011). After randomization, there was a steady increase in the

percentage of subjects assigned to the placebo group who lost their remitter status, ranging from 5% at Week 4 of the DB phase to 42% at Week 36 (last time point where at least 10 subjects had data). By comparison, the percentage of subjects randomized to the PP3M group who lost their remitter status after randomization remained low and stable across the same time period (range, 6 to 12%).

Data from the 17-week open-label Transition phase of Study PSY-3012 showed the effectiveness of PP1M in improving the symptoms of schizophrenia, as reflected by substantial mean decreases in the PANSS total, subscale, and factor scores, coupled with mean increases in the PSP score and a greater proportion of subjects with favorable CGI-S ratings. Additional improvements were seen in the PANSS total and CGI-S scores following conversion from PP1M to PP3M at Week 17 of the Maintenance phase and the functional improvements (based on PSP scores) achieved with PP1M during the Transition phase were maintained following the switch to PP3M during the Maintenance phase. The mean PANSS total scores (with last observation carried forward [LOCF] imputation) during the DB phase essentially remained unchanged in the PP3M group, but increased (ie, worsened) in the placebo group (Figure 6). While the difference between the 2 groups in change from DB baseline in PANSS total score was statistically significant at Weeks 12, 24, 36, and 48 (all $p \leq 0.008$), the magnitude of the treatment effect increased from -2.7 at Week 12 to -6.9 at Week 48. A similar pattern of results showing deterioration in the placebo group and maintenance of effect in the PP3M group was seen for the analysis of the PANSS subscale and factor scores over the DB phase.

Figure 6 **Arithmetic Mean (± SE) PANSS Total Scores Over Time (LOCF) (Study R092670-PSY-3012: ITT [DB] Analysis Set)**



Key: BL=baseline; DB=double-blind; ITT=intent-to-treat; LOCF=last observation carried forward; OL=open-label; PANSS=Positive and Negative Syndrome Scale; PP3M=paliperidone palmitate 3-month formulation; SE=standard error; TR/MA=transition/maintenance.

3.3. Discussion of the Efficacy of PP3M

Overall, the results of the Phase 3 studies PSY-3011 and PSY-3012 demonstrate the ability of PP3M to prevent relapse in adult patients with schizophrenia who had been adequately treated

with PP1M over a period of 4 months. PP3M demonstrated superiority to placebo in delaying the time to relapse (Study PSY-3012). Additionally, PP3M was non-inferior to PP1M in preventing relapse over 48 weeks of treatment (Study PSY-3011).

The Phase 3 Study PSY-3011, with a design finalized based on scientific advice from CHMP, indicated that PP3M was non-inferior to PP1M as measured by the percentage of subjects who remained relapse-free over a period of 48 weeks after they had been adequately treated with PP1M for 4 months. The percentage of subjects who remained relapse-free through Week 48 of DB phase was 91.9% on PP3M and 90.8% on PP1M; the lower bound of the 95% CI (-2.7%) for the difference in relapse-free rates was larger than the prespecified margin of -15% [or -10% margin as proposed by CHMP] and the CI included zero, which suggested that the 2 treatments were similar. The efficacy results demonstrating non-inferiority of PP3M to PP1M were similar in the primary (PP) and secondary (mITT [DB]) analysis sets, as well as across prespecified population subgroups defined by age, sex, BMI, race, dose, and geographic region. PP3M also showed similar clinical activity to PP1M as measured by changes from baseline in secondary outcome measures including PANSS, CGI-S, and PSP, providing further evidence that efficacy of PP3M is comparable to that of PP1M in the maintenance treatment of adult subjects with schizophrenia who have been adequately treated with PP1M for 4 months. Results indicated that PP3M was not less effective than continued PP1M treatment in preserving improvements in global outcome with respect to severity of illness (CGI-S) and functional outcome (PSP) initially seen during the Open-label phase with PP1M. Almost 60% of subjects in the PP3M group (58%) showed symptomatic remission based on PANSS scores for the 6 months preceding the EOS during the DB phase, which was similar to the remission rate of 59% seen in the PP1M group. These rates are notably higher than the remission estimates of approximately 30% reported in the literature among treated patients with schizophrenia (Brisso 2011; Mosolov 2012).

Results of Phase 3 Study PSY-3012 were supportive of the efficacy of PP3M seen in Study PSY-3011. In Study PSY-3012, administration of PP3M every 3 months demonstrated clinically relevant and statistical superiority to placebo in delaying the time to first relapse in subjects who had achieved satisfactory and stable symptom control during 29 weeks of open-label treatment with paliperidone palmitate (4 months of PP1M treatment followed by single PP3M dose), based on the preplanned interim analysis and confirmed by the final analysis. Analyses of the instantaneous risk (hazard ratio) of relapse of schizophrenia symptoms indicated that continued treatment with PP3M was associated with a 74% decrease in risk based on the final analysis. The efficacy of PP3M with regard to time to relapse was consistent within population subgroups defined by age, sex, race, geographic region, and prior use of a LAI antipsychotic. Analyses of all secondary efficacy outcomes in Study PSY-3012 were supportive of the primary efficacy findings.

4. BENEFITS OF THE 3 MONTH PALIPERIDONE FORMULATION

Data from the multicenter, double-blind, randomized, Phase 3 studies in adults with schizophrenia stabilized on PP1M demonstrate that PP3M is non-inferior to PP1M with respect to the relapse rate at Week 48 (Study PSY-3011) and superior to placebo in delaying the time to relapse (Study PSY-3012). The design of both studies was in accord with CHMP guidelines (EMA 2012).

Additionally, the Company sought and incorporated advice from CHMP on specific design elements for Study PSY-3011 and Study PSY-3012. In Study PSY-3011, few subjects in either the PP3M (8.1%) or PP1M (9.2%) treatment groups demonstrated a relapse within 48 weeks of the start of DB treatment, and the lower limit of the 95% CI of the difference in relapse-free rates between PP3M and PP1M (-2.7%) was larger than the prespecified non-inferiority margin of -15% or the CHMP-suggested margin of -10%, indicating that the efficacy of these 2 LAI antipsychotics was comparable in preventing relapse. In Study PSY-3012, the relapse rate for subjects maintained on PP3M (7.4%; prespecified interim analysis) was similar to that for PP3M in Study PSY-3011, and the risk (hazard) of relapse of schizophrenia symptoms was estimated to be reduced by 71% compared to subjects switched from PP3M to placebo after randomization.

This finding from Study PSY-3012 parallels the benefits seen for the PPM1 product and for orally administered once daily paliperidone ER in similarly designed, long-term, randomized withdrawal studies (Kramer 2007; Hough 2010). Each of these Company-sponsored studies also had similar subject eligibility criteria and prespecified criteria for randomization into the DB phase, and the relapse criteria for each the 3 studies were identical. These similarities permit indirect comparison of efficacy for Study PSY-3012 with these earlier studies. In comparing results of these studies with those from Study PSY-3012 (prespecified interim analyses in all cases), it appears that as the apparent half-life of paliperidone increases across the formulations evaluated (ER → PP1M → PP3M), there is an incremental delay in the time to first relapse among subjects who are switched from active treatment to placebo (Table 3 and Figure 7). It is possible that in addition to the differences in apparent half-life between the paliperidone formulations, differences across the 3 studies in design (eg, duration of open-label phase, number of relapses required for interim analysis, equivalent doses of paliperidone evaluated) and conduct (eg, rate of enrollment/randomization in the DB phase, rate of early withdrawal from DB phase) could have also contributed to the observed differences in the median time to first relapse among subjects switched to placebo between the 3 studies.

Nevertheless, the data shown in Table 3 and Figure 7 suggests that treatment with PP3M offers a longer interval of protection against relapse of psychotic symptoms to patients with schizophrenia in the event of intentional or accidental nonadherence relative to currently available monthly injectable or daily oral antipsychotic treatments.

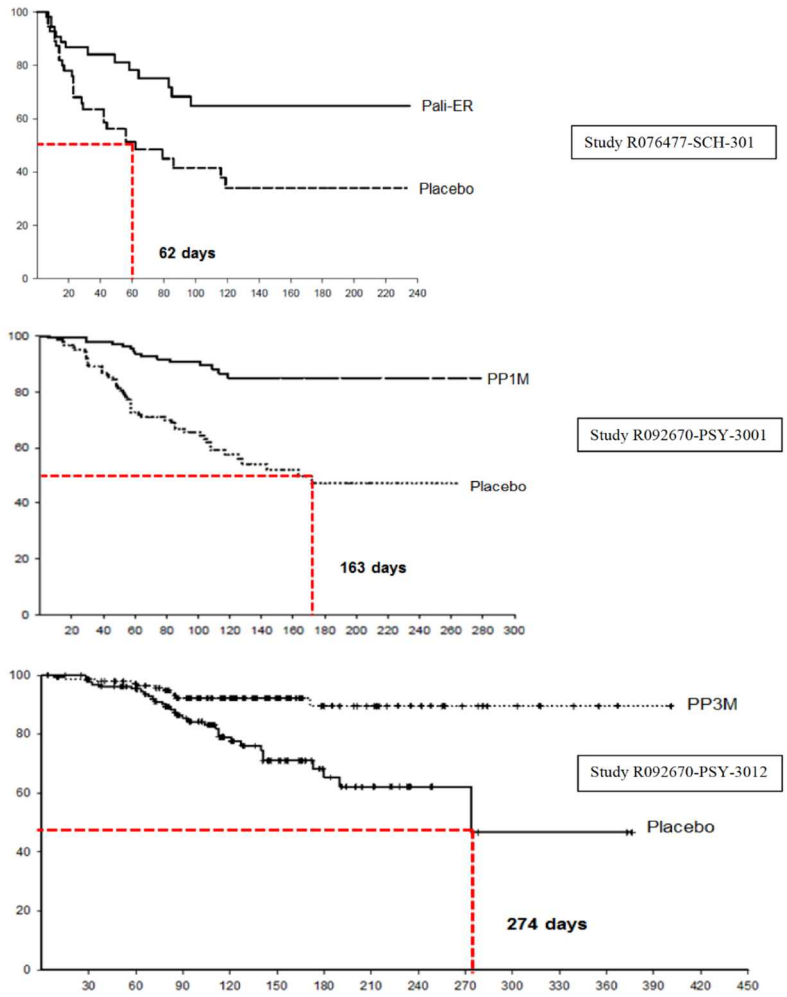
Table 3: Comparison of Time to Relapse During the Double-blind Phase and Number (%) of Subjects that Remained Relapse Free (Interim Analysis) Across Pivotal Randomized Withdrawal Studies with Paliperidone Palmitate 3-Month, Paliperidone Palmitate 1-Month, and Paliperidone ER Formulations

	Study PSY-3012		Study PSY-3001		Study SCH-301	
Descriptive	PP3M	Placebo	PP1M	Placebo	Pali ER	Placebo
Time to Relapse						
No. assessed	148	135	156	156	56	55
No. relapsed (%)	11 (7.4)	31 (23.0)	15 (9.6)	53 (34.0)	14 (25.0)	29 (52.7)
Median time to relapse[a] (95% CI), days	NE	274 (190; NE)	NE	163 (108; NE)	NE (97, NE)	62 (42; 119)
Statistical test (p-value)[b]	<0.001		<0.0001		0.0053	

[a] Based on Kaplan-Meier product limit estimates.
[b] Based on log-rank test.
Key: CI=confidence interval; NE=not estimable (<50% subjects experienced a relapse event); Pali ER=paliperidone extended-release; PP1M=paliperidone palmitate 1-month injection; PP3M=paliperidone palmitate 3-month injection.

Figure 7: Kaplan-Meier Plots of Time to Relapse During the Double-blind Phase: Results of 3 Similarly designed Randomized Withdrawal Studies Conducted with Paliperidone ER, PP1M, and PP3M

(Studies R076477-SCH-301, R092670-PSY-3001, and R092670-PSY-3012; Interim Analysis)



Key: ER=extended release; Pali-ER=oral paliperidone extended release; PP1M=paliperidone palmitate 1-month injection; PP3M=paliperidone palmitate 3-month injection.

The designs of the studies above provide insight into what might happen in the real world when schizophrenia patients suddenly stop taking their medications. The placebo group in each of the studies reflects sudden discontinuation. Based on indirect comparisons above, a patient who receives PP3M who suddenly discontinues is protected from relapse, on average, for nearly 1 year. This is far longer than other formulations of the same molecule and suggests that longer-acting agents provide better protection in this vulnerable population as compared to shorter acting products.

Lengthening the dosing interval to once every 3 months with PP3M reduces the time needed for monitoring and follow-up of patients for medication adherence, potentially providing health care providers with additional time for implementing or monitoring psychosocial programs. Treatment programs for schizophrenia that combine antipsychotic medication with a range of psychosocial therapies (eg, assertive community treatment, cognitive behavioral therapy, skills training) are associated with improved outcomes (APA 2010; Torres-González 2014) but psychosocial programs are most useful when implemented while patient's psychotic symptoms are adequately managed by antipsychotic therapy. By providing effective, safe antipsychotic drug coverage for 3 months between visits, the use of PP3M could lessen the burden on therapists or other individuals involved in intensive psychiatric outreach programs. Further, the 3-month dosing interval with PP3M means that once nonadherence is identified in a patient, there is a wider window than with other available antipsychotic formulations within which patients can be encouraged to become adherent before plasma levels drop below therapeutic thresholds.

Following intramuscular (IM) injection of PP3M, paliperidone palmitate is completely hydrolyzed to circulating paliperidone, and thus the influence of various intrinsic and extrinsic factors on the absorption and disposition of PP3M is assumed to be no different from PP1M or paliperidone ER. The minimal likelihood of drug-drug interactions with paliperidone palmitate also makes the use of PP3M particularly valuable since a sizeable percentage of patients with schizophrenia have comorbid medical and/or psychiatric conditions, many of which require pharmacological treatment. PP3M is supplied in prefilled syringes that do not require reconstitution or refrigeration, further enhancing the ease of use of this LAI antipsychotic, especially in remote areas with limited healthcare provisions.

The demonstrated efficacy of PP3M, together with its long duration of action and every 3-month dosing interval, make this LAI antipsychotic an important treatment option for the long-term management of schizophrenia in adult patients who have been stabilized on PP1M.

4.1. Real World Evidence Showing Improved Persistence of PP3M over PP1M

Results from 3 real-world studies which monitored adult patients with schizophrenia maintained on PP3M who transitioned from PP1M demonstrated improvements in adherence and persistence, and a reduction in healthcare resource utilization (HRU), including a reduction in the length of hospital stay. National Provider Database Analysis: In a real-world study by Joshi (2017), pharmacy and medical claims data in the Symphony Health Solutions database were analyzed for adult patients with schizophrenia maintained on PP3M. The study aimed to describe baseline characteristics and treatment patterns of patients with schizophrenia who transitioned from PP1M

to PP3M. Patients initiated on PP3M demonstrated increased adherence and decreased HRU in quarters closer to PP3M initiation and were more persistent on their PP3M treatment. Veterans Health Administration (VHA) Electronic Health Record Analysis: A retrospective analysis of electronic health records data from the VHA by DerSarkissian (2018) for veterans with schizophrenia who transitioned from PP1M to PP3M according to prescribing-information guidelines showed that after transitioning to PP3M treatment, veterans had significantly reduced HRU. The mean proportion of days covered (PDC) of any antipsychotic agent was significantly increased, from 0.90 to 0.97, in the 6 months before PP3M to the 6 months after PP3M ($p < 0.0001$, see Table 4). This finding is important because patients were taking PP1M prior to switching to PP3M, which indicates that reduction of injection frequency can have a notable impact on adherence.

Table 4: Antipsychotic Medication Use 6 Months Before and After Transition to PP3M Among Patients With at Least 6 Months of Follow-up after PP3M transition (N=197)

Parameter	6 Mo Before PP3M Transition	6 Mo After PP3M Transition	P*
Mental health–related medication use,† no. (%)			
Antidepressant	98 (49.7)	94 (47.7)	0.4142
Anxiolytic	71 (36.0)	68 (34.5)	0.6015
Mood stabilizer	42 (21.3)	44 (22.3)	0.5637
Other	58 (29.4)	60 (30.5)	0.6698
Oral AP use, no. (%)			
Any	98 (49.7)	85 (43.1)	0.0326‡
Atypical	93 (47.2)	77 (39.1)	0.0094‡
Typical	11 (5.6)	14 (7.1)	0.3173
PDC parameters			
Any AP§			
PDC ≥0.80, no. (%)	175 (88.8)	180 (91.4)	0.3532
PDC, mean (SD) [median]	0.90 (0.11) [0.92]	0.97 (0.10) [1.00]	<0.0001‡
Paliperidone palmitate LAI§,‖			
PDC ≥0.80, no. (%)	148 (75.1)	166 (84.3)	–
PDC, mean (SD) [median]	0.85 (0.14) [0.90]	0.94 (0.13) [1.00]	–

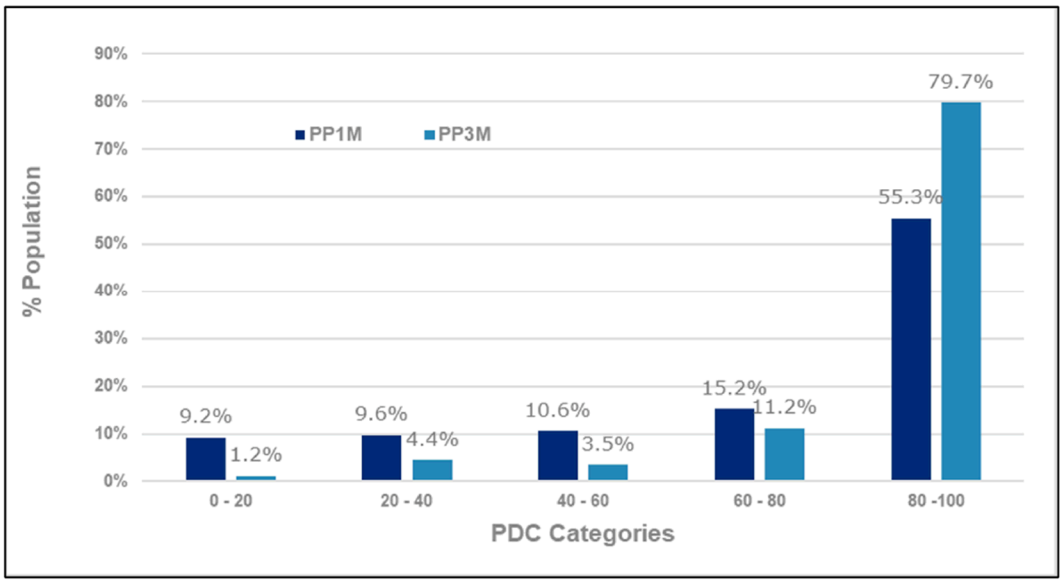
AP=antipsychotic; LAI = long-acting injectable therapy; PDC = proportion of days covered; PP1M=paliperidone palmitate 3-month product; PP3M=paliperidone palmitate 3-month product; SD=standard deviation
* Wilcoxon signed rank test (continuous variables) or McNemar test (categorical variables).
† Mental health-related medications included antidepressants, anxiolytics, and mood stabilizers.
‡ Statistically significant.
§ The denominator used for calculating the percentages of patients with a PDC of 0.
‖ PP1M was assessed in the 6 months prior to PP3M transition; PP3M was assessed post transition. Days' supply was extended by 14 days on calculation of PDC with PP1M and by 28 days on calculation of PDC with PP3M.
Source: Adapted from DerSarkissian et al[13] Table III

Four-state Medicaid Claims Data Analysis: Another retrospective analysis by Lin (2020) used 4-state Medicaid data from 2014 to 2019 to compare medication adherence, persistence and HRU between patients with schizophrenia who transitioned to PP3M and those who remained on PP1M. Patients who received at least 4 months of continuous PP1M coverage and transitioned to PP3M were matched 1:1 to patients who received at least 4 months of continuous PP1M coverage but did not transition to PP3M, through propensity score matching adjusting for differences in patient characteristics. Over a 12-month follow-up period, patients who transitioned to PP3M were

2.4 times more likely to be adherent (PDC ≥80%) and 4.6 times more likely to be persistent (no gap >90 days for PP3M cohort or >30 days for PP1M cohort), compared to patients who remained on PP1M (all p <0.001).

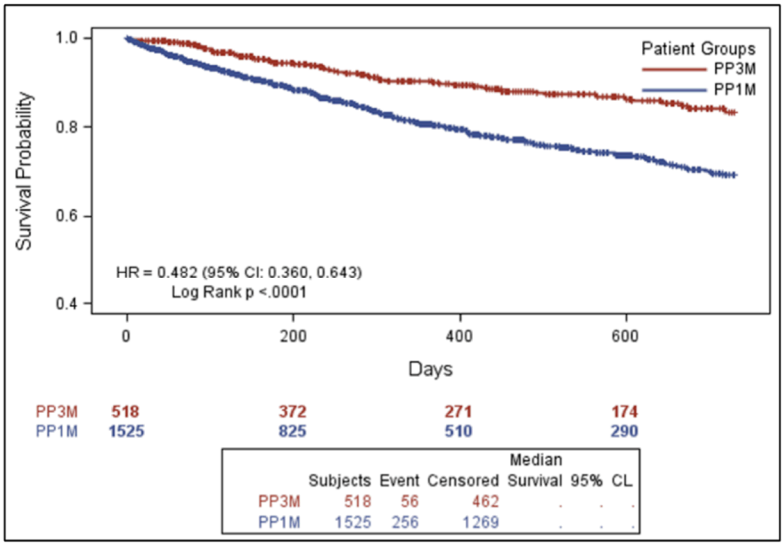
MarketScan Multi-State Medicaid Database Analysis: A large retrospective cohort study was performed using the IBM MarketScan Multi-State Medicaid database in the United States to evaluate the relapse risk associated with PP1M and PP3M in adult patients with schizophrenia. After propensity score matching, rates of adherence and relapse were measured. The results showed that PP3M use was associated with significantly greater rates of adherence as measured by PDC (Figure 8; unpublished data) and lower risk of relapse as compared to PP1M treatment (Figure 9; unpublished data). Furthermore, the relapse rate was negatively correlated with the PDC (Figure 10; unpublished data). The proportion of patients with PDC >80% was 55.3% and 79.7% for patients treated with PP1M and PP3M, respectively. Although the rates of adherence in this real-world study were lower than what was reported in clinical trials, this difference may be due to visit reminders, blister packs, extra time spent with study staff, among others.

Figure 8: Distribution of Patients by PDC Category



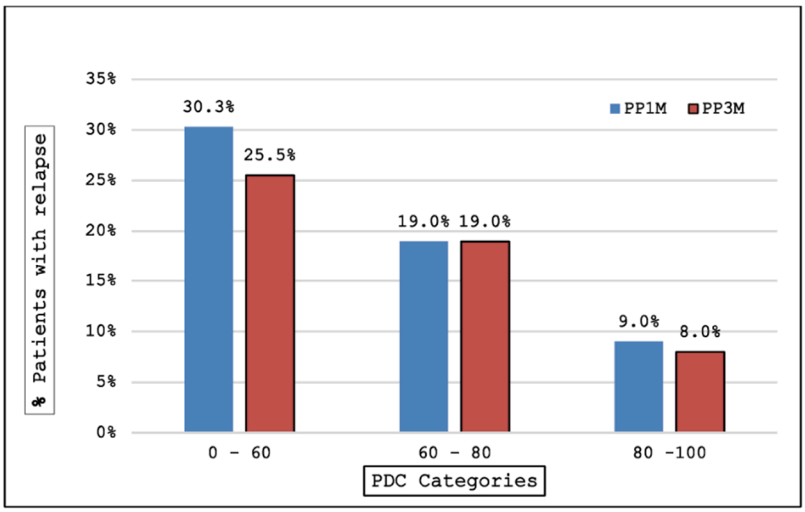
Key: PDC=proportion of days covered; PP1M=paliperidone palmitate 1-month product; PP3M=paliperidone palmitate 3-month product.

Figure 9: Time to Relapse – PP3M vs. PP1M



Key: CI=confidence interval; HR=hazard ratio; PDC=proportion of days covered; PP1M=paliperidone palmitate 1-month product; PP3M=paliperidone palmitate 3-month product.

Figure 10: Relapse Rates by Injection Frequency at PDC Categories



Key: PDC=proportion of days covered; PP1M=paliperidone palmitate 1-month product; PP3M=paliperidone palmitate 3-month product.

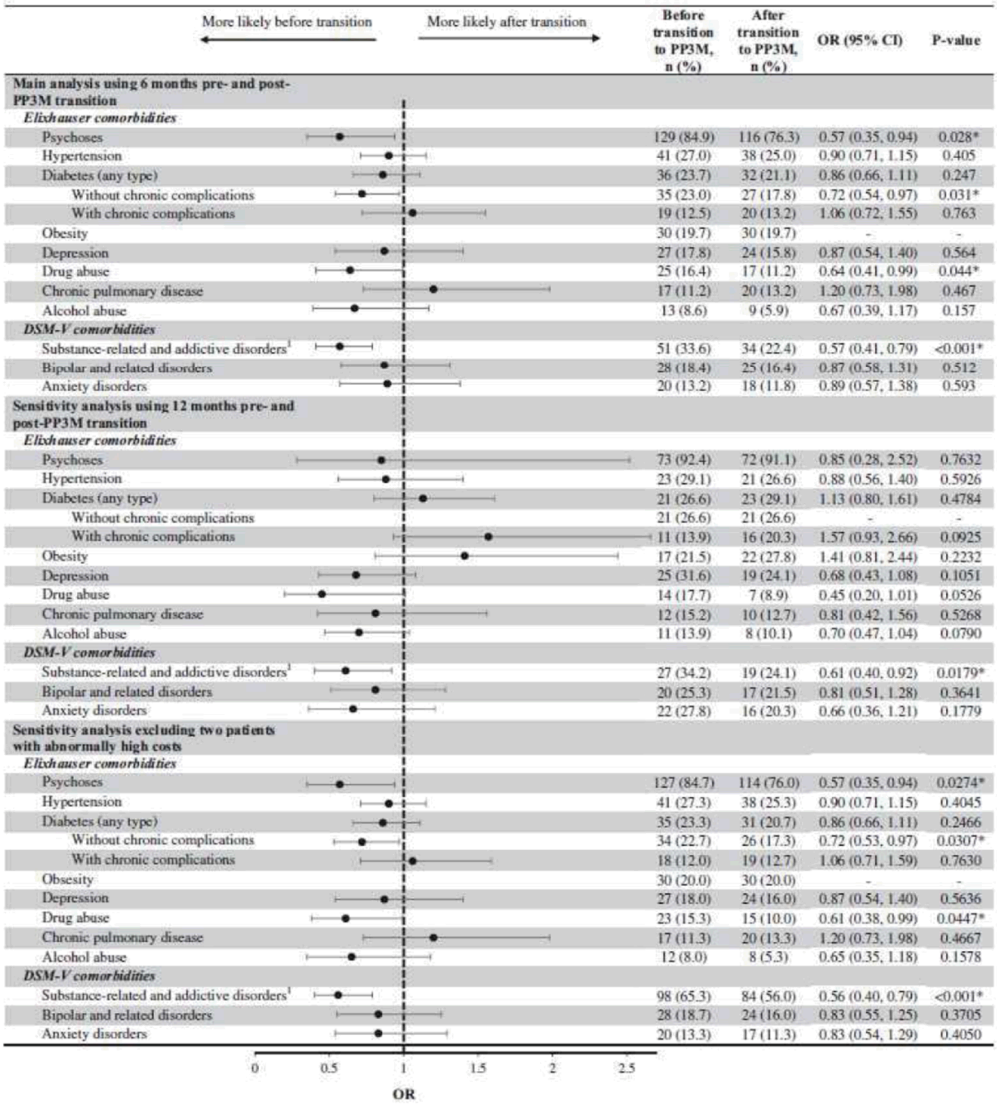
Thus, Janssen proposes that the PP3M LAI formulation, by virtue of its longer duration of action, may provide additional delay in relapse when patients discontinue therapy.

4.2. Impact of Adherence on Comorbidity Related Outcomes

A study by Farley (2012) used Medstat MarketScan Medicaid databases and examined patterns of adherence to both antipsychotics and medications for comorbid cardiometabolic health conditions (diabetes, hypertension and hyperlipidemia) in patients with schizophrenia newly initiated on second generation antipsychotic treatment. After adjusting differences in patient characteristics, the results found that being adherent to antipsychotics was associated with better adherence to

cardiometabolic medications and a potential reduction in emergency department utilization in patients with schizophrenia and preexisting cardiometabolic conditions. Additional supportive evidence of the impact of antipsychotic adherence on other medications for comorbid conditions is provided in a retrospective analysis of claims data (IQVIA PharMetrics Plus) by Emond (2015) from May 2014 to February 2018. Commercially insured patients with schizophrenia who transitioned from PP1M to PP3M were less likely to have future claims with a diagnosis for substance-related and addictive disorders, psychoses, drug abuse and diabetes without chronic complications; see Figure 11. PP3M patients were likely to be more adherent to antipsychotic medications compared to the period when they were taking PP1M (odds ratio [OR]=2.01, p = 0.007).

Figure 11: Comparison of the Proportion of Patients With Claims With a Diagnosis of Selected Elixhauser and DSM-V comorbidities Before and After Transitioning to PP3M



	Before transition to PP3M, n (%)	After transition to PP3M, n (%)	OR (95% CI)	P-value
Main analysis using 6 months pre- and post-PP3M transition				
Elixhauser comorbidities				
Psychoses	129 (84.9)	116 (76.3)	0.57 (0.35, 0.94)	0.028*
Hypertension	41 (27.0)	38 (25.0)	0.90 (0.71, 1.15)	0.405
Diabetes (any type)	36 (23.7)	32 (21.1)	0.86 (0.66, 1.11)	0.247
Without chronic complications	35 (23.0)	27 (17.8)	0.72 (0.54, 0.97)	0.031*
With chronic complications	19 (12.5)	20 (13.2)	1.06 (0.72, 1.55)	0.763
Obesity	30 (19.7)	30 (19.7)	-	-
Depression	27 (17.8)	24 (15.8)	0.87 (0.54, 1.40)	0.564
Drug abuse	25 (16.4)	17 (11.2)	0.64 (0.41, 0.99)	0.044*
Chronic pulmonary disease	17 (11.2)	20 (13.2)	1.20 (0.73, 1.98)	0.467
Alcohol abuse	13 (8.6)	9 (5.9)	0.67 (0.39, 1.17)	0.157
DSM-V comorbidities				
Substance-related and addictive disorders[1]	51 (33.6)	34 (22.4)	0.57 (0.41, 0.79)	<0.001*
Bipolar and related disorders	28 (18.4)	25 (16.4)	0.87 (0.58, 1.31)	0.512
Anxiety disorders	20 (13.2)	18 (11.8)	0.89 (0.57, 1.38)	0.593
Sensitivity analysis using 12 months pre- and post-PP3M transition				
Elixhauser comorbidities				
Psychoses	73 (92.4)	72 (91.1)	0.85 (0.28, 2.52)	0.7632
Hypertension	23 (29.1)	21 (26.6)	0.88 (0.56, 1.40)	0.5926
Diabetes (any type)	21 (26.6)	23 (29.1)	1.13 (0.80, 1.61)	0.4784
Without chronic complications	21 (26.6)	21 (26.6)	-	-
With chronic complications	11 (13.9)	16 (20.3)	1.57 (0.93, 2.66)	0.0925
Obesity	17 (21.5)	22 (27.8)	1.41 (0.81, 2.44)	0.2232
Depression	25 (31.6)	19 (24.1)	0.68 (0.43, 1.08)	0.1051
Drug abuse	14 (17.7)	7 (8.9)	0.45 (0.20, 1.01)	0.0526
Chronic pulmonary disease	12 (15.2)	10 (12.7)	0.81 (0.42, 1.56)	0.5268
Alcohol abuse	11 (13.9)	8 (10.1)	0.70 (0.47, 1.04)	0.0790
DSM-V comorbidities				
Substance-related and addictive disorders[1]	27 (34.2)	19 (24.1)	0.61 (0.40, 0.92)	0.0179*
Bipolar and related disorders	20 (25.3)	17 (21.5)	0.81 (0.51, 1.28)	0.3641
Anxiety disorders	22 (27.8)	16 (20.3)	0.66 (0.36, 1.21)	0.1779
Sensitivity analysis excluding two patients with abnormally high costs				
Elixhauser comorbidities				
Psychoses	127 (84.7)	114 (76.0)	0.57 (0.35, 0.94)	0.0274*
Hypertension	41 (27.3)	38 (25.3)	0.90 (0.71, 1.15)	0.4045
Diabetes (any type)	35 (23.3)	31 (20.7)	0.86 (0.66, 1.11)	0.2466
Without chronic complications	34 (22.7)	26 (17.3)	0.72 (0.53, 0.97)	0.0307*
With chronic complications	18 (12.0)	19 (12.7)	1.06 (0.71, 1.59)	0.7630
Obesity	30 (20.0)	30 (20.0)	-	-
Depression	27 (18.0)	24 (16.0)	0.87 (0.54, 1.40)	0.5636
Drug abuse	23 (15.3)	15 (10.0)	0.61 (0.38, 0.99)	0.0447*
Chronic pulmonary disease	17 (11.3)	20 (13.3)	1.20 (0.73, 1.98)	0.4667
Alcohol abuse	12 (8.0)	8 (5.3)	0.65 (0.35, 1.18)	0.1578
DSM-V comorbidities				
Substance-related and addictive disorders[1]	98 (65.3)	84 (56.0)	0.56 (0.40, 0.79)	<0.001*
Bipolar and related disorders	28 (18.7)	24 (16.0)	0.83 (0.55, 1.25)	0.3705
Anxiety disorders	20 (13.3)	17 (11.3)	0.83 (0.54, 1.29)	0.4050

*p-value <0.5

[1]Substance-related and addictive disorders include alcohol, cannabis, hallucinogen, opioid, sedative, hypnotic, anxiolytic, cocaine, nicotine, inhalant, any other stimulant, and any other psychoactive substance abuse or dependence, as well as tobacco use and gambling.

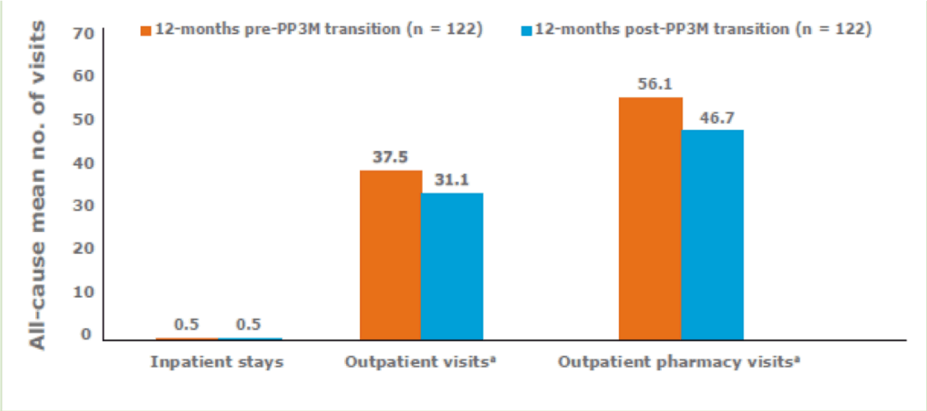
Key: CI=confidence interval; OR=odds ratio; PP3M=paliperidone palmitate 3-month injection; DSM-V=Diagnostic and Statistical Manual of Mental Disorders – 5th Edition.

4.3. Fewer Hospitalizations and Better Health Outcomes

Risk of hospitalization has been shown to be lower with LATs compared to corresponding oral treatments (Tiihonen 2017). Results of a recent study (Garcia-Portilla 2020) evaluating the efficacy and safety of converting patients with schizophrenia from PP1M to PP3M, indicate the patients achieved and maintained symptom stability. Personal and social functioning were also maintained with some incremental continuous improvements. High proportions of both patients and physicians were satisfied with PP3M at the end of the study, which was also reflected in the very high study completion rate of (95.4%). In addition, a decrease in the number of psychiatric hospitalizations was observed over the length of the study period, and a reduction in caregiver burden.

Pre- vs. Post-PP3M Outcomes among Veterans: A study by Patel (2014a; 2014b) aimed to compare treatment patterns, HRU, and costs during the 12 months before and after transition to PP3M per on-label criteria in veterans diagnosed with schizophrenia using the VHA database. There was a substantial decrease observed in concomitant medication use, including antidepressants, among veterans after PP3M transition. Veterans had a significantly lower number of all-cause outpatient visits post-PP3M transition (31.1) vs. pre-PP3M transition (37.5, p <0.0001), and outpatient pharmacy visits (46.7 vs. 56.1, p <0.0001) during the 12 months post-PP3M transition compared with the pre-PP3M period (Figure 12). The overall study findings indicated that transitioning from PP1M to PP3M may improve clinical outcomes among VHA patients diagnosed with schizophrenia.

Figure 12: Comparison of All-cause Healthcare Resource Utilization During the 12 Months Pre- and Post-PP3M Transition Among Veterans Treated with PP1M



[a]Significant at $P < 0.05$.
PP1M, once-monthly paliperidone palmitate; PP3M, once-every-3-months paliperidone palmitate.

Adapted from Patel (2019a), Figure 2.

PP3M vs. PP1M among Veterans: Another retrospective real-world evidence analysis using the VHA database examined treatment patterns and HRUs in veterans with schizophrenia who transitioned to PP3M versus those who remained on PP1M treatment, after at least 4 months of continuous PP1M treatment. Veterans who transitioned to PP3M experienced a significantly shorter all-cause inpatient length of stay (2.5 vs. 14.1 days, p=0.0176), and a shorter schizophrenia-related inpatient length of stay (1.4 vs. 11.3, p=0.0362) per patient per year, compared to those

who remained on PP1M (unpublished data). PP3M vs. PP1M among Medicaid Beneficiaries: In a study by Lin (2020) using 4-state Medicaid data, patients who transitioned from PP1M to PP3M were compared with those who remained on PP1M, after at least 4 months of continuous PP1M treatment. Patients who transitioned to PP3M had lower likelihood of having any inpatient admission (OR=0.67, p=0.011) and lower likelihood of having any day with home care services (OR=0.68, p=0.012), compared to those who remained on PP1M. These findings demonstrated that among patients with schizophrenia who had been adequately treated with PP1M, a transition to PP3M was associated with lower rates of HRU, in addition to improved medication adherence and persistence.

4.4. Benefits of Longer Acting Injectables in Public Health Emergencies Such as COVID-19

Longer acting LAIs like PP6M can reduce the need for patients with schizophrenia to come into the clinic biweekly or monthly, which can be advantageous during local outbreaks as in the case of COVID-19. The once-every-3-months dosing frequency of PP3M could help ensure medication continuity in these patients.

A clinical guideline was recently issued by Serious Mental Illness (SMI) Adviser (an initiative from the American Psychiatric Association [APA] and the Substance Abuse and Mental Health Services Administration [SAMHSA]), which suggested that longer-acting formulations of antipsychotics may be helpful to limit the possibility of exposure to coronavirus (SMIA 2020).

In addition, patients who are older or who have preexisting conditions should minimize their exposure to the community, including coming to a clinic. A particular area of concern is people in self-quarantine or isolation at their home, group home, or facility in which they live, due to COVID-19. Under these circumstances, it is recommended that patients should have as few direct interpersonal contact as medically prudent, some solutions proposed to reduce the number of visits are (SMIA 2020):

- Move patients from Risperdal CONSTA (dosed every 2 weeks) to INVEGA SUSTENNA (PP1M) or INVEGA TRINZA (PP3M).
- Move INVEGA SUSTENNA (PP1M) patients to INVEGA TRINZA (PP3M).

An article by Ifteni (2020) discusses the challenges posed by restrictions or limitations of prescription and administration of LAIs caused by the COVID-19 pandemic. The authors advocate for improved access to long-acting antipsychotics in the treatment of patients who have been on LAIs for years, in the prevention of relapses in patients with previous nonadherence and for young patients in the early stages of schizophrenia, even in difficult times. Individuals with schizophrenia have an increased risk of premature mortality.

Long-acting injectables are usually reserved for patients with chronic schizophrenia who are at high-risk of noncompliance. Increasing data suggest that long-acting risperidone is associated with good efficacy and tolerability leading to high acceptance, and treatment continuation rates are higher than with oral antipsychotics. The benefits of an atypical antipsychotic coupled with the assurance of medication delivery in the form of a long-acting injection imply that these novel

formulations should be considered in first-episode patients, for whom optimal outcome is frequently compromised by early treatment discontinuation and poor adherence as they are characterized by poor persistence with treatment leading to high relapse rates within 5 years of recovery from their first episode (Chue 2007). Evidence therefore suggests that LAIs can be safely and effectively used in early stages of the illness, and that they may be associated with better outcomes than with oral medications (Emsley 2013).

Co-occurring medical conditions, such as heart disease, liver disease, and diabetes, contribute to the higher premature mortality rate among individuals with schizophrenia (Olfson 2015). In another guidance document, the American Psychiatric Association's Committee on Psychiatric Dimensions of Disaster and COVID-19 encourages hospitals and other facilities to include the ongoing use of LAIs for patients with high-risk chronic illness as a necessary procedure (NCPA 2020).

5. SUMMARY OF REGULATORY STATUS, MARKET AVAILABILITY, AND COST-EFFECTIVENESS OF THE MEDICINES

PP3M are currently approved in 91 countries, including the US, EU and Japan, Table 5.

Table 5: Countries and Regions Where PP3M is Approved

Asia Pacific	EMEA			Latin America	North America
Australia	Albania	Iceland	Poland	Nicaragua	Canada
Brunei Darussalam	Algeria	Ireland	Portugal	Argentina	United States
China	Austria	Israel	Qatar	Aruba	
Hong Kong	Azerbaijan	Italy	Romania	Brazil	
Indonesia	Bahrain	Jordan	Russian Federation	Chile	
Japan	Belarus	Kazakhstan	Rwanda	Colombia	
Korea	Belgium	Kuwait	Saudi Arabia	Costa Rica	
Macao	Bosnia and Herzegovin	Latvia	Serbia	Curacao	
Malaysia	Bulgaria	Lebanon	Slovakia	Dominican Republic	
New Zealand	Croatia	Liechtenstein	Slovenia	Ecuador	
Philippines	Cyprus	Lithuania	South Africa	Guatemala	
Singapore	Czech Republic	Luxembourg	Spain	Honduras	
Taiwan	Denmark	Macedonia	Sudan	Jamaica	
Thailand	Egypt	Malta	Sweden	Peru	
	Estonia	Moldova	Switzerland		
	Finland	Montenegro	Turkey		
	France	Morocco	Ukraine		
	Germany	Namibia	United Arab Emirates		
	Ghana	Netherlands	United Kingdom		
	Greece	Norway			
	Hungary	Oman			

Key: EMEA=Europe, Middle East and Africa, PP3M=paliperidone palmitate 3-month product.

From its launch where PP3M is marketed in 2015 up to the data cutoff date of 30 June 2020, over 1.3 million treatment courses of PP3M have been dispensed globally.

Paliperidone palmitate 3-month injection demonstrates economic benefits versus comparators in the treatment of schizophrenia. Paliperidone palmitate 3-month injection has been shown to decrease the likelihood of hospitalization and to lower costs. Hospitalization rates and costs of PP3M are similar to PP1M. The PP1M/PP3M treatment system has been demonstrated to be cost effective for the maintenance treatment of schizophrenia across a number of healthcare systems. Paliperidone palmitate 3-month injection has the potential for important cost offsets

across healthcare settings. At a minimum, PP3M should confer cost savings related to administration fees; PP3M may also reduce costs associated with relapse management.

6. SUMMARY AND CONCLUSIONS

If added to the WHO Essential Medicines List, PP3M has the potential to improve serious outcomes associated with poor medication adherence in adult patients with schizophrenia. The characteristics of the PP3M product make it a useful and proven treatment option for patients at the highest risk of relapse due to treatment nonadherence, such as:

- Patients with recent-onset schizophrenia, who are more likely nonadherent to antipsychotic medications and who may benefit more from consistent antipsychotic coverage with a 3-month LAI agent to help prevent relapse, which is unfavorable due to the additional cost and burden both for the patients and caregivers. In addition, relapse can negatively impact medical, social, and potentially, functional outcomes.
- Patients who live in rural or remote areas who may receive services through telepsychiatry but have infrequent contact with healthcare professionals who can provide injections 4 times a year on a regular basis.
- Homeless patients who often have only infrequent contact with outreach workers and are particularly likely to be nonadherent due to cognitive limitations, substance abuse, lack of insight, and poor psychosocial support.
- Patients with schizophrenia who are at risk or have a history of violence, since sustained treatment with antipsychotic medication is associated with a reduction of violence and recidivism.
- Patients with schizophrenia and a history of suicide attempts due to nonadherence or otherwise at an increased risk of suicide, since continued treatment with a 3-month LAI may reduce the risk of nonadherence.
- Fewer injections are associated with less stigma, which is a barrier in patients with severe mental illness.
- During times of a global pandemic such as COVID-19, to minimize contact with hospital systems and reduce transmission of communicable disease.

Data from the Phase 3 study R092670-PSY-3011 demonstrate that PP3M is as effective as PP1M for the prevention of relapse in participants with schizophrenia. Furthermore, real-world evidence indicates that longer-acting LAIs with reduced frequency of injections improve adherence in patients with schizophrenia, leading to better management and prognosis of this chronic mental illness.

Disadvantaged patients such as those who have limited access to psychiatric care, those who cannot coordinate frequent travel, and those who are homeless or from underserved populations will benefit the most from the inclusion of PP3M to the WHO model list of essential medicines for the maintenance treatment of schizophrenia in adults.

In terms of safety, Studies PSY-3011 and PSY-3012 indicate that the PP3M formulation is safe in adults with schizophrenia treated for periods of up to 12 to 15 months. In addition, data previously

obtained during studies to evaluate the safety of PP1M in patients with schizophrenia did not identify any safety concerns during long-term therapy.

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