

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207946Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 207-946

**Supplement #:** Original

**Drug Name:** INVEGA TRINZA® (paliperidone palmitate extended-release injectable suspension)

**Indication(s):** Schizophrenia in adults

**Applicant:** Janssen Research & Development, LLC

**Date(s):** Receipt Date: Nov 18, 2014  
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**Review Priority:** Priority

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## **1 EXECUTIVE SUMMARY**

The sponsor has demonstrated a favorable effect of 3-month formulation of paliperidone palmitate extended-release injectable suspension (INVEGA TRINZA®) compared with placebo in delaying the time to first occurrence of relapse of the symptoms of schizophrenia, in adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months.

## 2 INTRODUCTION

### 2.1 Overview

Janssen has developed 3 formulations of paliperidone: an oral extended-release formulation (INVEGA® Extended Release [ER] tablets), and 2 long-acting injectable (LAI) formulations (paliperidone palmitate, 1-month [PP1M] and 3-month [PP3M]). The oral formulation of paliperidone (INVEGA®) tablets has been approved by the FDA for the acute treatment of schizophrenia in December 2006 (NDA 21999), for the maintenance treatment of schizophrenia in April 2007, for the treatment of schizoaffective disorder in July 2009, and for the treatment of schizophrenia in adolescents aged 12 to 17 years in April 2011. The PP1M formulation (INVEGA SUSTENNA®) was approved by the FDA for the acute and maintenance treatment of schizophrenia in adults in July 2009 (NDA 22264), and for the treatment of schizoaffective disorder in November 2014.

The new 3-month formulation of paliperidone palmitate extended-release injectable suspension, i.e. PP3M (INVEGA TRINZA®), is currently submitted for the (b) (4) treatment (b) (4) in adult subjects with schizophrenia who have been adequately treated with PP1M for at least four months (17 weeks). It includes a phase III, multicenter, double-blind, placebo-controlled randomized withdrawal (relapse prevention) study, R092670PSY3012. The original protocol was reviewed under IND 76952.

An Erratum was submitted under SN0014 (SDN15) on Mar 25, 2015, to correct the following errors in the original Clinical Study Report (CSR):

1. Subject Disposition over time during the open-label and double-blind phases (mislabeling of frequency categories)
2. Primary Efficacy Analysis-Time to Relapse (double counting of certain events)
3. The Adverse Events (AE) of influenza that was not entered in the database.

Overall, the conclusions as stated in the CSR remain valid after correction of these errata.

**Table: List of all studies included in analysis**

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
<i>R092670PSY3012</i>	<i>Phase 3</i>	<i>Variable duration</i>	-	<i>145 subjects were in the Placebo group and 160 in the PP3M group</i>	<i>18 to 70 years of age (inclusive) with a diagnosis of schizophrenia.</i>

The primary objective of this study was to evaluate the efficacy of PP3M compared with placebo in delaying the time to first occurrence of relapse of the symptoms of schizophrenia.

## 2.2 Data Sources

The following data sources were considered in this review:

a) Applicant's study report

(\\CDSESUB1\evsprod\NDA207946\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5351-stud-rep-contr\r092670psy3012)

b) Data sets

(\\CDSESUB1\evsprod\NDA207946\0000\m5\datasets\r092670psy3012\analysis\adam\datasets)  
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c) Software code

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d) Response to FDA information request

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## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

The sponsor has complied with our requests for providing necessary datasets, definition files, and statistical programs for their analyses. This reviewer found the quality of their submissions acceptable and was able to replicate the primary results from the sponsor's CSR.

### 3.2 Evaluation of Efficacy

#### 3.2.1 Study Design and Endpoints

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study, consisting of 4 phases: a Screening Phase (up to 3 weeks); a 17-week, flexible dose, open-label (OL) Transition Phase; a 12-week, fixed dose, OL Maintenance Phase; and a randomized, double-blind, fixed dose, placebo-controlled relapse prevention phase (referred to as the DB Phase).

Study centers are scattered in Colombia (5 sites), Malaysia (3 sites), Mexico (5 sites), Romania (5 sites), South Korea (3 sites), Turkey (2 sites), United States (14 sites) and Ukraine (27 sites).

Screening Phase (up to 3 weeks): The Screening Phase was used for screening, washout, and tolerability testing for subjects as either inpatients or outpatients.

Transition Phase (17-week): A full injection cycle must have elapsed between the time of the last depot injection and the administration of the first dose of PP1M on Day 8, for those switching from other LAI antipsychotics and those who were already on PP1M prior to study entry. All other subjects received the first injection of PP1M (150 milligram equivalents [mg eq.]) on Day 1 and the second injection of PP1M (100 mg eq.) on Day 8 of the study. Injections on Day 36 and on Day 64 were flexibly dosed (50, 75, 100, or 150 mg eq.). On Day 92, subjects received

the dose of PP1M that was administered on Day 64. Those subjects who completed the Transition Phase and who met the prospectively defined criteria entered the Maintenance Phase.

**Maintenance Phase (12-week):** Starting on Day 120/Week 17), subjects received a single injection of PP3M (using a 3.5-fold multiple of the PP1M dose received on Day 92 during the Transition Phase). Subjects who met specific stabilization criteria entered the DB Phase at Week 29.

**Table 1: Conversion between PP1M Dose and PP3M Dose Using 3.5-Fold Multiple**

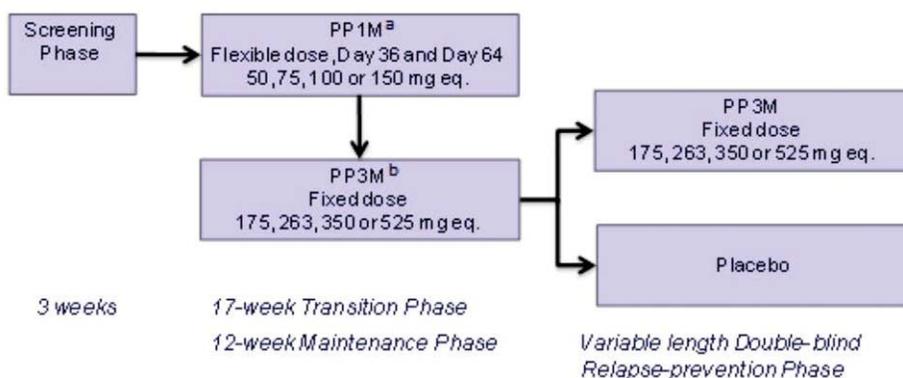
PP1M Dose (mg paliperidone palmitate)	PP1M Dose (mg eq. paliperidone)	PP3M Dose (mg paliperidone palmitate)	PP3M Dose (mg eq. paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

Source: table 3 on page 40 of CSR.

Note: mg eq.=milligram equivalents.

**Double-blind Phase (variable duration):** At the start of the DB Phase (Day 204/Week 29), subjects were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M, same as the dose they received in the maintenance phase, or placebo. The randomization was balanced using permuted blocks across the 2 treatment groups and stratified by study center to ensure balance of treatment allocation within a center. Subjects assigned to PP3M received the same dose administered on Day 120 of the Maintenance Phase. Subjects remained in the DB Phase until they experienced a relapse event (based on prospectively defined criteria), they met one or more of the study discontinuation / withdrawal criteria, or the study was terminated by the sponsor based on positive results of the interim analysis or because 70 relapse events had occurred when interim analysis was not positive.

**Figure 1: Flowchart**



Source: figure 1 on page 30 of CSR.

Note:

a. PP1M doses: 50, 75, 100, or 150 mg eq. (ie, 78, 117, 156, or 234 mg). All subjects (except those continuing from prior PP1M or switching from other long-acting injectable antipsychotics) 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. On Day 92 (not shown in this figure), subjects received the same dose of PP1M that was administered on Day 64.

b. PP3M doses: 175, 263, 350, or 525 mg eq. (ie, 273, 410, 546, or 819 mg).

**Table 2: Dosing Administration Schedule**

Visit	Transition Phase					Maintenance Phase			Double-blind Phase			
	2	3	4	5	6	8	9	10	11	12	13	Every 12 weeks
Day	1(a)	8(a)	36	64	92	120	148	176	204	232	260	
PP1M Dose	150 mg eq.	100 mg eq.	50-150 mg eq.	50-150 mg eq.	50-150 mg eq.	--	--	--	--	--	--	--
Muscle	D	D	D or G	D or G	D or G	D or G			D or G			D or G
Flexible or Fixed PP3M/ Placebo Dose	Fixed	Fixed	Flexible	Flexible	Fixed (b)	Fixed (c)	--	--	Fixed (c)	--	--	Fixed (c)
	--	--	--	--	--	X	--	--	X	--	--	X

Source: table 2 on page 39 of CSR.

Note: D=deltoid muscle; G=gluteal muscle.

(a) Refer to Table 1 and Table 2 in the protocol (Appendix 1 of CSR), respectively, for subjects who were stable on PP1M at study entry and for subjects who were switching from other depot antipsychotics.

(b) Dose on this visit should be the same as given on Visit 5 (Day 64).

(c) The dose of PP3M given was a 3.5-fold multiple of the PP1M dose given on Visit 6 (Day 92).

The primary efficacy end point for this study was the time between subject randomization into the DB Phase and the first documentation of a relapse event, based on 1 or more of the following predetermined relapse criteria:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or
- For PANSS
  - The subject had an increase of 25% in PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, or
  - The subject had a 10-point increase in the PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was ≤40, or
  - For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness):
    - The subject had a score of ≥5 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was ≤3 at randomization, or
    - The subject had a score of ≥6 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was 4 at randomization.
  - The subject inflicted deliberate self-injury or exhibited violent behavior resulting in suicide, clinically significant injury to him/herself or another person, or significant property damage, or
  - The subject had suicidal or homicidal ideation and aggressive behavior that was clinically significant (in frequency and severity) in the investigator's judgment.

Subjects who met at least 1 of the criteria for relapse while on Double-blind treatment at the time of study completion for the primary analysis were considered to have had a relapse event. All other subjects without a relapse at the end of study (end of DB Phase) were considered censored. The date of relapse was the date of the first assessment for symptoms of relapse.

### **3.2.2 Statistical Methodologies**

#### **3.2.2.1 Primary Analysis for Primary Endpoint**

The primary analysis for time to relapse was carried out by log-rank test on the intent-to-treat (ITT) population, defined as all subjects who receive at least 1 dose of Double-blind medication during the DB Phase.

There was one interim efficacy analysis for superiority. See details of the interim analysis in section 3.2.2.2.

#### **3.2.2.2 Interim Analysis**

An Independent Data Monitoring Committee (IDMC) was established to review the blinded efficacy and safety data on an ongoing basis. In addition, the IDMC was to meet and review the results of the interim analysis and provide recommendation to the sponsor on whether to continue the study or to terminate the study.

An interim analysis was to be conducted by the IDMC after at least 42 relapse events had occurred. If the interim analysis using 2-sided log-rank test was to show a statistically significant difference (at the nominal significance level of 0.0101) between PP3M and placebo in the time to relapse, the study was to be terminated. The interim analysis would then be considered as the primary analysis and the final analysis, performed after study termination, would be reported as confirmative results. If interim analysis failed to show a significant difference, the study was to continue until 70 relapse events had been obtained, and the final analysis, now considered primary analysis was to be performed at the nominal significance level of 0.0464.

#### **3.2.2.3 Sample Size Determination**

It was assumed that the 12-month relapse rates for PP3M and placebo would be 20% and 40%, respectively, resulting in a relative risk of 0.44. Approximately, 196 subjects were expected to be randomized in the DB Phase in a 1:1 ratio to either PP3M or placebo in order to obtain 70 relapse events to show that PP3M was significantly different from placebo at the 2-sided significance level of 0.05, with 90% power to detect a relative risk of 0.44 (ie, hazard rate of PP3M/ hazard rate of Placebo=0.44).

A 2-stage group sequential design with 1 interim analysis was to be implemented to allow for early stopping if there was significant evidence of efficacy based upon the interim analysis after 60% (ie, 42 events) of the projected relapse events had occurred. The O'Brien-Fleming boundary

(corresponding to the Wang and Tsiatis power boundary with shape parameter 0) was to be used for sequential monitoring.

It was assumed that at least 50% of subjects who entered the Transition Phase would discontinue the study or not meet the criteria for randomization in the DB Phase. To meet the expected number of 196 subjects (98 per treatment group) to be randomized in the DB Phase, a total of at least 392 subjects were expected to be enrolled. The total number of subjects enrolled would depend on the time that it took to obtain 70 relapse events. Blinded surveillance of the total number of events in the DB Phase was to be performed during the study to assess the appropriateness of the 50% dropout assumption and the time necessary to obtain 70 relapse events. The total number of subjects enrolled could be increased up to approximately 500.

Overall, 506 subjects with schizophrenia were enrolled into and dosed in the Open-label Phase and 305 subjects with schizophrenia were randomized into in the DB Phase.

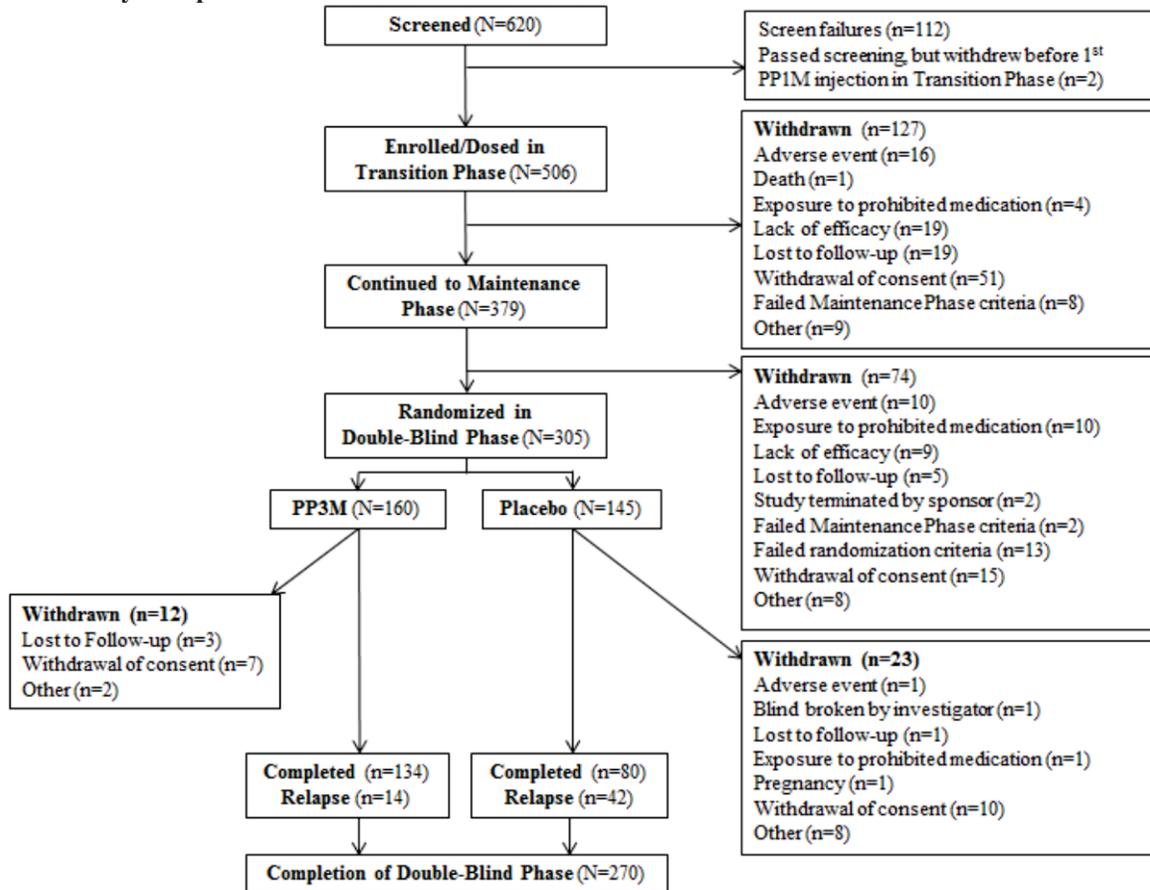
### **3.2.3 Patient Disposition, Demographic and Baseline Characteristics**

#### **3.2.3.1 Patient Disposition**

The ITT (DB) analysis set for the interim analysis included all subjects who qualified for inclusion (N=283) at the time of the interim analysis data cutoff (January 24, 2014). 135 subjects were randomized to Placebo and 148 subjects to PP3M. Of the 42 Interim ITT (DB) subjects who experienced a relapse event, 31 subjects (23.0%) were in the Placebo group and 11 subjects (7.4%) were in PP3M group.

The ITT (DB) analysis set for the final analysis included all subjects enrolled in the DB Phase (N=305) up to study completion (09 April 2014). 145 subjects were in the Placebo group and 160 subjects were in the PP3M group. Of the 270 subjects (89%) who completed the DB Phase, 56 subjects (18%) experienced a relapse. A higher percentage of subjects in the Placebo group than the PP3M experienced a relapse during the DB Phase, 42 out of 145 subjects (29.0%) in the Placebo group vs. 14 out of 160 subjects (8.8%) subjects in PP3M group. 35 subjects (11%) discontinued from the DB Phase. A higher percentage of subjects in the PP3M group than the Placebo group (93% vs. 84%) completed the study during the DB Phase.

Figure 2: Study Completion and Withdrawal Information



Source: figure 2 on page 67 of CSR.

Table 3: Completion/Withdrawal Information During the Double-Blind Phase

	Placebo (N=145)	PP3M (N=160)	Total (N=305)
<b>Subject Completed Trial</b>			
<b>Reason For Withdrawal/Termination</b>	n (%)	n (%)	n (%)
<b>Completed</b>	122 ( 84)	148 ( 93)	270 ( 89)
Completed DB due to study termination	80 ( 55)	134 ( 84)	214 ( 70)
Relapse during DB phase	42 ( 29)	14 ( 9)	56 ( 18)
<b>Withdrawn</b>	23 ( 16)	12 ( 8)	35 ( 11)
Adverse event	1 ( 1)	0	1 (<1)
Blind broken by investigator	1 ( 1)	0	1 (<1)
Lost to follow-up	1 ( 1)	3 ( 2)	4 ( 1)
Exposure to prohibited medications	1 ( 1)	0	1 (<1)
Pregnancy	1 ( 1)	0	1 (<1)
Withdrawal of consent	10 ( 7)	7 ( 4)	17 ( 6)
Other	8 ( 6)	2 ( 1)	10 ( 3)

Source: table 11 on page 69 of CSR.

### 3.2.3.2 Patient Demographic

Demographic characteristics for the ITT (OL) and ITT (DB) analysis sets are presented in Table 4. At DB baseline, more male (75%) than female (25%) subjects were enrolled in the study. A majority of subjects were white (64%), with a mean (SD) age of 37.8 (11.01) years (range: 18 to 64 years). 137 subjects (45%) were studied in Ukraine, while 58 subjects (19%) were studied in the US. The demographic data was similar between the Placebo and PP3M groups at OL baseline.

**Table 4: Demographic Characteristics for all Analysis Sets**

	ITT(OL)		ITT(DB)		Total Intent-to-Treat (DB) (N=305)
	Pali Palmitate (N=506)	Not Randomized to Double-Blind (N=201)	Placebo (N=145)	PP3M (N=160)	
<b>Age (yrs)</b>					
N	506	201	145	160	305
Category, n (%)					
18-25	69 ( 14)	21 ( 10)	20 ( 14)	28 ( 18)	48 ( 16)
26-50	356 ( 70)	145 ( 72)	103 ( 71)	108 ( 68)	211 ( 69)
51-65	79 ( 16)	33 ( 16)	22 ( 15)	24 ( 15)	46 ( 15)
>65	2 (<1)	2 ( 1)	0	0	0
Mean (SD)	38.4 (11.15)	39.5 (11.30)	38.5 (11.16)	37.1 (10.87)	37.8 (11.01)
Median	37.0	39.0	37.0	35.0	37.0
Range	(18;68)	(19;68)	(18;64)	(18;61)	(18;64)
<b>Sex, n (%)</b>					
N	506	201	145	160	305
Male	379 ( 75)	151 ( 75)	110 ( 76)	118 ( 74)	228 ( 75)
Female	127 ( 25)	50 ( 25)	35 ( 24)	42 ( 26)	77 ( 25)
<b>Race, n (%)</b>					
N	506	201	145	160	305
White	297 ( 59)	102 ( 51)	91 ( 63)	104 ( 65)	195 ( 64)
Black or African American	110 ( 22)	65 ( 32)	21 ( 14)	24 ( 15)	45 ( 15)
Asian	41 ( 8)	12 ( 6)	15 ( 10)	14 ( 9)	29 ( 10)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	0	0	0
Other	55 ( 11)	20 ( 10)	18 ( 12)	17 ( 11)	35 ( 11)
Multiple	2 (<1)	1 (<1)	0	1 ( 1)	1 (<1)
<b>Ethnicity, n (%)</b>					
N	506	201	145	160	305
Hispanic or Latino	92 ( 18)	38 ( 19)	26 ( 18)	28 ( 18)	54 ( 18)
Not Hispanic or Latino	410 ( 81)	160 ( 80)	118 ( 81)	132 ( 83)	250 ( 82)
Not reported	2 (<1)	1 (<1)	1 ( 1)	0	1 (<1)
Unknown	2 (<1)	2 ( 1)	0	0	0
<b>Country, n (%)</b>					
N	506	201	145	160	305
Colombia	41 ( 8)	16 ( 8)	12 ( 8)	13 ( 8)	25 ( 8)
Malaysia	29 ( 6)	6 ( 3)	11 ( 8)	12 ( 8)	23 ( 8)
Mexico	28 ( 6)	10 ( 5)	10 ( 7)	8 ( 5)	18 ( 6)
Romania	42 ( 8)	15 ( 7)	14 ( 10)	13 ( 8)	27 ( 9)
South Korea	10 ( 2)	4 ( 2)	4 ( 3)	2 ( 1)	6 ( 2)
Turkey	17 ( 3)	6 ( 3)	5 ( 3)	6 ( 4)	11 ( 4)
Ukraine	181 ( 36)	44 ( 22)	63 ( 43)	74 ( 46)	137 ( 45)
United States	158 ( 31)	100 ( 50)	26 ( 18)	32 ( 20)	58 ( 19)

Source: table 12 on page 70 of CSR.

### 3.2.3.3 Patient Dose Levels

152 (50%) of all 305 DB subjects, consisting of 74 subjects (51%) in the placebo group and 78 (49%) in the PP3M group, received the maintenance dose at 350 mg eq. in the DB phase, 113 (37%) received 525 mg eq., 32 (10%) received 263 mg eq. and 8 (3%) received 175 mg eq..

**Figure 3: Dose Level Information During the Double-Blind Phase**

Maintenance dose (mg eq.)	Placebo (N=145) n(%)	PP3M (N=160) n(%)	Total (N=305) n(%)
175	2 (1)	6 (4)	8 (3)
263	17 (12)	15 (9)	32 (10)
350	74 (51)	78 (49)	152 (50)
525	52 (36)	61 (38)	113 (37)

Source: reviewer's table.

### 3.2.4 Results and Conclusions

#### 3.2.5 Primary Analysis (Interim Analysis) of Primary Endpoint

Since the study was stopped in accordance with the recommendation of the IDMD, because of the statistical significance shown in favor of PP3M over placebo by the pre-planned interim analysis of time to relapse, the interim analysis was considered as the primary analysis, and the final analysis of data was considered confirmatory.

In the DB Phase, PP3M was superior to placebo in delaying relapse of symptoms of schizophrenia in subjects with  $p < 0.001$  based on the log-rank test compared to the threshold to stop the study early for efficacy at  $p < 0.0101$ .

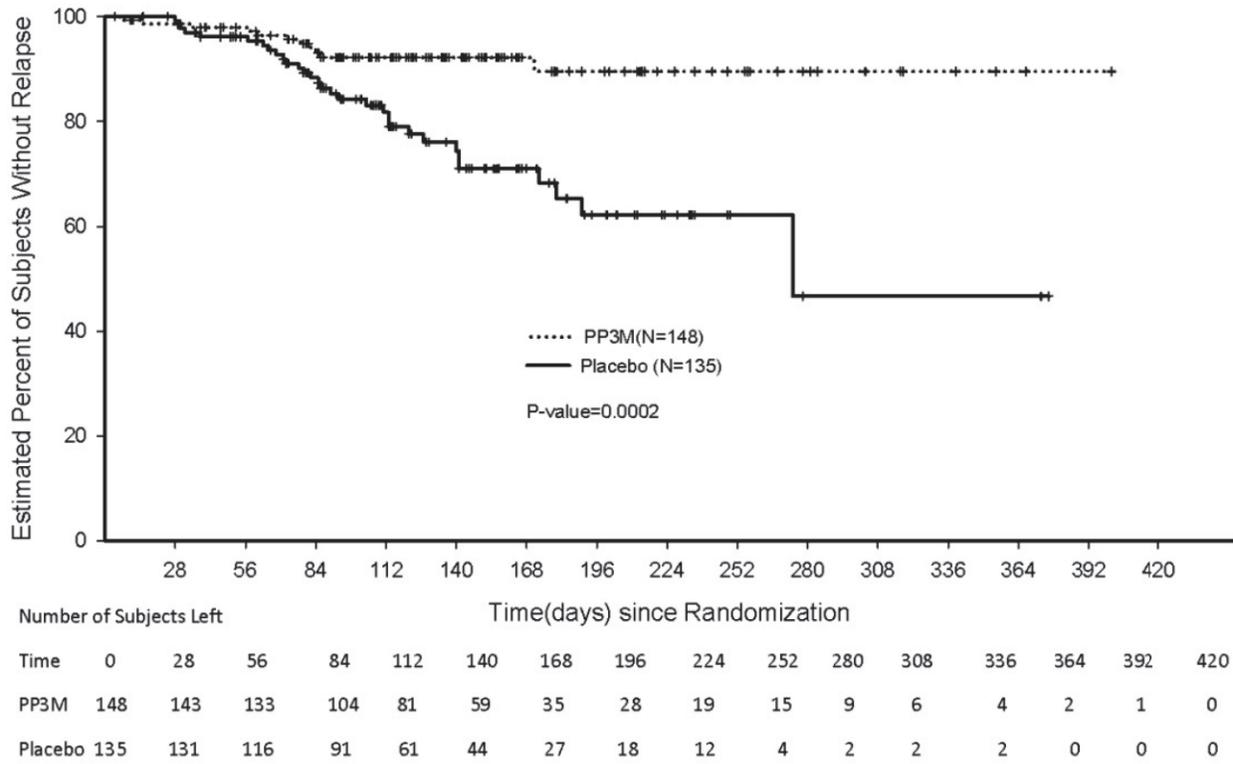
*Reviewer's note: the p-value is 0.0002 to be exact.*

**Table 5: Time to Relapse During the DB Phase and Number (%) of Subjects that Remained Relapse Free - Interim Analysis**

Descriptive (a)	Placebo	PP3M	Total	Overall		
				Chisq	DF	P-value(b)
<b>Time to Relapse</b>						
Number of Assessed	135	148	283			
Number of Censored (%)	104 (77.0)	137 (92.6)	241 (85.2)			
Number of Events (%)	31 (23.0)	11 (7.4)	42 (14.8)			
25% Quantile (95% CI)	140.0 ( 104.0; 190.0)	( ; )	274.0 ( 171.0; )			
Median (95% CI)	274.0 ( 190.0; )	( ; )	( ; )			
75% Quantile (95% CI)	( 274.0; )	( ; )	( ; )			
Statistical Test				14.072	1	<0.001

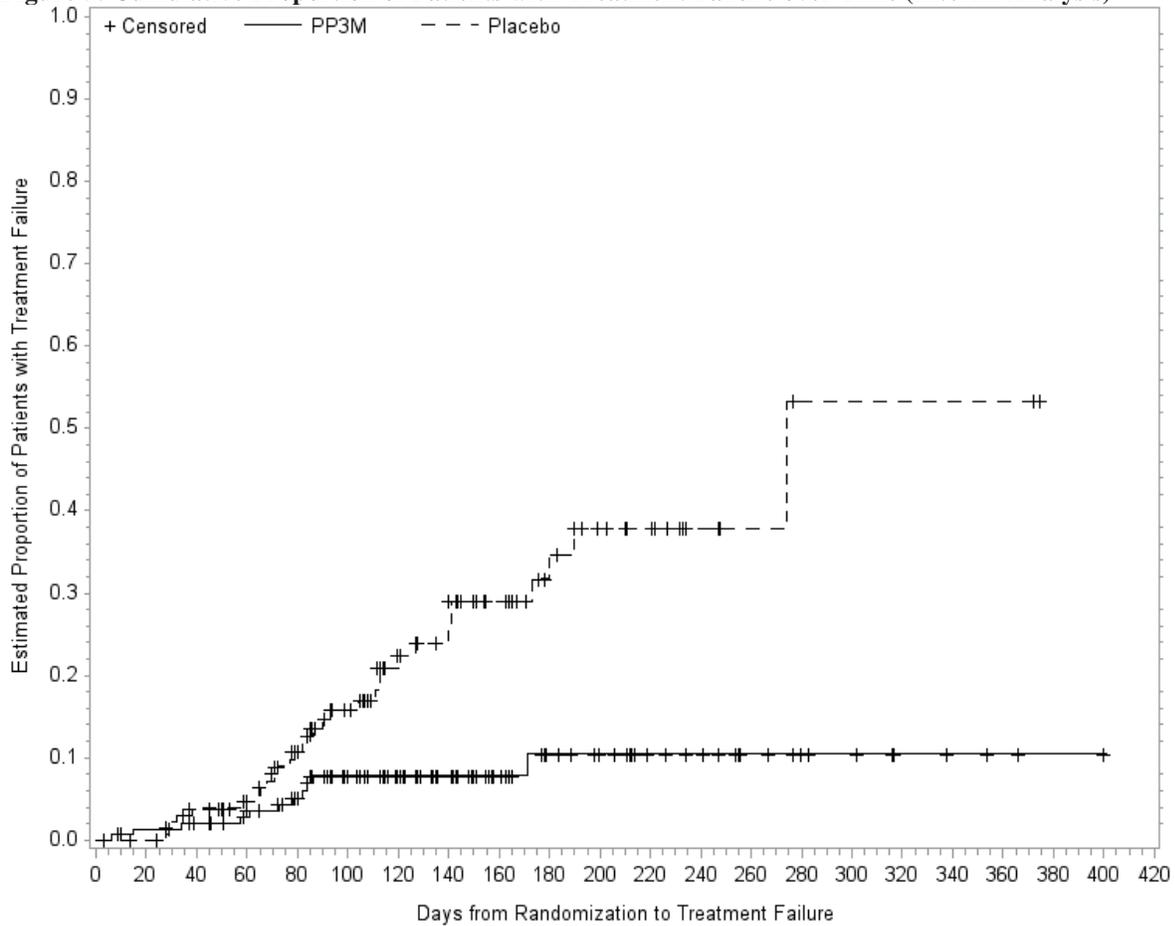
Source: table 29 on page 88 of CSR.

**Figure 4: Kaplan-Meier Plot of Time to Relapse During the DB Phase - Interim Analysis**



Source: figure 4 on page 89 of CSR.

**Figure 5: Cumulative Proportion of Patients with Treatment Failure over Time (Interim Analysis)**



Source: reviewer's plot.

The most common reasons for relapses across both treatment groups in the interim analysis were an increase of  $\geq 25\%$  in the PANSS total score value (25 subjects [19%] in the Placebo group vs. 8 subjects [5%] in the PP3M group) and psychiatric hospitalizations (6 subjects [4%] in the Placebo group vs. 2 subjects [1%] in the PP3M group).

Table 6: Frequency Distribution of Relapse Types and Reasons During the DB Phase - Interim Analysis

Type Of Recurrence	Placebo (N=135)	PP3M (N=148)	Total (N=283)
Reason	n (%)	n (%)	n (%)
<b>Total Subjects with Relapse</b>	<b>31 (23)</b>	<b>11 (7)</b>	<b>42 (15)</b>
<b>Psychiatric hospitalization</b>	<b>6 (4)</b>	<b>2 (1)</b>	<b>8 (3)</b>
Subject had psychiatric hospitalization	6 (4)	2 (1)	8 (3)
<b>PANSS total score</b>	<b>26 (19)</b>	<b>8 (5)</b>	<b>34 (12)</b>
Increase of ≥25% in total PANSS score	25 (19)	8 (5)	33 (12)
10 point increase in total PANSS score	1 (1)	0	1 (<1)
<b>Suicidal or homicidal ideation</b>	<b>1 (1)</b>	<b>2 (1)</b>	<b>3 (1)</b>
Suicide attempt	0	1 (1)	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)
Homicidal ideation	0	1 (1)	1 (<1)
<b>PANSS items (P1, P2, P3, P6, P7, G8)</b>	<b>5 (4)</b>	<b>1 (1)</b>	<b>6 (2)</b>
A score of ≥5 after randomization	5 (4)	1 (1)	6 (2)

Source: based on table 30 on page 7 of sponsor's erratum dated Mar 25, 2015 (SN0014 [SDN15]).

Note: Percentages calculated with the number of subjects in each group as denominator.

### 3.2.6 Final Analysis of Primary Endpoint

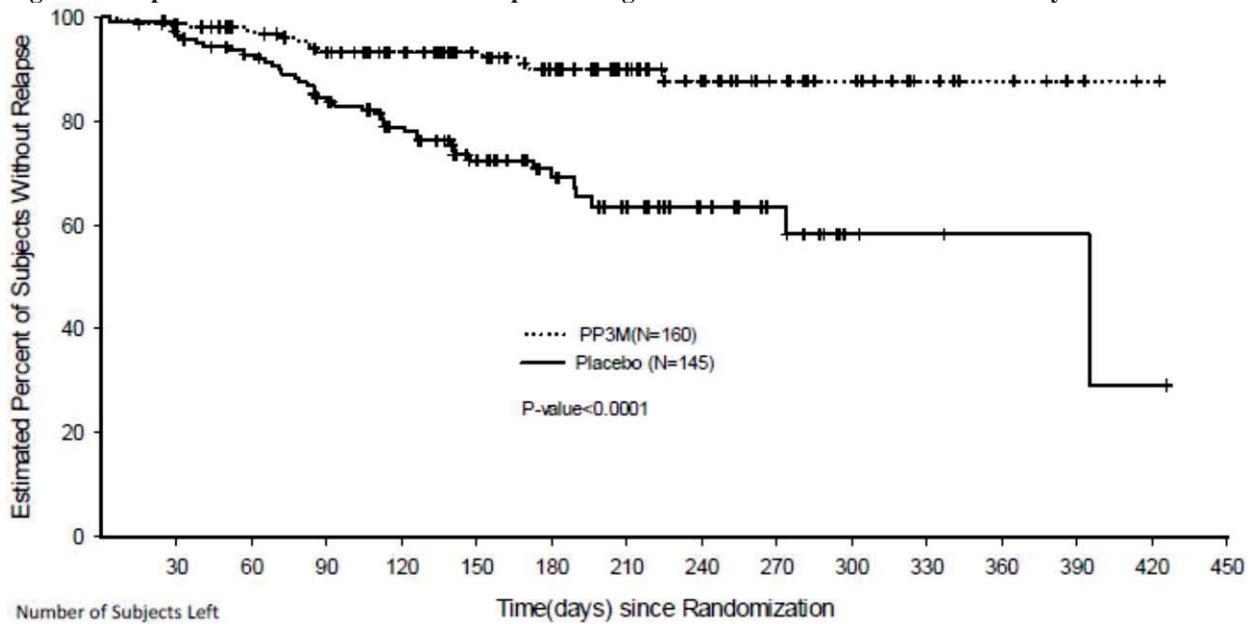
The final analysis of the relapse data confirmed the findings of the interim analysis. There was a statistically significant difference in the time to relapse with a longer time to relapse in subjects assigned to PP3M at  $p < 0.001$  based on the log-rank test, consistent with that at the interim analysis of  $p < 0.001$ .

Table 7: Time to Relapse During the Double-Blind Phase and Number (%) of Subjects That Remained Relapse Free - Final Analysis

Descriptive (a)	Placebo	PP3M	Total	Overall		
				Chisq	DF	P-value(b)
<b>Time to Relapse</b>						
Number of Assessed	145	160	305			
Number of Censored (%)	103 (71.0)	146 (91.3)	249 (81.6)			
Number of Events (%)	42 (29.0)	14 (8.8)	56 (18.4)			
25% Quantile (95% CI)	141.0 ( 104.0; 190.0)	( ; )	274.0 ( 180.0; )			
Median (95% CI)	395.0 ( 274.0; )	( ; )	( 395.0; )			
75% Quantile (95% CI)	( 395.0; )	( ; )	( ; )			
Statistical Test				21.646	1	<0.001

Source: table 31 on page 91 of CSR.

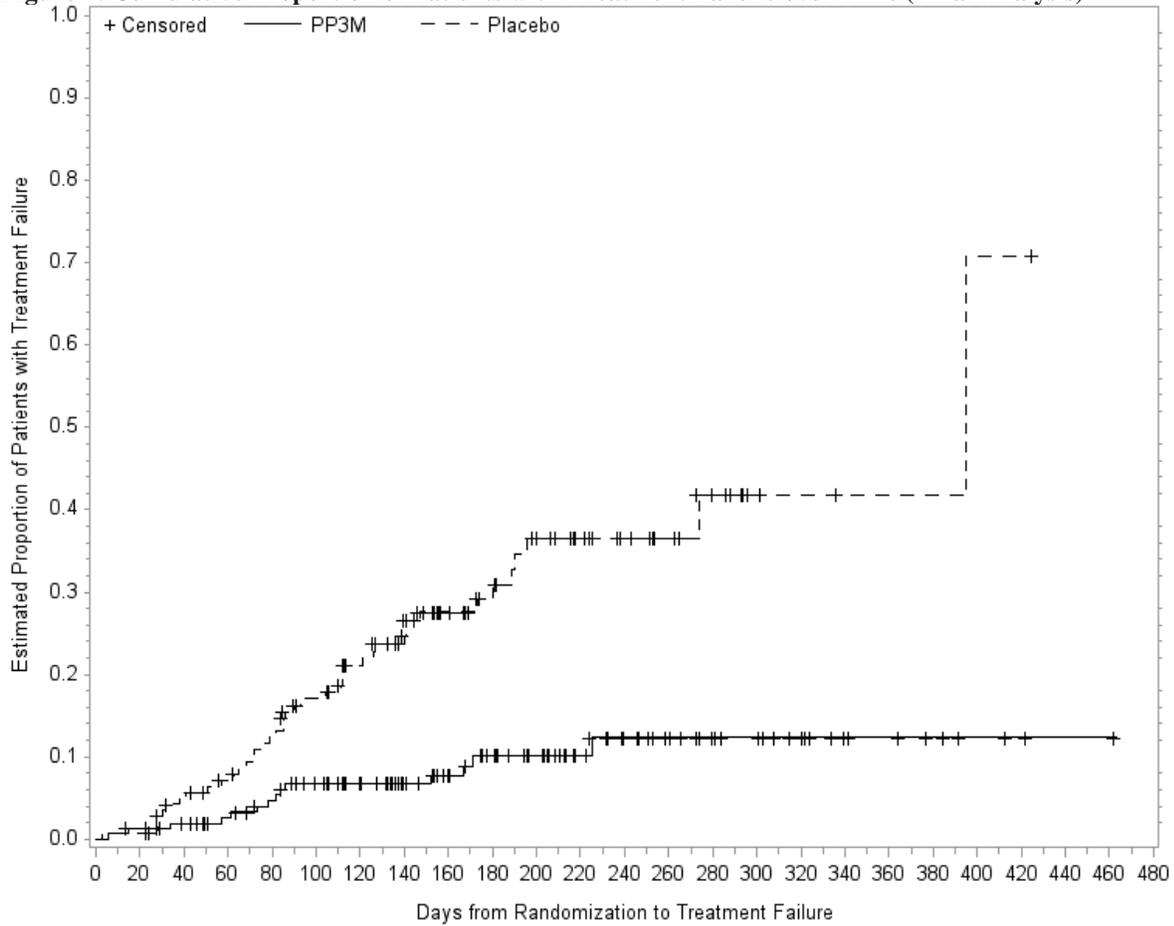
Figure 6: Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase - Final Analysis



Number of Subjects Left		Time(days) since Randomization															
Time	0	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450	
PP3M	160	151	143	131	121	93	67	47	30	22	17	10	7	4	2	1	
Placebo	145	134	124	108	91	66	41	29	20	12	4	3	2	2	1	0	

Source: figure 5 on page 92 of CSR.

**Figure 7: Cumulative Proportion of Patients with Treatment Failure over Time (Final Analysis)**



Source: reviewer's plot.

The most common reasons for relapses were an increase of  $\geq 25\%$  in total PANSS score (34 subjects [23%] in the Placebo group vs. 10 subjects [6%] in the PP3M group) and psychiatric hospitalizations (10 subjects [7%] in the Placebo group vs. 2 subjects [1%] in the PP3M group). Overall, the distribution of reasons for relapse in the final analysis was consistent with that in the interim analysis.

**Table 8: Frequency Distribution of Relapse Types and Reasons During the Double-Blind Phase - Final Analysis**

Type Of Recurrence	Placebo (N=145)	PP3M (N=160)	Total (N=305)
Reason	n (%)	n (%)	n (%)
<b>Total Subjects with Relapse</b>	42 (29)	14 (9)	56 (18)
<b>Psychiatric hospitalization</b>	10 (7)	2 (1)	12 (4)
Subject had psychiatric hospitalization	10 (7)	2 (1)	12 (4)
<b>PANSS total score</b>	35 (24)	10 (6)	45 (15)
Increase of $\geq 25\%$ in total PANSS score	34 (23)	10 (6)	44 (14)
10 point increase in total PANSS score	1 (1)	0	1 (<1)
<b>Deliberate self-injury, violent behavior</b>	0	1 (1)	1 (<1)
Violent behavior resulting in suicide	0	1 (1)	1 (<1)
<b>Suicidal or homicidal ideation</b>	2 (1)	3 (2)	5 (2)
Suicide attempt	0	2 (1)	2 (1)
Suicidal ideation	2 (1)	0	2 (1)
Homicidal ideation	0	1 (1)	1 (<1)
<b>PANSS items (P1, P2, P3, P6, P7, G8)</b>	7 (5)	1 (1)	8 (3)
A score of $\geq 5$ after randomization	7 (5)	1 (1)	8 (3)

Source: based on table 32 on page 8 of sponsor's erratum dated Mar 25, 2015 (SN0014 [SDN15]).

Note: Percentages calculated with the number of subjects in each group as denominator.

### 3.2.7 Additional Analyses

An analysis of effect of continuing treatment of PP3M on the time to relapse of symptoms of schizophrenia in the DB Phase was performed using Cox proportional hazards regression analysis with treatment as a factor in the interim ITT (DB) analysis set and final ITT (DB) analysis set. There was a statistically significant difference between the 2 treatment groups in the time to relapse in favor of PP3M ( $p \leq 0.0004$ , based on the Cox proportional hazards model).

The instantaneous risk (hazard ratio) of relapse of schizophrenia symptoms was 3.45 (95% CI: 1.73, 6.88) times higher in the interim analysis, and 3.81 (95% CI: 2.08, 6.99) times higher in the final analysis, for a subject switching to placebo than for a subject continuing to receive PP3M. This indicates that there was a 71% decrease in relapse risk based on the interim analysis and 74% decrease based on the final analysis with continued PP3M treatment.

**Table 9: Cox Regression of Time to Relapse of Symptoms of Schizophrenia with Treatment as a Factor - Interim Analysis**

Descriptive (a)	Placebo	PP3M	Total
<b>Time to Relapse</b>			
Number of Assessed	135	148	283
Number of Censored (%)	104 (77.0)	137 (92.6)	241 (85.2)
Number of Events (%)	31 (23.0)	11 ( 7.4)	42 (14.8)
25% Quantile (95% CI)	140.0 ( 111.0; 190.0)	( ; )	274.0 ( 171.0; )
Median (95% CI)	274.0 ( 190.0; )	( ; )	( ; )
75% Quantile (95% CI)	( 274.0; )	( ; )	( ; )
P-value(over PP3M)(b)	0.0004		
Hazard Ratio (95% CI)(b)	3.45 (1.73;6.88)		

Source: table TEFRELP04a on page 1265 of CSR.

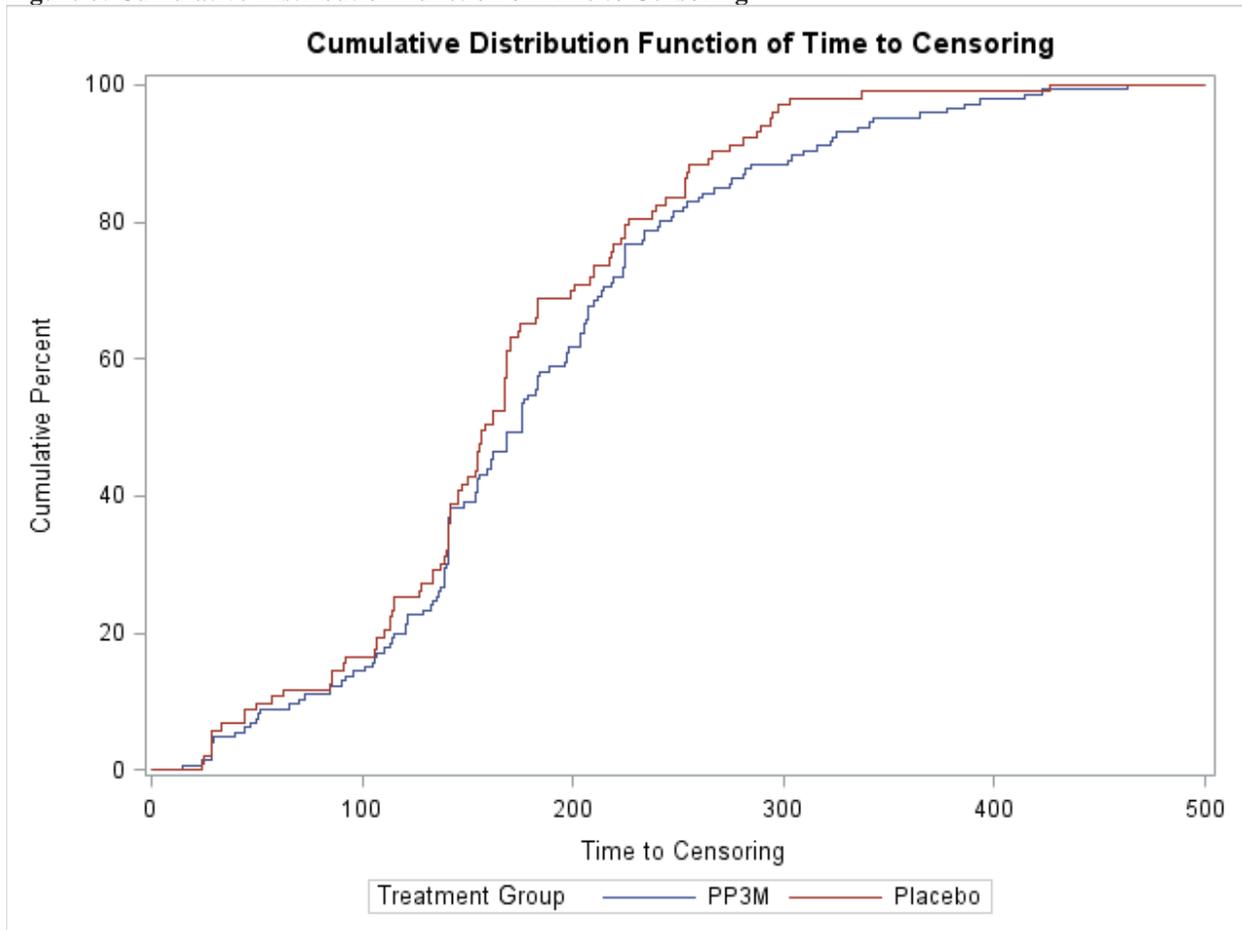
**Table 10: Cox Regression of Time to Relapse of Symptoms of Schizophrenia with Treatment as a Factor - Final Analysis**

Descriptive (a)	Placebo	PP3M	Total
<b>Time to Relapse</b>			
Number of Assessed	145	160	305
Number of Censored (%)	103 (71.0)	146 (91.3)	249 (81.6)
Number of Events (%)	42 (29.0)	14 ( 8.8)	56 (18.4)
25% Quantile (95% CI)	141.0 ( 111.0; 196.0)	( ; )	274.0 ( 180.0; )
Median (95% CI)	395.0 ( 274.0; )	( ; )	( 395.0; )
75% Quantile (95% CI)	( 395.0; )	( ; )	( ; )
P-value(over PP3M)(b)	<0.0001		
Hazard Ratio (95% CI)(b)	3.81 (2.08;6.99)		

Source: table TRFELP04b on page 1266 of CSR.

The cumulative distribution function (CDF) of time to censoring for all the censored subjects was shown in Figure 8.

Figure 8: Cumulative Distribution Function of Time to Censoring



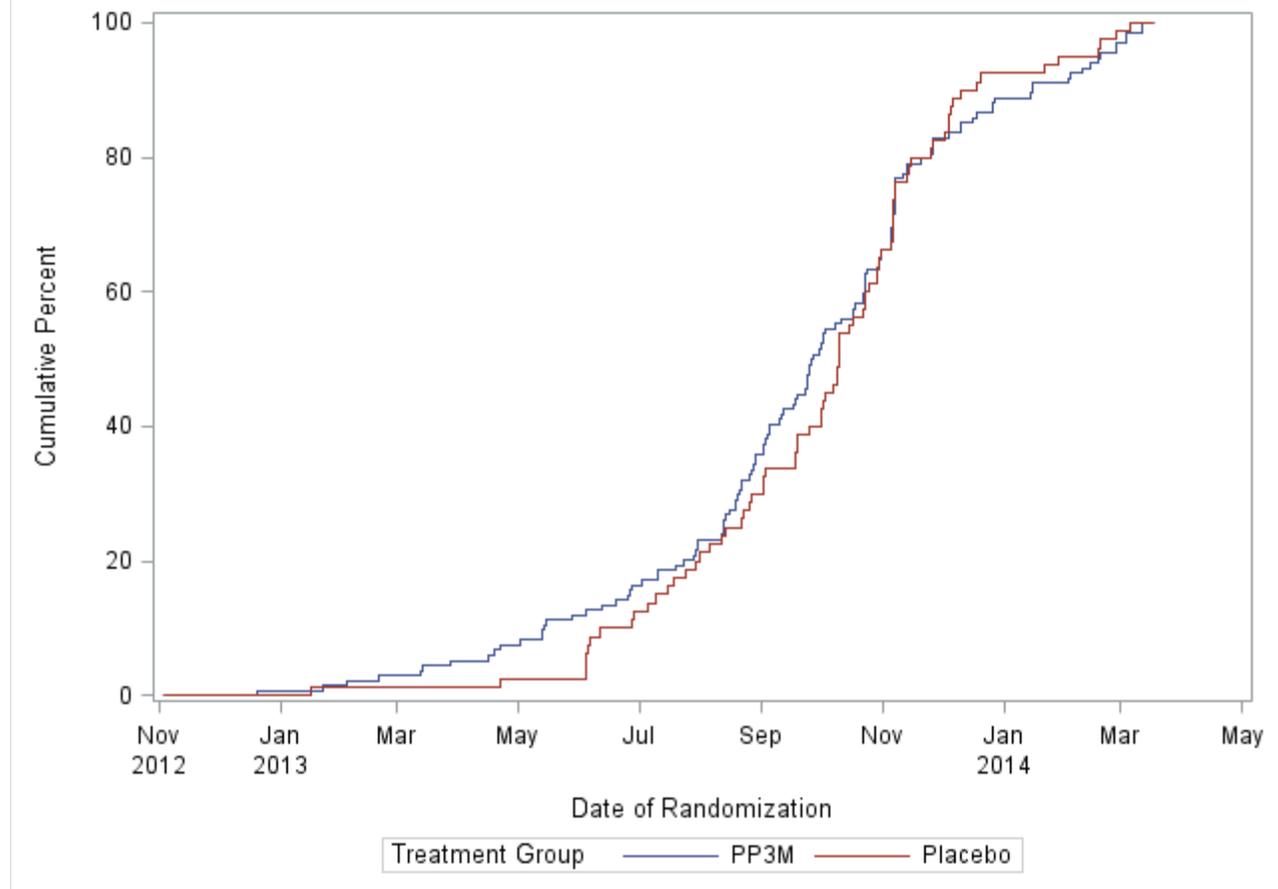
Source: reviewer's plot.

The censoring CDF curves among censored patients only (Figure 8) appear to be slightly apart from each other with placebo on the top. This suggests that the primary result might be slightly biased in favor of placebo. Thus, the result could have been further in favor of PP3M, if the bias had been corrected in some way in the following sense: Suppose some patients were wrongly censored, one possible way to fix them is to treat them as having a relapse, which would lead to a stronger evidence to support drug's efficacy because time to relapse on these patients would be on average shorter for placebo patients than for PP3M patients. Based on the information in Table 3, the visual separation of the censoring CDF curves is probably mainly driven by (a) the imbalance in the number of patients who withdrew (23 on placebo vs 12 on PP3M), and/or (b) imbalance in the number of patients who completed the study due to study termination (80 on placebo vs 134 on PP3M).

If we consider the worst case scenario where all the withdrawn patients are supposed to be relapsed if staying, (a) would conclude that the drug effect is underestimated. To address (b), the cumulative percentages of patients randomized to placebo or treatment over time were plotted by randomization date below. Randomized patients who completed the study due to study

termination (80 vs 134) were considered here. The curves are fairly close to each other when not crossing, suggesting that the randomization appears to have worked out relatively well.

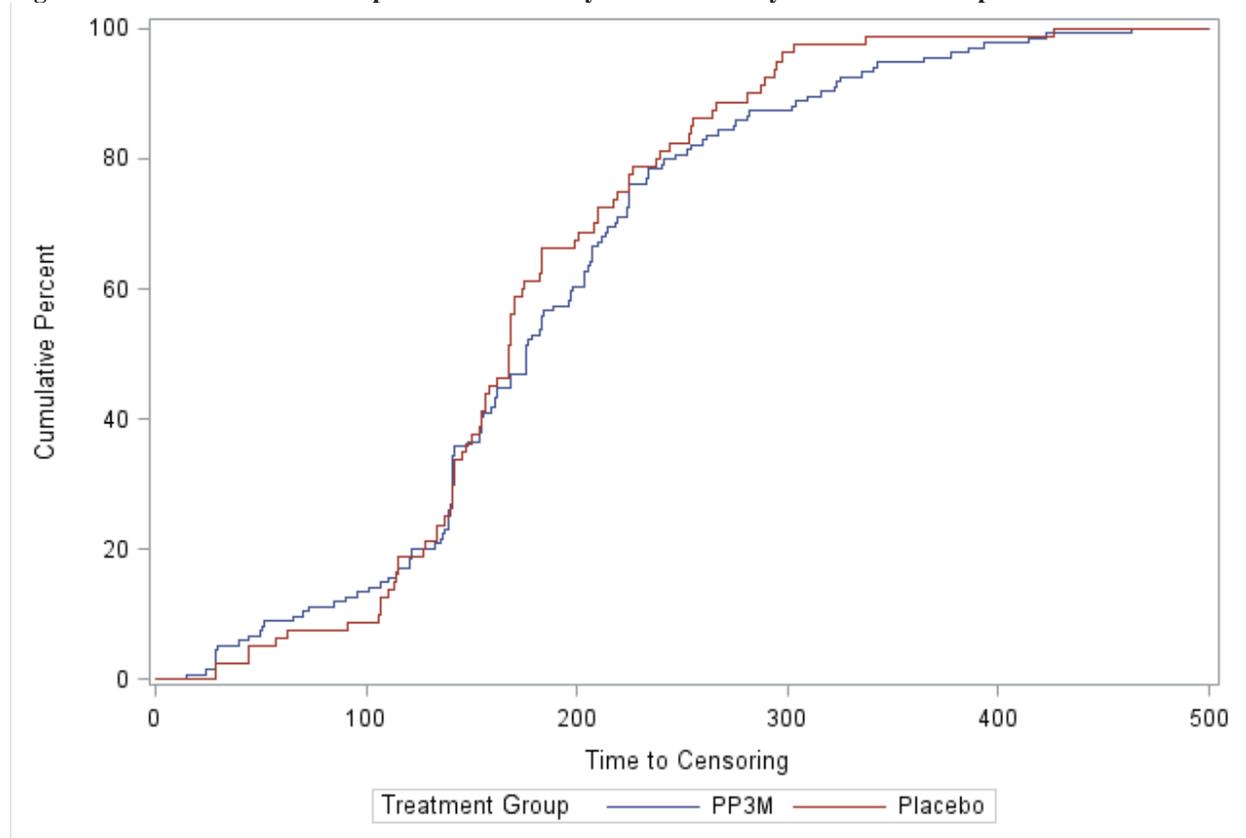
**Figure 9: Cumulative Distribution Function of Time of Randomization**



Source: reviewer's plot.

The CDFs of the completers due to study termination are shown below. There is some imbalance shown in distributions between the treatment groups. But it seems to share the same trend as we see in the CDF curves of time to censoring for all censored patients by the treatment groups.

**Figure 10: Distributions of Completers due to Study Termination by Treatment Group**



Source: reviewer's plot.

Also as seen earlier, the most common reasons for relapses were an increase of  $\geq 25\%$  in total PANSS score and psychiatric hospitalizations for both the interim analysis and the final analysis. They are also the reasons that deviate the numbers of relapse in the placebo group vs the PP3M group. However, if we examine the psychiatric diagnosis at the DB baseline (Table 11), the sponsor has shown that the psychiatric characteristics of subjects in the placebo and PP3M groups were generally similar, except for the mean (SD) duration of psychiatric hospitalization, which at study entry was numerically higher in the Placebo group than in the PP3M group (106.2 [322.88] vs. 80.7 [161.47]). They also suggested interpreting this information with caution because of large and unbalanced standard deviations and the imputation of missing dates/months.

In general, based on our findings in the exploratory analyses conducted, the evidence to conclude the efficacy of PP3M seems persuasive.

**Table 11: Selective Demographic Characteristics by treatment groups**

	Placebo (N=145)	PP3M (N=160)	Total ITT (DB) (N=305)
<b>Duration of psychiatric hospitalization prior to entry(days)</b>			
N	127	146	273
Mean (SD)	106.2 (322.88)	80.7 (161.47)	92.6 (249.71)
Median	36.0	31.5	33.0
Range	(1;2880)	(1;1159)	(1;2880)
<b>Baseline(DB) PANSS total</b>			
N	145	160	305
Mean (SD)	54.2 (9.34)	54.9 (9.95)	54.5 (9.66)
Median	55.0	57.0	56.0
Range	(31;69)	(32;69)	(31;69)

Source: reviewer's table based on table 13 on page 72.

### **3.3 Evaluation of Safety**

Please refer to Dr. Burkhart's clinical review for details on the safety evaluation.

## **4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

### **4.1 Gender, Race, Age, and Geographic Region**

Exploratory analyses based on Cox-proportional hazard models within each of these subgroups suggested that the efficacy of PP3M with regard to time to relapse of symptoms of schizophrenia was consistent regardless of age, sex, race, or region.

#### **Age**

Relapse occurred more frequently among subjects in the placebo group than PP3M for all 3 age groups.

**Table 12: Age group vs. Censor by Treatment Group**

Age group vs. Censor		PP3M	Placebo	Total
18-25	Relapse	4 (36.36%)	7 (63.64%)	11
	Censor	24 (64.86%)	13 (35.14%)	37
	Total	28	20	48
26-50	Relapse	10 (25.64%)	29 (74.36%)	39
	Censor	98 (56.98%)	74 (43.02%)	172
	Total	108	103	211
51-65	Relapse	0 (0%)	6 (100%)	6
	Censor	24 (60%)	16 (40%)	40
	Total	24	22	46

Source: reviewer's table.

### **Sex**

The proportion of subjects who experienced a relapse in the DB period was comparable between men and women.

**Table 13: Sex vs. Censor by Treatment Group**

Sex vs. Censor		PP3M	Placebo	Total
Female	Relapse	3 (23.08%)	10 (76.92%)	13
	Censor	39 (60.94%)	25 (39.06%)	64
	Total	42	35	77
Male	Relapse	11 (25.58%)	32 (74.42%)	43
	Censor	107 (57.84%)	78 (42.16%)	185
	Total	118	110	228

Source: reviewer's table.

### **Race**

A greater proportion of subjects in the placebo group experienced a relapse than in the PP3M group in all race groups of black subjects, white subjects and other.

**Table 14: Race vs. Censor by Treatment Group**

Race vs. Censor		PP3M	Placebo	Total
Black or African American	Relapse	4 (36.36%)	7 (63.64%)	11
	Censor	20 (58.82%)	14 (41.18%)	34
	Total	24	21	45
Other	Relapse	3 (33.33%)	6 (66.67%)	9
	Censor	29 (51.79%)	27 (48.21%)	56
	Total	32	33	65
White	Relapse	7 (19.44%)	29 (80.56%)	36
	Censor	97 (61.01%)	62 (38.99%)	159
	Total	104	91	195

Source: reviewer's table.

## **Region**

A greater proportion of subjects in the placebo group experienced a relapse than in the PP3M group in both the US and non-US regions.

**Table 15: Region vs. Censor by Treatment Group**

Region vs. Censor		PP3M	Placebo	Total
Non-US	Relapse	8 (20%)	32 (80%)	40
	Censor	120 (57.97%)	87 (42.03%)	207
	Total	128	119	247
US	Relapse	6 (37.5%)	10 (62.5%)	16
	Censor	26 (61.9%)	16 (38.1%)	42
	Total	32	26	58

Source: reviewer's table.

## **5 SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues**

No statistical issues identified.

### **5.2 Collective Evidence**

The 3-month formulation of paliperidone palmitate extended-release injectable suspension is shown to be superior compared with placebo in delaying the time to first occurrence of relapse at the nominal significance level of 0.0101 based on the interim analysis result ( $p=0.0002$ ) and confirmed by the final analysis result ( $p<0.001$ ).

### **5.3 Conclusions and Recommendations**

This reviewer concluded a favorable effect of the 3-month formulation of paliperidone palmitate extended-release injectable suspension in prolonging time to first occurrence of relapse.

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/s/  
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YANG WANG  
04/16/2015

PEILING YANG  
04/23/2015

HSIEN MING J HUNG  
04/23/2015



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 207-946

**Supplement #:** Original

**Drug Name:** INVEGA TRINZA® (paliperidone palmitate extended-release injectable suspension)

**Indication(s):** Schizophrenia in adults

**Applicant:** Janssen Research & Development, LLC

**Date(s):** Receipt Date: Nov 18, 2014  
PDUFA Date: May 18, 2015

**Review Priority:** Priority

**Biometrics Division:** Division of Biometrics I

**Statistical Reviewer:** Yang Wang, Ph.D.

**Concurring Reviewers:** Peiling Yang, Ph. D., Team Leader  
H.M. James Hung, Ph.D., Division Director

**Medical Division:** Division of Psychiatry Products

**Clinical Team:** Christina Burkhart, M.D., Clinical Reviewer  
Mark Ritter, M.D., Clinical Team Leader

**Project Manager:** Ann Sohn, Pharm.D.

**Keywords:**

Link to keywords:

[http://intranetapps.fda.gov/scripts/ob\\_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm](http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm)

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## **1 EXECUTIVE SUMMARY**

The sponsor has demonstrated a favorable effect of 3-month formulation of paliperidone palmitate extended-release injectable suspension (INVEGA TRINZA®) compared with placebo in delaying the time to first occurrence of relapse of the symptoms of schizophrenia, in adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months.

## 2 INTRODUCTION

### 2.1 Overview

Janssen has developed 3 formulations of paliperidone: an oral extended-release formulation (INVEGA® Extended Release [ER] tablets), and 2 long-acting injectable (LAI) formulations (paliperidone palmitate, 1-month [PP1M] and 3-month [PP3M]). The oral formulation of paliperidone (INVEGA®) tablets has been approved by the FDA for the acute treatment of schizophrenia in December 2006 (NDA 21999), for the maintenance treatment of schizophrenia in April 2007, for the treatment of schizoaffective disorder in July 2009, and for the treatment of schizophrenia in adolescents aged 12 to 17 years in April 2011. The PP1M formulation (INVEGA SUSTENNA®) was approved by the FDA for the acute and maintenance treatment of schizophrenia in adults in July 2009 (NDA 22264), and for the treatment of schizoaffective disorder in November 2014.

The new 3-month formulation of paliperidone palmitate extended-release injectable suspension, i.e. PP3M (INVEGA TRINZA®), is currently submitted for the maintenance treatment in the prevention of relapse in adult subjects with schizophrenia who have been adequately treated with PP1M for at least four months (17 weeks). It includes a phase III, multicenter, double-blind, placebo-controlled randomized withdrawal (relapse prevention) study, R092670PSY3012. The original protocol was reviewed under IND 76952.

**Table: List of all studies included in analysis**

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
<i>R092670PSY3012</i>	<i>Phase 3</i>	<i>Variable duration</i>	-	<i>145 subjects were in the Placebo group and 160 in the PP3M group</i>	<i>18 to 70 years of age (inclusive) with a diagnosis of schizophrenia.</i>

The primary objective of this study was to evaluate the efficacy of PP3M compared with placebo in delaying the time to first occurrence of relapse of the symptoms of schizophrenia.

### 2.2 Data Sources

The following data sources were considered in this review:

a) Applicant's study report

[\(\\CDSESUB1\evsprod\NDA207946\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5351-stud-rep-contr\r092670psy3012\)](#)

b) Data sets

[\(\\CDSESUB1\evsprod\NDA207946\0000\m5\datasets\r092670psy3012\analysis\adam\datasets\)](#)  
[\(\\CDSESUB1\evsprod\NDA207946\0000\m5\datasets\r092670psy3012\tabulations\sdtm\)](#)

c) Software code

(\\CDSESUB1\evsprod\NDA207946\0000\m5\datasets\r092670psy3012\analysis\adam\programs)

d) Response to FDA information request

(\\CDSESUB1\evsprod\NDA207946\0000\m1\us)

### 3 STATISTICAL EVALUATION

#### 3.1 Data and Analysis Quality

The sponsor has complied with our requests for providing necessary datasets, definition files, and statistical programs for their analyses. This reviewer found the quality of their submissions acceptable and was able to replicate the primary results from the sponsor's Clinical Study Report (CSR).

#### 3.2 Evaluation of Efficacy

##### 3.2.1 Study Design and Endpoints

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study, consisting of 4 phases: a Screening Phase (up to 3 weeks); a 17-week, flexible dose, open-label (OL) Transition Phase; a 12-week, fixed dose, OL Maintenance Phase; and a randomized, double-blind, fixed dose, placebo-controlled relapse prevention phase (referred to as the DB Phase).

Study centers are scattered in Colombia (5 sites), Malaysia (3 sites), Mexico (5 sites), Romania (5 sites), South Korea (3 sites), Turkey (2 sites), United States (14 sites) and Ukraine (27 sites).

Screening Phase (up to 3 weeks): The Screening Phase was used for screening, washout, and tolerability testing for subjects as either inpatients or outpatients.

Transition Phase (17-week): A full injection cycle must have elapsed between the time of the last depot injection and the administration of the first dose of PP1M on Day 8, for those switching from other LAI antipsychotics and those who were already on PP1M prior to study entry. All other subjects received the first injection of PP1M (150 milligram equivalents [mg eq.]) on Day 1 and the second injection of PP1M (100 mg eq.) on Day 8 of the study. Injections on Day 36 and on Day 64 were flexibly dosed (50, 75, 100, or 150 mg eq.). On Day 92, subjects received the dose of PP1M that was administered on Day 64. Those subjects who completed the Transition Phase and who met the prospectively defined criteria entered the Maintenance Phase.

Maintenance Phase (12-week): Starting on Day 120/Week 17), subjects received a single injection of PP3M (using a 3.5-fold multiple of the PP1M dose received on Day 92 during the Transition Phase). Subjects who met specific stabilization criteria entered the DB Phase at Week 29.

**Table 1: Conversion between PP1M Dose and PP3M Dose Using 3.5-Fold Multiple**

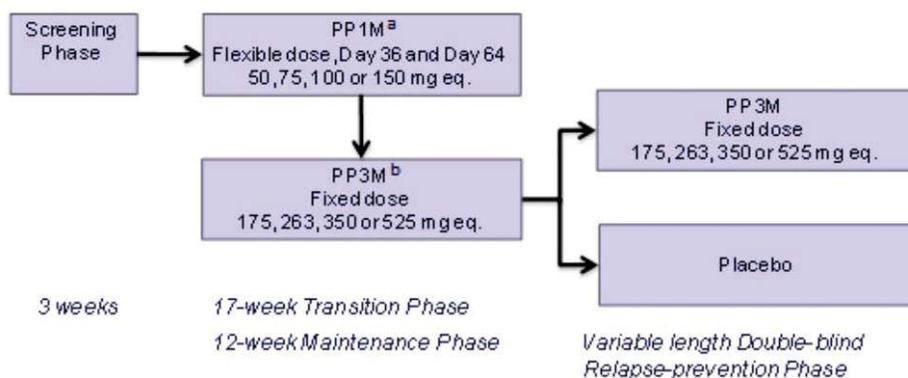
PP1M Dose (mg paliperidone palmitate)	PP1M Dose (mg eq. paliperidone)	PP3M Dose (mg paliperidone palmitate)	PP3M Dose (mg eq. paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

Source: table 3 on page 40 of CSR.

Note: mg eq.=milligram equivalents.

Double-blind Phase (variable duration): At the start of the DB Phase (Day 204/Week 29), subjects were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M, same as the dose they received in the maintenance phase, or placebo. The randomization was balanced using permuted blocks across the 2 treatment groups and stratified by study center to ensure balance of treatment allocation within a center. Subjects assigned to PP3M received the same dose administered on Day 120 of the Maintenance Phase. Subjects remained in the DB Phase until they experienced a relapse event (based on prospectively defined criteria), they met one or more of the study discontinuation / withdrawal criteria, or the study was terminated by the sponsor based on positive results of the interim analysis or because 70 relapse events had occurred when interim analysis was not positive.

**Figure 1: Flowchart**



Source: figure 1 on page 30 of CSR.

Note:

a. PP1M doses: 50, 75, 100, or 150 mg eq. (ie, 78, 117, 156, or 234 mg). All subjects (except those continuing from prior PP1M or switching from other long-acting injectable antipsychotics) 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. On Day 92 (not shown in this figure), subjects received the same dose of PP1M that was administered on Day 64.

b. PP3M doses: 175, 263, 350, or 525 mg eq. (ie, 273, 410, 546, or 819 mg).

**Table 2: Dosing Administration Schedule**

Visit	Transition Phase					Maintenance Phase			Double-blind Phase			
	2	3	4	5	6	8	9	10	11	12	13	Every 12 weeks
Day	1(a)	8(a)	36	64	92	120	148	176	204	232	260	
PP1M Dose	150 mg eq.	100 mg eq.	50-150 mg eq.	50-150 mg eq.	50-150 mg eq.	--	--	--	--	--	--	--
Muscle	D	D	D or G	D or G	D or G	D or G			D or G			D or G
Flexible or Fixed	Fixed	Fixed	Flexible	Flexible	Fixed (b)	Fixed (c)	--	--	Fixed (c)	--	--	Fixed (c)
PP3M/ Placebo Dose	--	--	--	--	--	X	--	--	X	--	--	X

Source: table 2 on page 39 of CSR.

Note: D=deltoid muscle; G=gluteal muscle.

(a) Refer to Table 1 and Table 2 in the protocol (Appendix 1 of CSR), respectively, for subjects who were stable on PP1M at study entry and for subjects who were switching from other depot antipsychotics.

(b) Dose on this visit should be the same as given on Visit 5 (Day 64).

(c) The dose of PP3M given was a 3.5-fold multiple of the PP1M dose given on Visit 6 (Day 92).

The primary efficacy end point for this study was the time between subject randomization into the DB Phase and the first documentation of a relapse event, based on 1 or more of the following predetermined relapse criteria:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or
- For PANSS
  - The subject had an increase of 25% in PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, or
  - The subject had a 10-point increase in the PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was ≤40, or
  - For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness):
    - The subject had a score of ≥5 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was ≤3 at randomization, or
    - The subject had a score of ≥6 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was 4 at randomization.
  - The subject inflicted deliberate self-injury or exhibited violent behavior resulting in suicide, clinically significant injury to him/herself or another person, or significant property damage, or
  - The subject had suicidal or homicidal ideation and aggressive behavior that was clinically significant (in frequency and severity) in the investigator's judgment.

Subjects who met at least 1 of the criteria for relapse while on Double-blind treatment at the time of study completion for the primary analysis were considered to have had a relapse event. All

other subjects without a relapse at the end of study (end of DB Phase) were considered censored. The date of relapse was the date of the first assessment for symptoms of relapse.

### **3.2.2 Statistical Methodologies**

#### **3.2.2.1 Primary Analysis for Primary Endpoint**

The primary analysis for time to relapse was carried out by log-rank test on the intent-to-treat (ITT) population, defined as all subjects who receive at least 1 dose of Double-blind medication during the DB Phase.

There was one interim efficacy analysis for superiority. See details of the interim analysis in section 3.2.2.2.

#### **3.2.2.2 Interim Analysis**

An Independent Data Monitoring Committee (IDMC) was established to review the blinded efficacy and safety data on an ongoing basis. In addition, the IDMC was to meet and review the results of the interim analysis and provide recommendation to the sponsor on whether to continue the study or to terminate the study.

An interim analysis was to be conducted by the IDMC after at least 42 relapse events had occurred. If the interim analysis using 2-sided log-rank test was to show a statistically significant difference (at the nominal significance level of 0.0101) between PP3M and placebo in the time to relapse, the study was to be terminated. The interim analysis would then be considered as the primary analysis and the final analysis, performed after study termination, would be reported as confirmative results. If interim analysis failed to show a significant difference, the study was to continue until 70 relapse events had been obtained, and the final analysis, now considered primary analysis was to be performed at the nominal significance level of 0.0464.

#### **3.2.2.3 Sample Size Determination**

It was assumed that the 12-month relapse rates for PP3M and placebo would be 20% and 40%, respectively, resulting in a relative risk of 0.44. Approximately, 196 subjects were expected to be randomized in the DB Phase in a 1:1 ratio to either PP3M or placebo in order to obtain 70 relapse events to show that PP3M was significantly different from placebo at the 2-sided significance level of 0.05, with 90% power to detect a relative risk of 0.44 (ie, hazard rate of PP3M/ hazard rate of Placebo=0.44).

A 2-stage group sequential design with 1 interim analysis was to be implemented to allow for early stopping if there was significant evidence of efficacy based upon the interim analysis after 60% (ie, 42 events) of the projected relapse events had occurred. The O'Brien-Fleming boundary (corresponding to the Wang and Tsatis power boundary with shape parameter 0) was to be used for sequential monitoring.

It was assumed that at least 50% of subjects who entered the Transition Phase would discontinue the study or not meet the criteria for randomization in the DB Phase. To meet the expected number of 196 subjects (98 per treatment group) to be randomized in the DB Phase, a total of at least 392 subjects were expected to be enrolled. The total number of subjects enrolled would depend on the time that it took to obtain 70 relapse events. Blinded surveillance of the total number of events in the DB Phase was to be performed during the study to assess the appropriateness of the 50% dropout assumption and the time necessary to obtain 70 relapse events. The total number of subjects enrolled could be increased up to approximately 500.

Overall, 506 subjects with schizophrenia were enrolled into and dosed in the Open-label Phase and 305 subjects with schizophrenia were randomized into in the DB Phase.

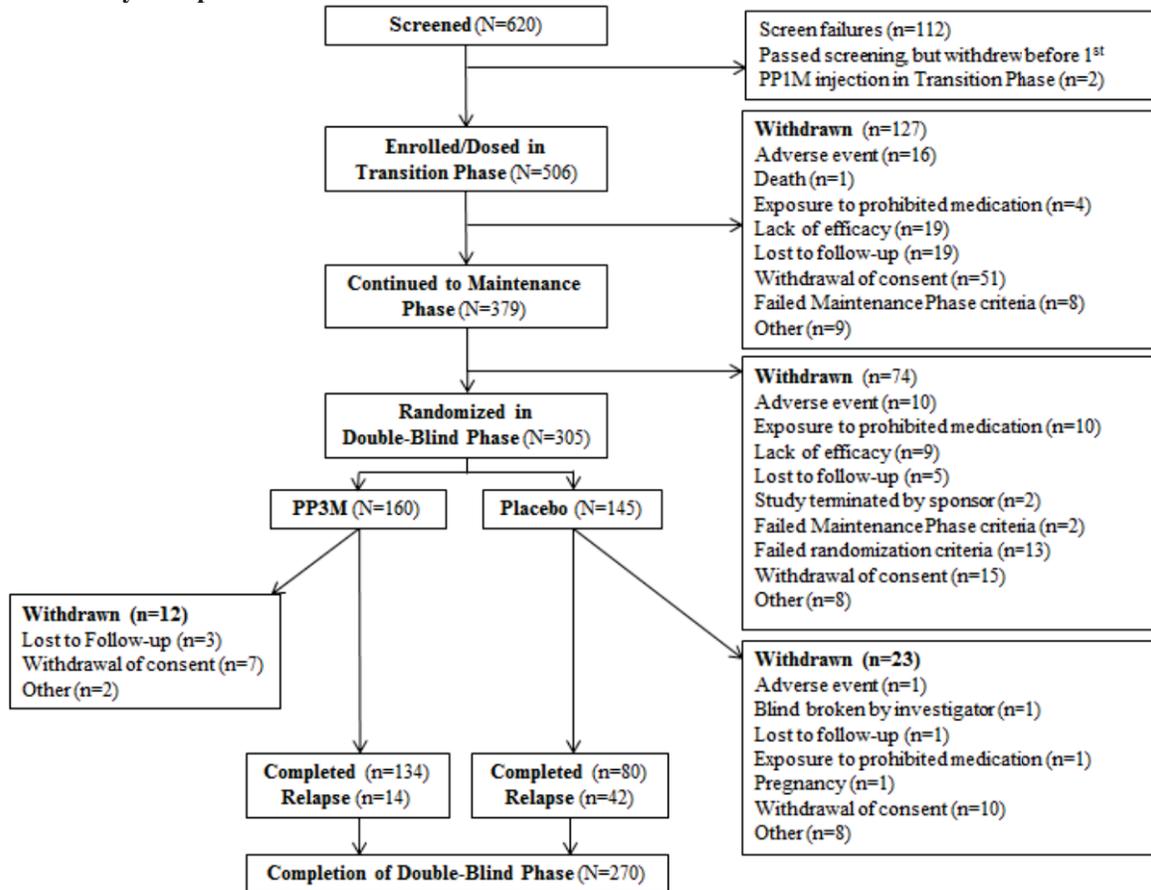
### **3.2.3 Patient Disposition, Demographic and Baseline Characteristics**

#### **3.2.3.1 Patient Disposition**

The ITT (DB) analysis set for the interim analysis included all subjects who qualified for inclusion (N=283) at the time of the interim analysis data cutoff (January 24, 2014). 135 subjects were randomized to Placebo and 148 subjects to PP3M. Of the 42 Interim ITT (DB) subjects who experienced a relapse event, 31 subjects (23.0%) were in the Placebo group and 11 subjects (7.4%) were in PP3M group.

The ITT (DB) analysis set for the final analysis included all subjects enrolled in the DB Phase (N=305) up to study completion (09 April 2014). 145 subjects were in the Placebo group and 160 subjects were in the PP3M group. Of the 270 subjects (89%) who completed the DB Phase, 56 subjects (18%) experienced a relapse. A higher percentage of subjects in the Placebo group than the PP3M experienced a relapse during the DB Phase, 42 out of 145 subjects (29.0%) in the Placebo group vs. 14 out of 160 subjects (8.8%) subjects in PP3M group. 35 subjects (11%) discontinued from the DB Phase. A higher percentage of subjects in the PP3M group than the Placebo group (93% vs. 84%) completed the study during the DB Phase.

Figure 2: Study Completion and Withdrawal Information



Source: figure 2 on page 67 of CSR.

Table 3: Completion/Withdrawal Information During the Double-Blind Phase

	Placebo (N=145)	PP3M (N=160)	Total (N=305)
<b>Subject Completed Trial</b>			
<b>Reason For Withdrawal/Termination</b>	n (%)	n (%)	n (%)
<b>Completed</b>	122 ( 84)	148 ( 93)	270 ( 89)
Completed DB due to study termination	80 ( 55)	134 ( 84)	214 ( 70)
Relapse during DB phase	42 ( 29)	14 ( 9)	56 ( 18)
<b>Withdrawn</b>	23 ( 16)	12 ( 8)	35 ( 11)
Adverse event	1 ( 1)	0	1 (<1)
Blind broken by investigator	1 ( 1)	0	1 (<1)
Lost to follow-up	1 ( 1)	3 ( 2)	4 ( 1)
Exposure to prohibited medications	1 ( 1)	0	1 (<1)
Pregnancy	1 ( 1)	0	1 (<1)
Withdrawal of consent	10 ( 7)	7 ( 4)	17 ( 6)
Other	8 ( 6)	2 ( 1)	10 ( 3)

Source: table 11 on page 69 of CSR.

### 3.2.3.2 Patient Demographic

Demographic characteristics for the ITT (OL) and ITT (DB) analysis sets are presented in Table 4. At DB baseline, more male (75%) than female (25%) subjects were enrolled in the study. A majority of subjects were white (64%), with a mean (SD) age of 37.8 (11.01) years (range: 18 to 64 years). 137 subjects (45%) were studied in Ukraine, while 58 subjects (19%) were studied in the US. The demographic data was similar between the Placebo and PP3M groups at OL baseline.

**Table 4: Demographic Characteristics for all Analysis Sets**

	ITT(OL)		ITT(DB)		Total Intent-to-Treat (DB) (N=305)
	Pali Palmitate (N=506)	Not Randomized to Double-Blind (N=201)	Placebo (N=145)	PP3M (N=160)	
<b>Age (yrs)</b>					
N	506	201	145	160	305
Category, n (%)					
18-25	69 ( 14)	21 ( 10)	20 ( 14)	28 ( 18)	48 ( 16)
26-50	356 ( 70)	145 ( 72)	103 ( 71)	108 ( 68)	211 ( 69)
51-65	79 ( 16)	33 ( 16)	22 ( 15)	24 ( 15)	46 ( 15)
>65	2 (<1)	2 ( 1)	0	0	0
Mean (SD)	38.4 (11.15)	39.5 (11.30)	38.5 (11.16)	37.1 (10.87)	37.8 (11.01)
Median	37.0	39.0	37.0	35.0	37.0
Range	(18;68)	(19;68)	(18;64)	(18;61)	(18;64)
<b>Sex, n (%)</b>					
N	506	201	145	160	305
Male	379 ( 75)	151 ( 75)	110 ( 76)	118 ( 74)	228 ( 75)
Female	127 ( 25)	50 ( 25)	35 ( 24)	42 ( 26)	77 ( 25)
<b>Race, n (%)</b>					
N	506	201	145	160	305
White	297 ( 59)	102 ( 51)	91 ( 63)	104 ( 65)	195 ( 64)
Black or African American	110 ( 22)	65 ( 32)	21 ( 14)	24 ( 15)	45 ( 15)
Asian	41 ( 8)	12 ( 6)	15 ( 10)	14 ( 9)	29 ( 10)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	0	0	0
Other	55 ( 11)	20 ( 10)	18 ( 12)	17 ( 11)	35 ( 11)
Multiple	2 (<1)	1 (<1)	0	1 ( 1)	1 (<1)
<b>Ethnicity, n (%)</b>					
N	506	201	145	160	305
Hispanic or Latino	92 ( 18)	38 ( 19)	26 ( 18)	28 ( 18)	54 ( 18)
Not Hispanic or Latino	410 ( 81)	160 ( 80)	118 ( 81)	132 ( 83)	250 ( 82)
Not reported	2 (<1)	1 (<1)	1 ( 1)	0	1 (<1)
Unknown	2 (<1)	2 ( 1)	0	0	0
<b>Country, n (%)</b>					
N	506	201	145	160	305
Colombia	41 ( 8)	16 ( 8)	12 ( 8)	13 ( 8)	25 ( 8)
Malaysia	29 ( 6)	6 ( 3)	11 ( 8)	12 ( 8)	23 ( 8)
Mexico	28 ( 6)	10 ( 5)	10 ( 7)	8 ( 5)	18 ( 6)
Romania	42 ( 8)	15 ( 7)	14 ( 10)	13 ( 8)	27 ( 9)
South Korea	10 ( 2)	4 ( 2)	4 ( 3)	2 ( 1)	6 ( 2)
Turkey	17 ( 3)	6 ( 3)	5 ( 3)	6 ( 4)	11 ( 4)
Ukraine	181 ( 36)	44 ( 22)	63 ( 43)	74 ( 46)	137 ( 45)
United States	158 ( 31)	100 ( 50)	26 ( 18)	32 ( 20)	58 ( 19)

Source: table 12 on page 70 of CSR.

### 3.2.3.3 Patient Dose Levels

152 (50%) of all 305 DB subjects, consisting of 74 subjects (51%) in the placebo group and 78 (49%) in the PP3M group, received the maintenance dose at 350 mg eq. in the DB phase, 113 (37%) received 525 mg eq., 32 (10%) received 263 mg eq. and 8 (3%) received 175 mg eq..

**Figure 3: Dose Level Information During the Double-Blind Phase**

Maintenance dose (mg eq.)	Placebo (N=145) n(%)	PP3M (N=160) n(%)	Total (N=305) n(%)
175	2 (1)	6 (4)	8 (3)
263	17 (12)	15 (9)	32 (10)
350	74 (51)	78 (49)	152 (50)
525	52 (36)	61 (38)	113 (37)

Source: reviewer's table.

### 3.2.4 Results and Conclusions

#### 3.2.5 Primary Analysis (Interim Analysis) of Primary Endpoint

Since the study was stopped in accordance with the recommendation of the IDMD, because of the statistical significance shown in favor of PP3M over placebo by the pre-planned interim analysis of time to relapse, the interim analysis was considered as the primary analysis, and the final analysis of data was considered confirmatory.

In the DB Phase, PP3M was superior to placebo in delaying relapse of symptoms of schizophrenia in subjects with  $p < 0.001$  based on the log-rank test compared to the threshold to stop the study early for efficacy at  $p < 0.0101$ .

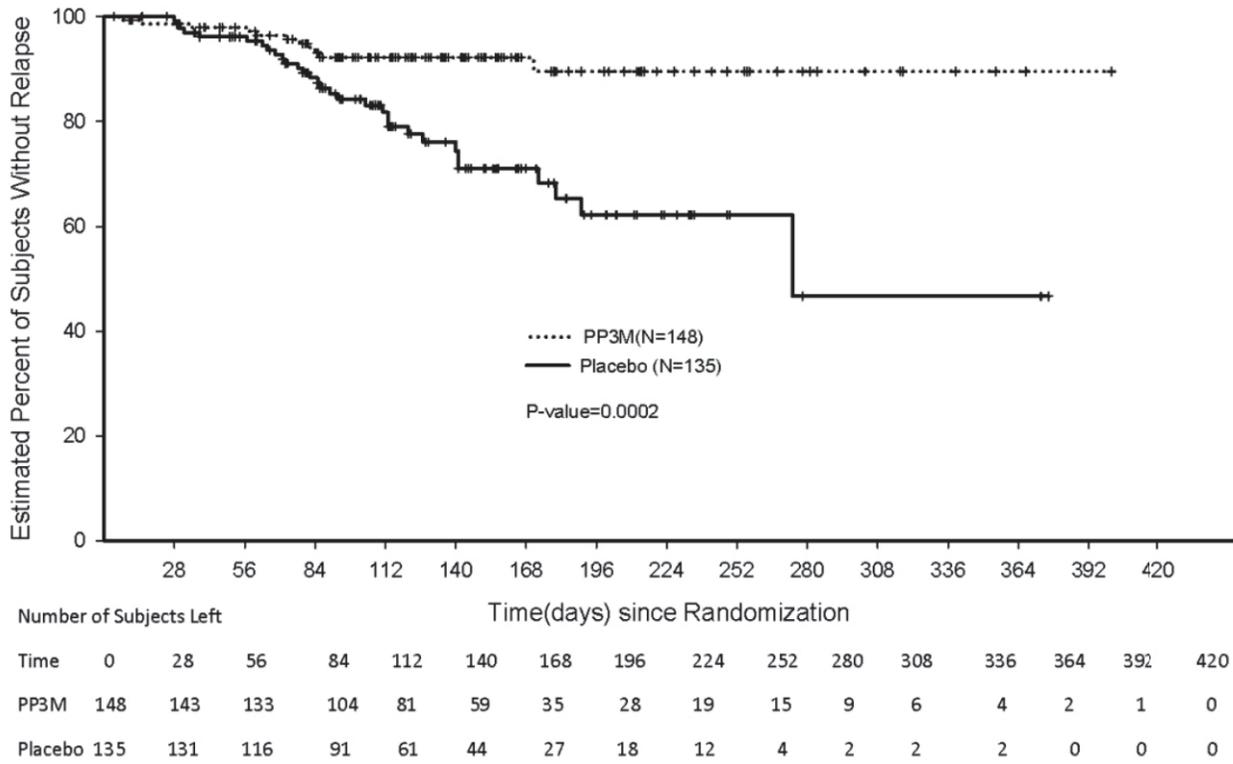
*Reviewer's note: the p-value is 0.0002 to be exact.*

**Table 5: Time to Relapse During the DB Phase and Number (%) of Subjects that Remained Relapse Free - Interim Analysis**

Descriptive (a)	Placebo	PP3M	Total	Overall		
				Chisq	DF	P-value(b)
<b>Time to Relapse</b>						
Number of Assessed	135	148	283			
Number of Censored (%)	104 (77.0)	137 (92.6)	241 (85.2)			
Number of Events (%)	31 (23.0)	11 (7.4)	42 (14.8)			
25% Quantile (95% CI)	140.0 ( 104.0; 190.0)	( ; )	274.0 (171.0; )			
Median (95% CI)	274.0 ( 190.0; )	( ; )	( ; )			
75% Quantile (95% CI)	( 274.0; )	( ; )	( ; )			
Statistical Test				14.072	1	<0.001

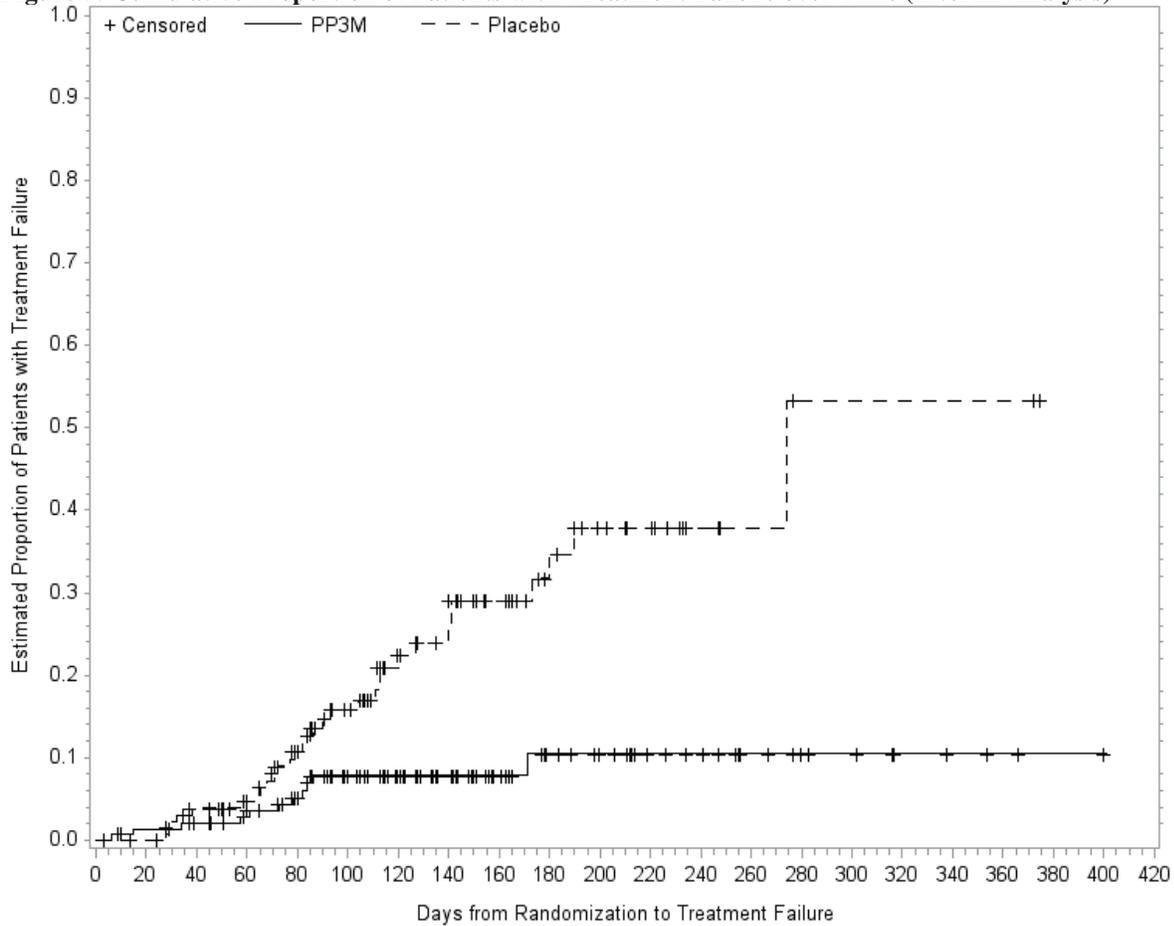
Source: table 29 on page 88 of CSR.

**Figure 4: Kaplan-Meier Plot of Time to Relapse During the DB Phase - Interim Analysis**



Source: figure 4 on page 89 of CSR.

**Figure 5: Cumulative Proportion of Patients with Treatment Failure over Time (Interim Analysis)**



Source: reviewer's plot.

The most common reasons for relapses across both treatment groups in the interim analysis were an increase of  $\geq 25\%$  in the PANSS total score value (25 subjects [19%] in the Placebo group vs. 8 subjects [5%] in the PP3M group) and psychiatric hospitalizations (8 subjects [6%] in the Placebo group vs. 3 subjects [2%] in the PP3M group).

**Table 6: Frequency Distribution of Relapse Types and Reasons During the DB Phase - Interim Analysis**

Type Of Recurrence Reason	Placebo (N=135) n (%)	PP3M (N=148) n (%)	Total (N=283) n (%)
<b>Total no. subjects Total Subjects with Relapse</b>	31 ( 23)	11 ( 7)	42 ( 15)
<b>Psychiatric hospitalization</b>	8 ( 6)	3 ( 2)	11 ( 4)
Subject had psychiatric hospitalization	8 ( 6)	3 ( 2)	11 ( 4)
<b>PANSS total score</b>	26 ( 19)	8 ( 5)	34 ( 12)
Increase of $\geq 25\%$ in total PANSS score	25 ( 19)	8 ( 5)	33 ( 12)
10 point increase in total PANSS score	1 ( 1)	0	1 (<1)
<b>Deliberate self-injury, violent behavior</b>	1 ( 1)	2 ( 1)	3 ( 1)
Has subject had a suicidal ideation	1 ( 1)	2 ( 1)	3 ( 1)
<b>Suicidal or homicidal ideation</b>	1 ( 1)	2 ( 1)	3 ( 1)
Suicide attempt	0	1 ( 1)	1 (<1)
Suicidal ideation	1 ( 1)	0	1 (<1)
Homicidal ideation	0	1 ( 1)	1 (<1)
<b>PANSS items (P1, P2, P3, P6, P7, G8)</b>	5 ( 4)	1 ( 1)	6 ( 2)
A score of $\geq 5$ after randomization	5 ( 4)	1 ( 1)	6 ( 2)

Source: table 30 on page 90 of CSR.

Note: Percentages calculated with the number of subjects in each group as denominator.

### 3.2.6 Final Analysis of Primary Endpoint

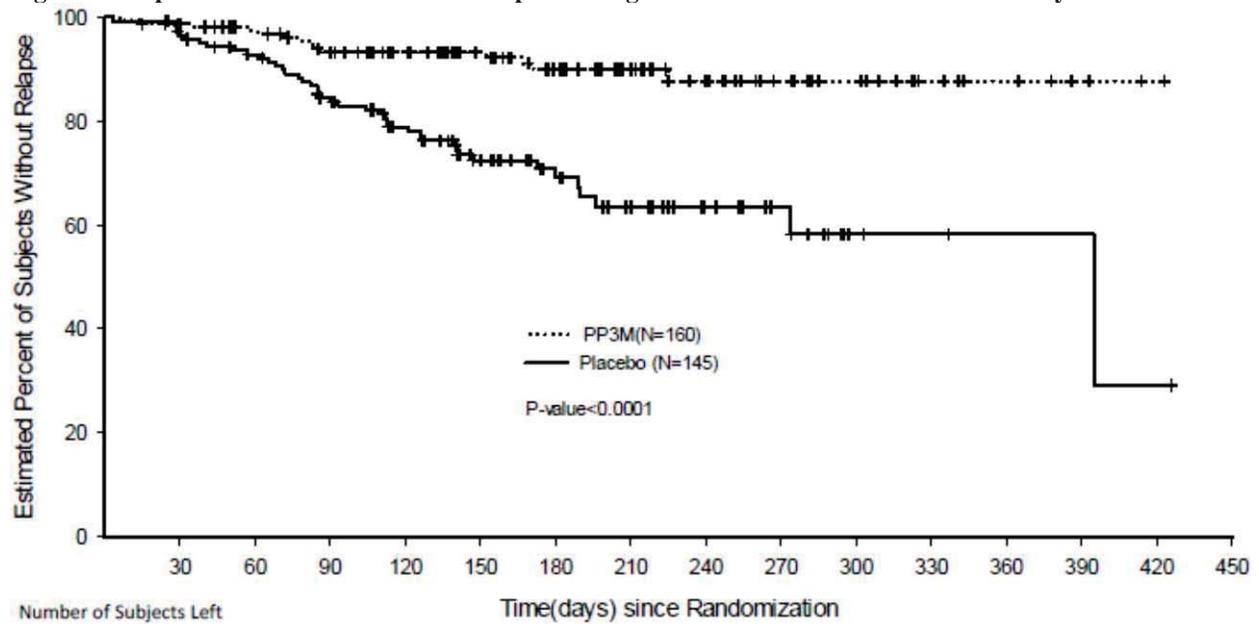
The final analysis of the relapse data confirmed the findings of the interim analysis. There was a statistically significant difference in the time to relapse with a longer time to relapse in subjects assigned to PP3M at  $p < 0.001$  based on the log-rank test, consistent with that at the interim analysis of  $p < 0.001$ .

**Table 7: Time to Relapse During the Double-Blind Phase and Number (%) of Subjects That Remained Relapse Free - Final Analysis**

Descriptive (a)	Placebo	PP3M	Total	Overall		
				Chisq	DF	P-value(b)
<b>Time to Relapse</b>						
Number of Assessed	145	160	305			
Number of Censored (%)	103 (71.0)	146 (91.3)	249 (81.6)			
Number of Events (%)	42 (29.0)	14 ( 8.8)	56 (18.4)			
25% Quantile (95% CI)	141.0 ( 104.0; 190.0)	( ; )	274.0 ( 180.0; )			
Median (95% CI)	395.0 ( 274.0; )	( ; )	( 395.0; )			
75% Quantile (95% CI)	( 395.0; )	( ; )	( ; )			
Statistical Test				21.646	1	<0.001

Source: table 31 on page 91 of CSR.

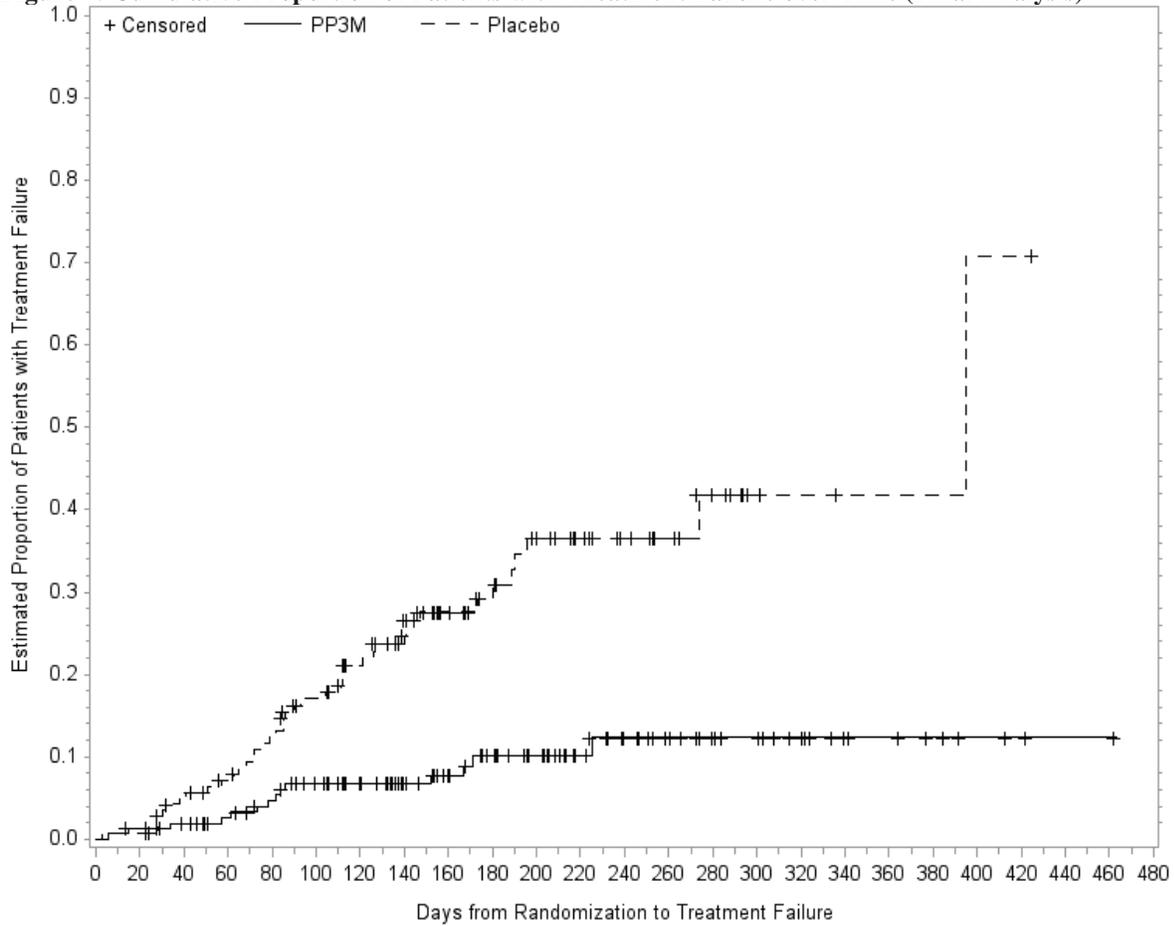
Figure 6: Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase - Final Analysis



Number of Subjects Left		Time(days) since Randomization															
Time	0	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450	
PP3M	160	151	143	131	121	93	67	47	30	22	17	10	7	4	2	1	
Placebo	145	134	124	108	91	66	41	29	20	12	4	3	2	2	1	0	

Source: figure 5 on page 92 of CSR.

**Figure 7: Cumulative Proportion of Patients with Treatment Failure over Time (Final Analysis)**



Source: reviewer's plot.

The most common reasons for relapses were an increase of  $\geq 25\%$  in total PANSS score (34 subjects [23%] in the Placebo group vs. 10 subjects [6%] in the PP3M group) and psychiatric hospitalizations (12 subjects [8%] in the Placebo group vs. 3 subjects [2%] in the PP3M group). Overall, the distribution of reasons for relapse in the final analysis was consistent with that in the interim analysis.

**Table 8: Frequency Distribution of Relapse Types and Reasons During the Double-Blind Phase - Final Analysis**

Type Of Recurrence Reason	Placebo (N=145) n (%)	PP3M (N=160) n (%)	Total (N=305) n (%)
<b>Total no. subjects Total Subjects with Relapse</b>	42 ( 29)	14 ( 9)	56 ( 18)
<b>Psychiatric hospitalization</b>	12 ( 8)	3 ( 2)	15 ( 5)
Subject had psychiatric hospitalization	12 ( 8)	3 ( 2)	15 ( 5)
<b>PANSS total score</b>	35 ( 24)	10 ( 6)	45 ( 15)
Increase of $\geq 25\%$ in total PANSS score	34 ( 23)	10 ( 6)	44 ( 14)
10 point increase in total PANSS score	1 ( 1)	0	1 (<1)
<b>Deliberate self-injury, violent behavior</b>	2 ( 1)	3 ( 2)	5 ( 2)
Has subject had a deliberate self-injury	0	1 ( 1)	1 (<1)
Violent behavior resulting in suicide	0	1 ( 1)	1 (<1)
Has subject had a suicidal ideation	2 ( 1)	3 ( 2)	5 ( 2)
<b>Suicidal or homicidal ideation</b>	2 ( 1)	3 ( 2)	5 ( 2)
Suicide attempt	0	2 ( 1)	2 ( 1)
Suicidal ideation	2 ( 1)	0	2 ( 1)
Homicidal ideation	0	1 ( 1)	1 (<1)
<b>PANSS items (P1, P2, P3, P6, P7, G8)</b>	7 ( 5)	1 ( 1)	8 ( 3)
A score of $\geq 5$ after randomization	7 ( 5)	1 ( 1)	8 ( 3)

Source: table 32 on page 93 of CSR.

### 3.2.7 Additional Analyses

An analysis of effect of continuing treatment of PP3M on the time to relapse of symptoms of schizophrenia in the DB Phase was performed using Cox proportional hazards regression analysis with treatment as a factor in the interim ITT (DB) analysis set and final ITT (DB) analysis set. There was a statistically significant difference between the 2 treatment groups in the time to relapse in favor of PP3M ( $p \leq 0.0004$ , based on the Cox proportional hazards model).

The instantaneous risk (hazard ratio) of relapse of schizophrenia symptoms was 3.45 (95% CI: 1.73, 6.88) times higher in the interim analysis, and 3.81 (95% CI: 2.08, 6.99) times higher in the final analysis, for a subject switching to placebo than for a subject continuing to receive PP3M. This indicates that there was a 71% decrease in relapse risk based on the interim analysis and 74 % decrease based on the final analysis with continued PP3M treatment.

**Table 9: Cox Regression of Time to Relapse of Symptoms of Schizophrenia with Treatment as a Factor - Interim Analysis**

Descriptive (a)	Placebo	PP3M	Total
<b>Time to Relapse</b>			
Number of Assessed	135	148	283
Number of Censored (%)	104 (77.0)	137 (92.6)	241 (85.2)
Number of Events (%)	31 (23.0)	11 ( 7.4)	42 (14.8)
25% Quantile (95% CI)	140.0 ( 111.0; 190.0)	( ; )	274.0 ( 171.0; )
Median (95% CI)	274.0 ( 190.0; )	( ; )	( ; )
75% Quantile (95% CI)	( 274.0; )	( ; )	( ; )
P-value(over PP3M)(b)	0.0004		
Hazard Ratio (95% CI)(b)	3.45 (1.73;6.88)		

Source: table TEFRELP04a on page 1265 of CSR.

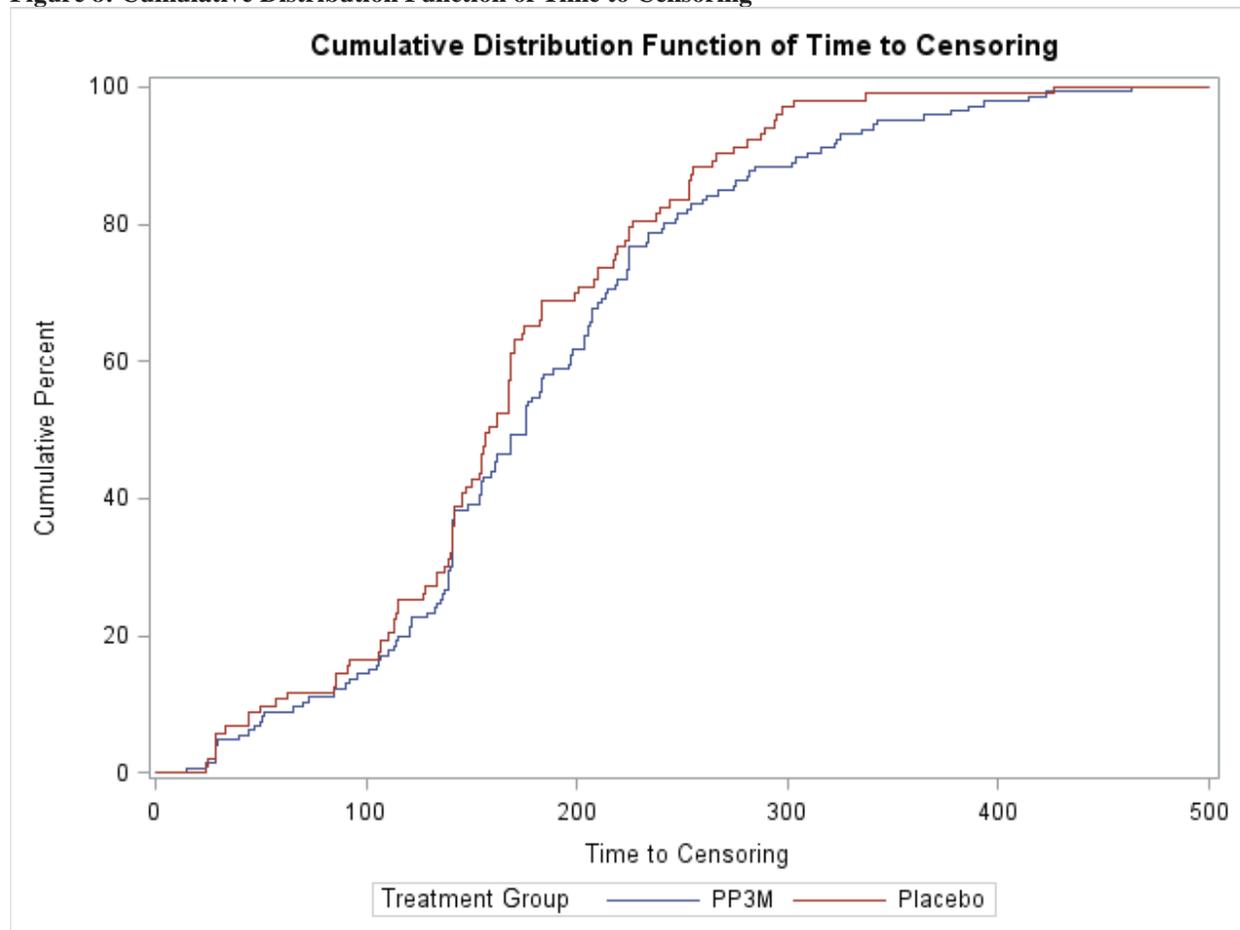
**Table 10: Cox Regression of Time to Relapse of Symptoms of Schizophrenia with Treatment as a Factor - Final Analysis**

Descriptive (a)	Placebo	PP3M	Total
<b>Time to Relapse</b>			
Number of Assessed	145	160	305
Number of Censored (%)	103 (71.0)	146 (91.3)	249 (81.6)
Number of Events (%)	42 (29.0)	14 ( 8.8)	56 (18.4)
25% Quantile (95% CI)	141.0 ( 111.0; 196.0)	( ; )	274.0 ( 180.0; )
Median (95% CI)	395.0 ( 274.0; )	( ; )	( 395.0; )
75% Quantile (95% CI)	( 395.0; )	( ; )	( ; )
P-value(over PP3M)(b)	<0.0001		
Hazard Ratio (95% CI)(b)	3.81 (2.08;6.99)		

Source: table TRFELP04b on page 1266 of CSR.

The cumulative distribution function (CDF) of time to censoring for all the censored subjects was shown in Figure 8.

Figure 8: Cumulative Distribution Function of Time to Censoring



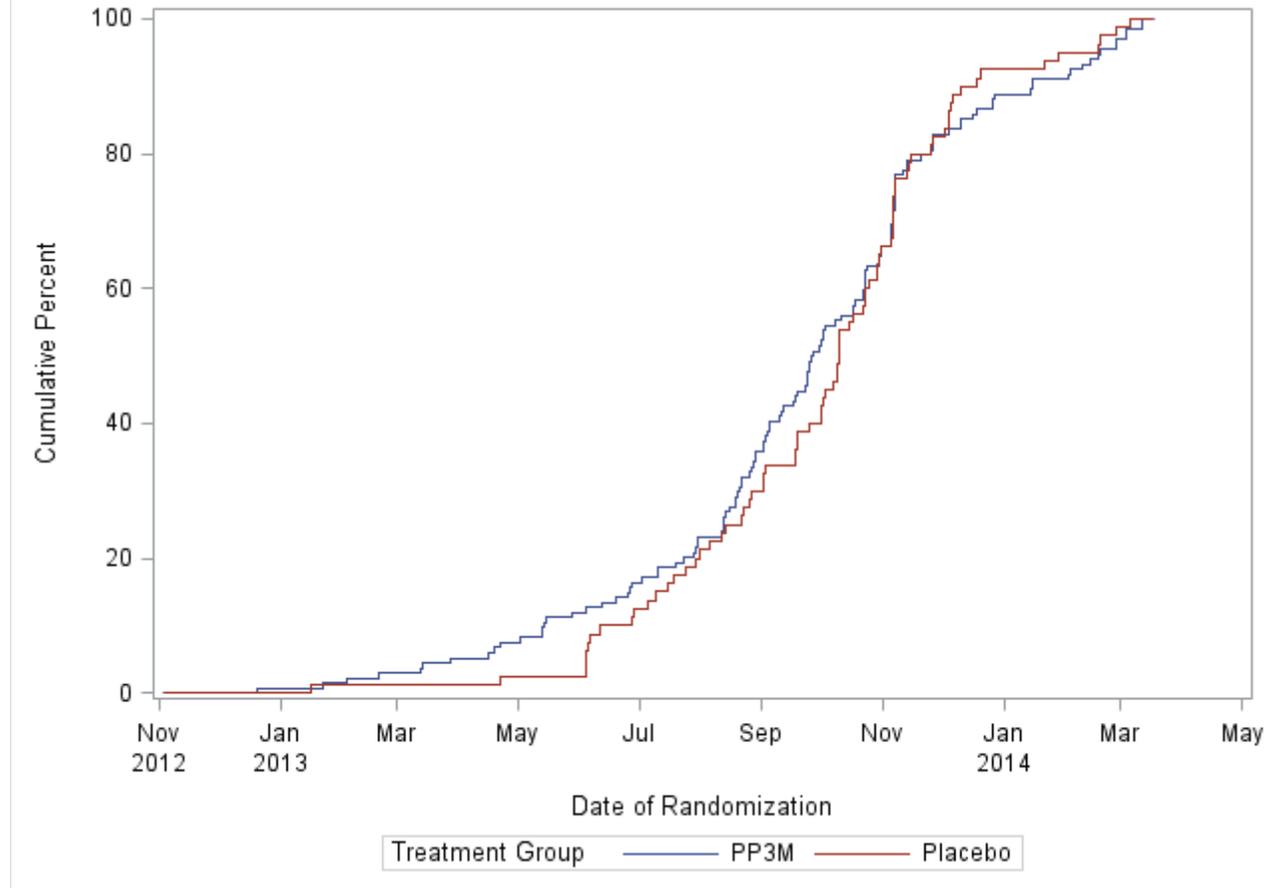
Source: reviewer’s plot.

The censoring CDF curves among censored patients only (Figure 8) appear to be slightly apart from each other with placebo on the top. This suggests that the primary result might be slightly biased in favor of placebo. Thus, the result could have been further in favor of PP3M, if the bias had been corrected in some way in the following sense: Suppose some patients were wrongly censored, one possible way to fix them is to treat them as having a relapse, which would lead to a stronger evidence to support drug’s efficacy because time to relapse on these patients would be on average shorter for placebo patients than for PP3M patients. Based on the information in Table 3, the visual separation of the censoring CDF curves is probably mainly driven by (a) the imbalance in the number of patients who withdrew (23 on placebo vs 12 on PP3M), and/or (b) imbalance in the number of patients who completed the study due to study termination (80 on placebo vs 134 on PP3M).

If we consider the worst case scenario where all the withdrawn patients are supposed to be relapsed if staying, (a) would conclude that the drug effect is underestimated. To address (b), the cumulative percentages of patients randomized to placebo or treatment over time were plotted by randomization date below. Randomized patients who completed the study due to study

termination (80 vs 134) were considered here. The curves are fairly close to each other when not crossing, suggesting that the randomization appears to have worked out relatively well.

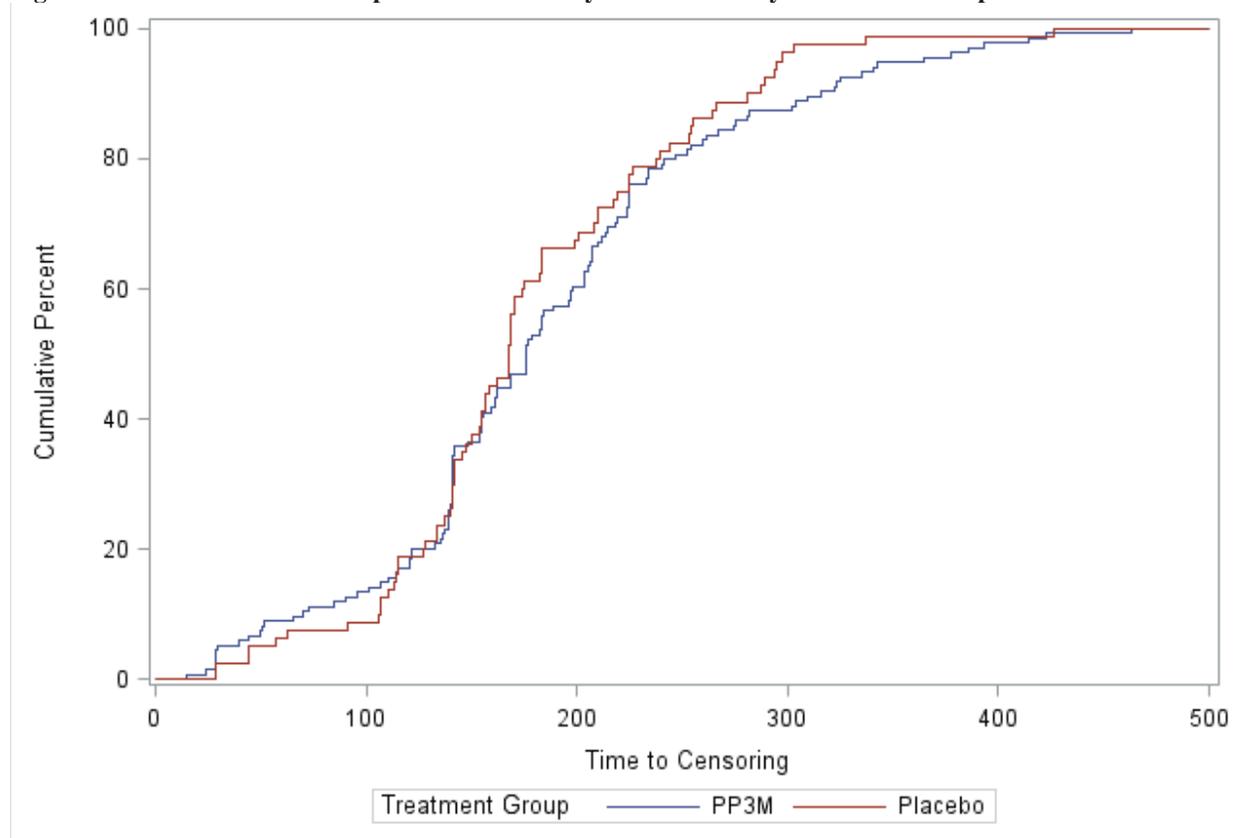
**Figure 9: Cumulative Distribution Function of Time of Randomization**



Source: reviewer's plot.

The CDFs of the completers due to study termination are shown below. There is some imbalance shown in distributions between the treatment groups. But it seems to share the same trend as we see in the CDF curves of time to censoring for all censored patients by the treatment groups.

**Figure 10: Distributions of Completers due to Study Termination by Treatment Group**



Source: reviewer's plot.

Also as seen earlier, the most common reasons for relapses were an increase of  $\geq 25\%$  in total PANSS score and psychiatric hospitalizations for both the interim analysis and the final analysis. They are also the reasons that deviate the numbers of relapse in the placebo group vs the PP3M group. However, if we examine the psychiatric diagnosis at the DB baseline (Table 11), the sponsor has shown that the psychiatric characteristics of subjects in the placebo and PP3M groups were generally similar, except for the mean (SD) duration of psychiatric hospitalization, which at study entry was numerically higher in the Placebo group than in the PP3M group (106.2 [322.88] vs. 80.7 [161.47]). They also suggested interpreting this information with caution because of large and unbalanced standard deviations and the imputation of missing dates/months.

In general, based on our findings in the exploratory analyses conducted, the evidence to conclude the efficacy of PP3M seems persuasive.

**Table 11: Selective Demographic Characteristics by treatment groups**

	Placebo (N=145)	PP3M (N=160)	Total ITT (DB) (N=305)
<b>Duration of psychiatric hospitalization prior to entry(days)</b>			
N	127	146	273
Mean (SD)	106.2 (322.88)	80.7 (161.47)	92.6 (249.71)
Median	36.0	31.5	33.0
Range	(1;2880)	(1;1159)	(1;2880)
<b>Baseline(DB) PANSS total</b>			
N	145	160	305
Mean (SD)	54.2 (9.34)	54.9 (9.95)	54.5 (9.66)
Median	55.0	57.0	56.0
Range	(31;69)	(32;69)	(31;69)

Source: reviewer's table based on table 13 on page 72.

### 3.3 Evaluation of Safety

Please refer to Dr. Burkhart's clinical review for details on the safety evaluation.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

Exploratory analyses based on Cox-proportional hazard models within each of these subgroups suggested that the efficacy of PP3M with regard to time to relapse of symptoms of schizophrenia was consistent regardless of age, sex, race, or region.

#### Age

Relapse occurred more frequently among subjects in the placebo group than PP3M for all 3 age groups.

**Table 12: Age group vs. Censor by Treatment Group**

Age group vs. Censor		PP3M	Placebo	Total
18-25	Relapse	4 (36.36%)	7 (63.64%)	11
	Censor	24 (64.86%)	13 (35.14%)	37
	Total	28	20	48
26-50	Relapse	10 (25.64%)	29 (74.36%)	39
	Censor	98 (56.98%)	74 (43.02%)	172
	Total	108	103	211
51-65	Relapse	0 (0%)	6 (100%)	6
	Censor	24 (60%)	16 (40%)	40
	Total	24	22	46

Source: reviewer's table.

### **Sex**

The proportion of subjects who experienced a relapse in the DB period was comparable between men and women.

**Table 13: Sex vs. Censor by Treatment Group**

Sex vs. Censor		PP3M	Placebo	Total
Female	Relapse	3 (23.08%)	10 (76.92%)	13
	Censor	39 (60.94%)	25 (39.06%)	64
	Total	42	35	77
Male	Relapse	11 (25.58%)	32 (74.42%)	43
	Censor	107 (57.84%)	78 (42.16%)	185
	Total	118	110	228

Source: reviewer's table.

### **Race**

A greater proportion of subjects in the placebo group experienced a relapse than in the PP3M group in all race groups of black subjects, white subjects and other.

**Table 14: Race vs. Censor by Treatment Group**

Race vs. Censor		PP3M	Placebo	Total
Black or African American	Relapse	4 (36.36%)	7 (63.64%)	11
	Censor	20 (58.82%)	14 (41.18%)	34
	Total	24	21	45
Other	Relapse	3 (33.33%)	6 (66.67%)	9
	Censor	29 (51.79%)	27 (48.21%)	56
	Total	32	33	65
White	Relapse	7 (19.44%)	29 (80.56%)	36
	Censor	97 (61.01%)	62 (38.99%)	159
	Total	104	91	195

Source: reviewer's table.

## **Region**

A greater proportion of subjects in the placebo group experienced a relapse than in the PP3M group in both the US and non-US regions.

**Table 15: Region vs. Censor by Treatment Group**

Region vs. Censor		PP3M	Placebo	Total
Non-US	Relapse	8 (20%)	32 (80%)	40
	Censor	120 (57.97%)	87 (42.03%)	207
	Total	128	119	247
US	Relapse	6 (37.5%)	10 (62.5%)	16
	Censor	26 (61.9%)	16 (38.1%)	42
	Total	32	26	58

Source: reviewer's table.

## **5 SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues**

No statistical issues identified.

### **5.2 Collective Evidence**

The 3-month formulation of paliperidone palmitate extended-release injectable suspension is shown to be superior compared with placebo in delaying the time to first occurrence of relapse at the nominal significance level of 0.0101 based on the interim analysis result ( $p=0.0002$ ) and confirmed by the final analysis result ( $p<0.001$ ).

### **5.3 Conclusions and Recommendations**

This reviewer concluded a favorable effect of the 3-month formulation of paliperidone palmitate extended-release injectable suspension in prolonging time to first occurrence of relapse.

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/s/  
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YANG WANG  
03/11/2015

PEILING YANG  
03/15/2015  
I concur with the primary review.

HSIEN MING J HUNG  
03/16/2015