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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Priority or Standard	Priority
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Division / Office	Division of Psychiatry Products/Office of New Drugs
Reviewer Name(s)	Christina P. Burkhart, M.D.
Review Completion Date	April 18, 2015
Established Name	Paliperidone Palmitate
(Proposed) Trade Name	INVEGA TRINZA
Therapeutic Class	Atypical Antipsychotic
Applicant	Janssen Pharmaceuticals, Inc.
Formulation(s)	Extended-Release Injectable Suspension for Intramuscular Use (3-month formulation)
Dosing Regimen	273, 410, 546, or 819 mg IM every 3 months
Indication(s)	Treatment of schizophrenia in adult patients who have been adequately treated with the 1- month paliperidone palmitate

injectable product for at least
four months
Intended Population(s) Adults with schizophrenia

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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.2	Risk Benefit Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	11
1.4	Recommendations for Postmarket Requirements and Commitments	11
2	INTRODUCTION AND REGULATORY BACKGROUND	11
2.1	Product Information	11
2.2	Currently Available Treatments for Proposed Indications.....	11
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues With Consideration to Related Drugs.....	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	12
2.6	Other Relevant Background Information	13
3	ETHICS AND GOOD CLINICAL PRACTICES.....	13
3.1	Submission Quality and Integrity	13
3.2	Compliance with Good Clinical Practices	14
3.3	Financial Disclosures.....	16
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	16
4.1	Chemistry Manufacturing and Controls	16
4.3	Preclinical Pharmacology/Toxicology	16
4.4	Clinical Pharmacology	16
4.4.1	Mechanism of Action.....	17
4.4.2	Pharmacodynamics.....	17
4.4.3	Pharmacokinetics.....	17
5	SOURCES OF CLINICAL DATA.....	18
5.1	Tables of Studies/Clinical Trials	18
5.2	Review Strategy	18
5.3	Discussion of Individual Studies/Clinical Trials.....	19
6	REVIEW OF EFFICACY	22
6.1	Indication.....	22
6.1.1	Methods	22
6.1.2	Demographics.....	30
6.1.3	Subject Disposition	43
6.1.4	Analysis of Primary Endpoint(s).....	47
6.1.5	Analysis of Secondary Endpoints(s).....	52
6.1.7	Subpopulations	57
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	57

7	REVIEW OF SAFETY	57
	Safety Summary	57
7.1	Methods	57
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	57
7.1.2	Categorization of Adverse Events	60
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	60
7.2	Adequacy of Safety Assessments	60
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	61
7.2.2	Explorations for Dose Response	61
7.2.3	Special Animal and/or In Vitro Testing	62
7.2.4	Routine Clinical Testing	62
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	62
7.3	Major Safety Results	62
7.3.1	Deaths	62
7.3.2	Nonfatal Serious Adverse Events	66
7.3.3	Dropouts and/or Discontinuations	70
7.3.4	Significant Adverse Events	72
7.3.5	Submission Specific Primary Safety Concerns	72
7.4	Supportive Safety Results	92
7.4.1	Common Adverse Events	92
7.4.2	Laboratory Findings	97
7.4.3	Vital Signs	102
7.4.4	Electrocardiograms (ECGs)	107
7.5	Other Safety Explorations	108
7.5.1	Dose Dependency for Adverse Events	108
7.5.2	Time Dependency for Adverse Events	108
7.5.3	Drug-Demographic Interactions	109
7.6	Additional Safety Evaluations	109
7.6.2	Human Reproduction and Pregnancy Data	109
7.6.3	Pediatrics and Assessment of Effects on Growth	110
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	110
7.7	Additional Submissions / Safety Issues	110
7.8	120 Day Safety Update for Study PSY-3011	115
8	POSTMARKET EXPERIENCE	119
9	APPENDICES	121
9.1	Literature Review/References	121
9.2	Labeling Recommendations	123
9.3	Advisory Committee Meeting	124
9.4	PSY-1005 Clinical Investigator Financial Disclosure	124
9.5	PSY-3012 Clinical Investigator Financial Disclosure	125

Clinical Review
Christina P. Burkhart, M.D.
NDA 207946
INVEGA TRINZA (Paliperidone Palmitate Extended-Release Injectable Suspension)

9.6	PSY-3011 Clinical Investigator Financial Disclosure	127
9.7	PSY-3012 Time and Events Schedule	129

Table of Tables

Table 1: Sites Requested for OSI Clinical Inspection	15
Table 2: Conversions Between PP1M Dose and PP3M Doses Using 3.5-Fold Multiple	25
Table 3: Study PSY-3012 Demographic and Baseline Characteristics for All Analysis Sets.....	31
Table 4: Study PSY-3012 Diagnosis and Psychiatric History at Baseline for All Analysis Sets.....	32
Table 5: Study PSY-3012 Psychotropic Medications Received Prior to Open-Label Phase by Double-Blind Analysis Set.....	34
Table 6: Study PSY-3012 Benzodiazepines Received During the Double-Blind Phase	35
Table 7: Study PSY-3012 Anti-EPS and Antihistamine Use During the Double-Blind Phase.....	35
Table 8: Study PSY-3012 Protocol Deviations During the Study--ITT (DB)	36
Table 9: PSY-3012 Protocol Deviations that Occurred During the Double-Blind Phase	37
Table 10: Study PSY-3012 Number of Injections of Open-Label Study Drug.....	40
Table 11: Study PSY-3012 Dose Levels Over Time During the Transition Phase	40
Table 12: Study PSY-3012 Dose Levels During the Maintenance Phase	40
Table 13: Study PSY-3012 Number of Injections of Double-Blind Study Drug.....	41
Table 14: Study PSY-3012 Cumulative Frequency Distribution of Total Drug Exposure (Days) During Double-Blind Phase	41
Table 15: Study PSY-3012 Extent of Exposure During Double-Blind Phase.....	42
Table 16: Study PSY-3012 Dose Levels Over Time and Final Dose During Double-Blind Phase.....	42
Table 17: Study PSY-3012 Cumulative Frequency of Total Drug Exposure (Days) of PP3M During Open-Label and Double-Blind Phases.....	43
Table 18: Study PSY-3012 Number of Subjects in Each Analysis Set by Study Phase	44
Table 19: Study PSY-3012 Completion/Withdrawal Information--Transition Phase	46
Table 20: Study PSY-3012 Completion/Withdrawal Information--Maintenance Phase .	46
Table 21: Study PSY-3012 Completion/Withdrawal Information--Double-Blind Phase .	47
Table 22: Study PSY-3012 Interim Analysis: Number (%) of Relapses by Treatment Group.....	48
Table 23: Study PSY-3012 Frequency Distribution of Relapse Types and Reasons During the Double-Blind Phase--Interim Analysis	49
Table 24: Study PSY-3012 Frequency Distribution of Relapse Types and Reasons During the Double-Blind Phase--Interim Analysis (Amended)	50
Table 25: Study PSY-3012 Final Analysis: Number (%) of Relapses by Treatment Group.....	51
Table 26: Study PSY-3012 PANSS Subscales/Marder Factor Scores--Change from Baseline (DB) to End Point (DB).....	54
Table 27: Study PSY-3012 Clinical Global Impression--Severity Score--Change from Baseline (DB) at End Point (DB).....	55
Table 28: Study PSY-3012 PSP--Change from Baseline (DB) (LOCF) at End Point (DB)	56

Table 29: Table of Studies Contributing Data to Summary of Clinical Safety	58
Table 30: Study PSY-3012 Overall Summary of TEAEs--Open-Label and Double-Blind Phases	62
Table 31: Ongoing Blinded Study PSY-3011 Deaths (as of May 31, 2014)	64
Table 32: PSY-3012 Treatment-Emergent SAEs During the Maintenance Phase	66
Table 33: PSY-3012 Treatment-Emergent SAEs During the Double-Blind Phase	67
Table 34: PSY-3011 Treatment-Emergent SAEs in Double-Blind Phase.....	68
Table 35: Study PSY-3012 TEAEs Leading to Study Drug Discontinuation During the Maintenance Phase	70
Table 36: PSY-3011 TEAEs Leading to Study Drug Discontinuation During the Double-blind Phase as of May 31, 2014.....	71
Table 37: PSY-3012 PP3M Severe TEAEs during Double-Blind Phase	72
Table 38: PSY-3012 Adverse Events of Special Interest	73
Table 39: PSY-3012 Most Severe Post Baseline (DB) Potentially Suicide-Related Category vs. Screening Based on C-SSRS During Double-Blind Phase	74
Table 40: PSY-3012 Treatment-Emergent EPS-Related AEs During the Maintenance Phase.....	75
Table 41: PSY-3012 Treatment-Emergent EPS-Related AEs During the Double-Blind Phase.....	76
Table 42: PSY-3012 Barnes Akathisia Rating Scale (BARS) Global Clinical Rating Score--Frequency Distribution at Baseline (DB) and End Point (DB).....	77
Table 43: PSY-3012 Anti-EPS and Antihistamine Drug Therapy Received During the Double-Blind Phase	77
Table 44: PSY-3012 Treatment-Emergent Potentially Prolactin-Related AEs During the Maintenance Phase	79
Table 45: PSY-3012 Treatment-Emergent Diabetes Mellitus and Hyperglycemia-Related AEs During the Double-Blind Phase.....	80
Table 46: PSY-3012 Injection Site Locations During Open-Label Phase (Week 17)	80
Table 47: PSY-3012 Injection Site Locations of Study Drug Over Time During the Double-Blind Phase	81
Table 48: PSY-3012 Subject Evaluation of Injection Site Pain Over Time During the Open-Label Phase	82
Table 49: PSY-3012 Investigator Evaluation of Injection Site INDURATION Over Time During the Double-Blind Phase.....	83
Table 50: PSY-3012 Investigator Evaluation of Injection Site REDNESS Over Time During the Double-Blind Phase.....	84
Table 51: PSY-3012 Investigator Evaluation of Injection Site SWELLING Over Time During the Double-Blind Phase.....	85
Table 52: PSY-3012 Subject Evaluation of Injection Site Pain Over Time During the Double-Blind Phase	86
Table 53: PSY-1005 Treatment-Emergent Injection Site-Related AEs	87
Table 54: PSY-3012 List of Subjects with Paliperidone Plasma Concentrations Higher than 125 ng/mL Checked for AEs After or Just Before the Observed High Concentration	90

Table 55: Study PSY-3012 TEAEs in at Least 2% of Subjects During Maintenance Phase.....	93
Table 56: Study PSY-3012 TEAEs in at Least 2% of Subjects in Either Treatment Group During the Double-Blind Phase.....	94
Table 57: Study PSY-3011 TEAEs During the Double-Blind Phase (Cut-Off Date of 5/31/14).....	96
Table 58: PSY-3012 Laboratory Values—Mean Change from Baseline (DB) to End Point (DB)	97
Table 59: PSY-3012 Fasting Glucose and Lipids in US Units—Mean Change from Baseline (DB) to End Point (DB).....	98
Table 60: Psy-3012 Fasting Glucose--Treatment-Emergent Shifts from Baseline (OL) to Maximum Post Baseline (DB) Value	99
Table 61: PSY-3012 Fasting Lipids: Treatment -Emergent Shifts from Baseline (DB) during the Double-Blind Phase	99
Table 62: Psy-3012 Number of Subjects with Treatment-Emergent Markedly Abnormal Lab Values Relative to Baseline (OL) at Any Time During the Double-Blind Phase.....	102
Table 63: Psy-3012 Vital Signs--Mean Change from Baseline (DB) to End Point (DB)	103
Table 64: PSY-3012 Number of Subjects with Treatment-Emergent Abnormal Vital Signs Relative to Baseline (DB) at Any Time During the Double-Blind Phase	104
Table 65: PSY-3012 Number of Subjects with Treatment-Emergent Abnormal vital Signs Relative to Predose (OL) at Any Time During the Double-Blind Phase	105
Table 66: PSY-3012 Weight, BMI, and Weight Circumference--Change from Baseline (OL) to End Point (DB).....	106
Table 67: PsSY-3012 Number of Subject with Abnormal Weight Percent Change from Baseline (DB and OL) at Endpoint (DB).....	107
Table 68: Psy-3012 Number of Subjects with Treatment-Emergent Abnormal ECG Values Relative to Average Predose at Any Time During the Double-Blind Phase.....	108
Table 69: Cumulative Frequency Distribution of Total Drug Exposure	116
Table 70: PSY-3011 Additional SAEs from SCS Cutoff to 4MSU Cutoff	117
Table 71: PSY-3011 TEAEs Leading to Study Drug Discontinuation During the DB Phase from SCS Cutoff to 4MSU Cutoff	118
Table 72: Study PSY-3011 Most Common TEAEs ($\geq 2\%$) During Double-Blind Phase as of November 11, 2014	119
Table 73: Applicant's Brief Summary of Publications (3/1/2014 to 5/31/2014)	122

Table of Figures

Figure 1: Diagrammatic Representation of Study PSY-3012	25
Figure 2: Study PSY-3012 Completion and Withdrawal Information	45
Figure 3: Study PSY-3012 Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase--Interim Analysis	48
Figure 4: Study PSY-3012 Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase--Final Analysis	51
Figure 5: Study PSY-3012 Arithmetic Mean PANSS Total Scores Over Time (LOCF) .	53
Figure 6: Study PSY-3012 Arithmetic Mean PSP Score Over Time (LOCF).....	56
Figure 7: Design of Phase 3 Noninferiority Study Psy-3011.....	59
Figure 8: PSY-1005 Injection Site Pain Ratings Based on VAS Scale.....	88
Figure 9: PSY-3012 Median Prolactin Values for Male Subjects Who Entered the Double-Blind Phase Over Time	100
Figure 10: PSY-3012 Median Prolactin Values for Female Subjects Who Entered the Double-Blind Phase Over Time	101
Figure 11: Injection Profile of Batch, 1.75-mL Syringe after 15 Seconds Shaking Time	113
Figure 12: Injection Profile of a Non-Shaken Batch, 1.75-mL Syringe	114

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that the Division take an Approval action for NDA 207946. The Applicant has submitted an adequate and well-controlled trial that demonstrates the efficacy of INVEGA TRINZA (PP3M), a 3-month formulation of paliperidone palmitate, in the treatment of schizophrenia. In the Double-blind Phase of the pivotal trial (PSY-3012), PP3M was superior to placebo in delaying relapse of symptoms of schizophrenia in subjects who had achieved satisfactory symptom control during the 29-week Open-label treatment. Based on the preplanned interim analysis conducted after the 42nd relapse event, there was a statistically significant difference between the 2 treatment groups in the time to relapse of symptoms of schizophrenia in favor of PP3M. Three times as many subjects in the Placebo group (23%) as in the PP3M group (7%) experienced a relapse event. Therefore, the trial was terminated early as prespecified in the Statistical Analysis Plan. In addition, the safety profile of PP3M appears to be generally consistent with that of the 1-month formulation of paliperidone palmitate (PP1M), INVEGA SUSTENNA. No new safety signals were detected.

1.2 Risk Benefit Assessment

Schizophrenia is a serious, disabling, and persistent psychiatric disease associated with significant impairment of functioning. Many patients with schizophrenia have difficulty adhering to a daily oral treatment regimen. The approval of INVEGA SUSTENNA (PP1M) offered these patients a 1-month treatment option to help with compliance. The approval of INVEGA TRINZA (PP3M) would offer the additional benefit of a 3-month treatment option. Currently, there are no other long-acting (3-month) formulations of depot antipsychotics available.

The safety of PP3M at doses of 175 to 525 mg eq. in the treatment of schizophrenia patients who had previously received PP1M injections over a period of at least 4 months is supported by the safety findings from 2 completed clinical studies (379 subjects in the pivotal Phase 3 Study PSY-3012 and 308 subjects in Phase 1 PK Study PSY-1005, who received at least one dose of PP3M) and limited blinded safety data from an estimated 508 subjects in an ongoing Phase 3 non-inferiority study for global registration (PSY-3011). As stated previously, the safety profile of PP3M in these studies has been generally consistent with that of PP1M. No new safety signals have been detected.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine risk minimization (i.e., FDA-approved product label) and routine pharmacovigilance will be adequate to manage the risk-benefit profile of INVEGA TRINZA in the treatment of schizophrenia.

1.4 Recommendations for Postmarket Requirements and Commitments

No Postmarket Requirements and Commitments are planned at this time.

2 Introduction and Regulatory Background

2.1 Product Information

PP3M is the 3-month formulation of paliperidone palmitate. Paliperidone palmitate is the palmitate ester prodrug of paliperidone (9-hydroxy-risperidone). It is a selective, monoaminergic antagonist that exhibits the dopamine Type 2 (D2) and serotonin type 2A (5HT2A) antagonism of the second-generation, antipsychotic drugs. The main differences between the 3-month formulation of paliperidone palmitate (PP3M) and the 1-month formulation of paliperidone palmitate (PP1M) are the (b) (4), the increased concentration, and the larger injection volume.

The target indication for PP3M is for treatment of schizophrenia in subjects who have been first treated for 4 or more months with paliperidone palmitate 1-month formulation (PP1M). Due to the slow release characteristics of PP3M, the product is not intended to be used for initiation of treatment in acutely symptomatic patients or in patients who are immediately transitioning from oral to long-acting injectable (LAI) antipsychotic therapy. Rather, PP3M is intended to be used in patients who have already demonstrated therapeutic effect and tolerability with PP1M during treatment over a period of at least 4 months at the time of initiation of PP3M.

2.2 Currently Available Treatments for Proposed Indications

Antipsychotic drugs are the treatment of choice for patients with schizophrenia. There are two broad classes of antipsychotic drugs: typical (“first-generation”) antipsychotic drugs and the atypical (“second-generation”) antipsychotics. Some examples of typical antipsychotics include haloperidol and perphenazine. Some examples of atypical antipsychotics include aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Some examples of long-acting injectable antipsychotics include Invega Sustenna, Risperdal Consta, and Abilify Maintena.

2.3 Availability of Proposed Active Ingredient in the United States

The PP3M formulation is not currently approved in any country. PP1M (INVEGA SUSTENNA®) is widely available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Important safety issues common to the class of atypical antipsychotics include:

- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
- Neuroleptic Malignant Syndrome
- QT Prolongation
- Tardive Dyskinesia
- Metabolic changes that may increase cardiovascular/cerebrovascular risk (e.g., hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain)
- Orthostatic Hypotension and Syncope
- Leukopenia, Neutropenia, and Agranulocytosis
- Hyperprolactinemia
- Potential for Cognitive and Motor Impairment
- Seizures

Injection site reaction is also an important safety issue with respect to long-acting injectable antipsychotics.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

INVEGA SUSTENNA (PP1M) was approved for the treatment of schizophrenia in adults on July 31, 2009 (NDA 22-264) and for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants on November 12, 2014 (NDA 22-264, S-013 and -014).

The Sponsor scheduled 4 meetings with the FDA in order to discuss the development of the PP3M formulation. The Sponsor first met with the FDA at a pre-Investigational New Drug (IND 76,952) meeting on 20 August 2007. At that meeting, the FDA and the Applicant reached the following agreements:

- We agreed that one adequate and well-controlled clinical efficacy and safety study would be needed to support review and approval of PP3M and that the Sponsor's proposed placebo-controlled relapse prevention study involving patients who had been treated and were currently clinically stable on PP1M would be acceptable to address this requirement.
- We agreed that the proposed nonclinical program including a preclinical local tolerability study comparing the PP1M vs. PP3M formulations was adequate.

- We agreed on the PK program consisting of a single-dose Phase 1 study in subjects with schizophrenia or schizoaffective disorder. The Applicant also proposed to use population PK modeling based on samples collected in the Phase 1 and Phase 3 studies to characterize the PK of multiple doses of PP3M.

An End-of-Phase 2 (EOP2) was held on 4 November 2011 to present initial findings from the Phase 1 PK and tolerability study with PP3M (R092670-PSY-1005) and to discuss the Phase 3 program. Overall, the Division was in agreement with the proposed PP3M program. The Division agreed with the adequacy of planned preclinical studies, PK program, and planned safety exposure for filing. With respect to the pivotal Phase 3 relapse prevention study (R092670-PSY-3012), agreement was reached at this meeting and following submission of the draft statistical analysis plan (SAP) for Study R092670-PSY-3012 on the number of relapse events to be observed prior to interim and final analyses. The final SAP for R092670-PSY-3012 was submitted to IND 76,952 on 28 January 2014. A separate EOP2 meeting to discuss Chemistry, Manufacturing and Controls (CMC) information was held on 8 December 2011.

A pre-NDA meeting, scheduled for 24 July 2014, was subsequently canceled after the Division indicated its overall agreement with the Sponsor's proposals in its preliminary comments regarding the content of the submission.

2.6 Other Relevant Background Information

The Applicant requested and was granted priority review status for this NDA.

The Applicant also requested and was granted a full waiver for conducting studies in pediatric patients (ages 0 to 17 years) with schizophrenia. The Applicant had previously requested and was granted a full waiver for conducting studies in a pediatric population for PP1M (Invega Sustenna). The Division of Psychiatry Products supported the request for a full waiver.

Loretta Holmes (DMEPA) has completed a review of the proposed proprietary name, INVEGA TRINZA, and has concluded that this name is acceptable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No problems with data quality or integrity were identified. The submission was organized and electronic navigation was not difficult.

The following clinical information requests were sent to the Applicant:

- The Applicant was asked to provide a list of protocol violations that occurred specifically during the Double-Blind Phase of Study PSY-3012.
- Incomplete doses of PP3M were administered during two panels of the pivotal PK study (Study PSY-1005). According to the Applicant, the staff was retrained and no further difficulties with incomplete administration of study drug occurred. The Applicant was asked to specifically describe the retraining process. Please see Section 7.7 for a discussion of this and related issues.

3.2 Compliance with Good Clinical Practices

The Applicant states that Study PSY-1005 and PSY-3012 were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. In addition, Janssen certified that they did not use in any capacity the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.

The Division requested an OSI Consult for routine inspections of the following clinical sites:

Table 1: Sites Requested for OSI Clinical Inspection

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects
Site#: 001933 Jason Bermak, M.D., Ph.D. SF-Care 1330 Lincoln Avenue, Suite 308 San Rafael, CA 94901, USA Phone: 949-683-1123 and Office is 415-747-8474 FAX: 415-785-3655 Email:Jason@sf-care.com	R092670-PSY-3012	14 enrolled 8 randomized to DB
Site#: 001970 John Sonnenberg, Ph.D. Uptown Research Institute, LLC. 1021 W Lawrence Ave Chicago, IL, 60640, USA Phone: 773-989-8313 x118 FAX: 773-989-9692 Email: jsonnenberg@uptownresearch.com	R092670-PSY-3012	15 enrolled 9 randomized to DB
Site#: 001971 Ronald Brenner, M.D. Neurobehavioral Research, Inc 74 Carman Ave Cedarhurst, NY, 11516 USA Phone: 516-295-7230 FAX: 516-295-7232 Email: RBrenner@NBRresearch.com	R092670-PSY-3012	20 enrolled 12 randomized to DB

In the Clinical Inspection Summary (2/25/2015), Dr. Jenn Sellers (OSI) states that the above three clinical investigator sites were inspected in support of this NDA and that no significant regulatory violations were noted at these sites. Based on results of these inspections, she states that it appears that the data submitted by the Applicant in support of the requested indication are acceptable and that the studies appear to have been conducted adequately.

3.3 Financial Disclosures

See Appendix 9.3, 9.4, and 9.5.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Given the drug substance and mechanism of release are identical for the approved paliperidone palmitate 1-month formulation (F013) and the 3-month formulation (F015), this NDA cross references the drug master file (DMF) 20902 and DMF 18915 for complete Chemistry, Manufacturing and Controls (CMC) information on the paliperidone palmitate Active Pharmaceutical Ingredient (API) in the PP3M formulation.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical toxicology support for the 3-month injectable formulation (F015) is largely derived from the nonclinical experience with the 1-month long acting injectable formulation (F013). The 3-month formulation (F015) has the same active ingredient and excipients as the 1-month formulation (F013) but at different concentrations. Because the **concentration** of the active ingredient and the excipients of the 3-month formulation are different from the 1-month formulation, the local tolerability of the 3-month formulation was not covered by existing data. Local tolerability studies with the 3-month injectable formulation (F015) in the minipig were conducted to investigate the effect of the injection of the higher volume of formulation and the higher amount of paliperidone palmitate. Minipigs were dosed up to the highest clinical dose of F015 and F013; a single injection of F015 at 525 mg was compared with 3 injections of F013 at 150 mg. According to the Applicant, "at necropsy, i.m. injection of the paliperidone palmitate formulations in the skeletal muscle resulted in dose-related local reactions, with no relevant differences between the 2 formulations. These local reactions were confirmed at the histological level. There were no clear-cut differences in quantitative (multi)focal chronic inflammation between the 2 formulations." Please see Dr. Elzbieta Chalecka-Franaszek's (Pharm/Tox) review for further details of the nonclinical program.

4.4 Clinical Pharmacology

Please see the review by Dr. Kofi Kumi for full details of the clinical pharmacology of PP3M. Please also see the Pharmacometrics Review by Dr. Dinko Rekić. I have discussed his conclusions on dosing in Section 9.2 Labeling Recommendations.

A brief discussion of the design and results of the pivotal PK study (PSY-1005) can be found in Section 5.3.

The following information is excerpted from the proposed label:

4.4.1 Mechanism of Action

The mechanism of action of paliperidone is unknown. It has been proposed that the therapeutic activity of paliperidone in schizophrenia is mediated through a combination of central dopamine Type 2 (D₂) and serotonin Type 2 (5HT_{2A}) receptor antagonism.

4.4.2 Pharmacodynamics

Paliperidone is a centrally active dopamine Type 2 (D₂) receptor antagonist and a serotonin Type 2 (5HT_{2A}) receptor antagonist. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H₁ histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β_1 - and β_2 -adrenergic receptors.

4.4.3 Pharmacokinetics

The 3-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The release of the drug starts as early as day 1 and lasts for as long as 18 months. Following a single intramuscular dose of PP3M, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T_{max} of 30-33 days. Following intramuscular injection of PP3M at doses of 273-819 mg in the deltoid muscle, on average, an 11-12% higher C_{max} was observed compared with injection in the gluteal muscle. The release profile and dosing regimen of PP3M results in sustained therapeutic concentrations. The total exposure of paliperidone following PP3M administration was dose-proportional over a 273-819 mg dose range (b) (4). The mean steady-state peak:trough ratio for a PP3M dose was 1.6 following gluteal administration and 1.7 following deltoid administration. Following administration of PP3M, the apparent volume of distribution of paliperidone is 1960 L. (b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study Type/ Protocol ID	Study Description	Study Treatments	No. of Subjects
Completed Phase 3 Relapse Prevention Study			
PSY-3012	Randomized, double-blind, placebo-controlled, multicenter, relapse prevention study of variable duration preceded by a 17-week, open-label transition phase ^a with PP1M and a 12-week open-label maintenance phase with PP3M	PP3M (fixed dose ^b : 175, 263, 350, or 525 mg eq./3 mos based on 3.5 times PP1M dose at end of OL transition phase) Placebo (DB phase only)	Number of Subjects Evaluable for Safety: 506 OL transition phase: 506 OL maintenance phase: 379 DB phase: PP3M: 160 Placebo: 145
Ongoing Blinded Phase 3 Noninferiority Study			
PSY-3011	Randomized, double-blind, parallel group, multicenter noninferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase ^c with PP1M	PP3M (fixed dose ^c : 175, 263, 350, or 525 mg eq./3 mos based on 3.5 times PP1M dose at end of OL stabilization phase) PP1M (fixed dose: 50, 75, 100, or 150 mg eq./4 wks based on PP1M dose at end of OL stabilization phase)	OL stabilization phase completed, n=1429 DB phase ongoing, n=1016 (blinded) Estimated 508 each on PP3M and PP1M based on 1:1 randomization ratio
Completed Phase 1 PK and Safety Study			
PSY-1005	Randomized, single-dose, open-label, parallel group, multicenter study consisting of 4 panels, with each panel including 2 single dose treatment periods (paliperidone IR in period 1 and PP3M in period 2). In each panel the single dose of PP3M was followed by a 364- to 544-day observation period for PK and safety evaluations.	PP3M: Panel A: 300 mg eq., gluteus (F015 wet or dry milled) Panel B: 75, 150, 450 mg eq., gluteus, or 300 or 450 mg eq., deltoid (F015 wet milled) Panel C: 150 mg eq., gluteus (F016 wet milled) Panel D: 175 or 525 mg eq., deltoid, or 350 or 525 mg eq., gluteus (F015 wet milled)	Number of Subjects Evaluable for Safety: 325 ^d Treated with PP3M: 308 Panel A: 66 Panel B: 120 Panel C: 24 Panel D: 98

Summary of Clinical Safety, p.7

PSY-3012 was the pivotal study to establish safety and efficacy. PSY-3011 is currently ongoing. Only limited blinded safety data has been submitted for this study. This study provides additional estimated exposure data for PP3M.

5.2 Review Strategy

I reviewed the following: Clinical Study Reports (PSY-1005 and PSY-3012), Clinical Overview, Summary of Clinical Safety, Meeting Minutes, Responses to Information Requests, Draft label, Postmarketing Experience, Literature Summary, 120 Safety Update, Identification of ADRs document, select JMP/JReview datasets, and narratives.

I also reviewed the draft/final reports submitted by the following disciplines/consultants:

- Proprietary Name Review by Loretta Holmes, BSN, Pharm. D. from the Division of Medication Error Prevention and Analysis (DMEPA)
- Review by Rakhi Dalal, Ph.D., CDRH/Office of Compliance/Division of Manufacturing and Quality/Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch [CDRH/OC/DMQ/REGO]
- Clinical Inspection Site Report by Dr. Jenn Sellers (OSI/DGCP)
- Review by Kathleen Fitzgerald (Nurse Consultant), CDRH/ODE/DAGRID/GHDB
- Statistical Review by Yang Wang, Ph.D., Office of Biostatistics
- Pharmacology/Toxicology review by Elzbieta Chalecka-Franaszek, Ph.D.
- Pharmacometrics review by Dinko Rekić, MSc, Ph.D.
- Patient Labeling Collaborative Review by Twanda Scales, RN, MSN/Ed., Division of Medical Policy Programs; and Susannah O'Donnell, MPH, Office of Prescription Drug Promotion
- Review by Kofi Kumi, Ph.D., OCP
- Labeling recommendations from the Division of Pediatric and Maternal Health

5.3 Discussion of Individual Studies/Clinical Trials

Study PSY-3012 is the pivotal study to establish efficacy and safety for PP3M. Study PSY-3012 will be reviewed in Section 6 (efficacy) and Section 7 (safety).

Study PSY-3011, an ongoing noninferiority study for global registration, primarily supplies further estimated exposure data for PP3M. Study PSY-3011 also supplies blinded safety data for major events (deaths, SAEs, and discontinuations secondary to AEs). The design of Study PSY-3011 and the currently available limited blinded safety data will be detailed in Section 7 of this review.

Study PSY-1005, a Phase 1 PK study, provides some additional exposure and safety data. The utility of this safety data is limited given that the study was an open-label study of a single dose against a background of oral antipsychotics (subjects were allowed to continue their oral antipsychotics). The design and major PK conclusions of Study PSY-1005 will be described below. Please see the review by Dr. Kofi Kumi (OCP) for further details. Safety data from Study PSY-1005 will be detailed in Section 7 of this NDA review.

Study PSY-1005 (excerpted from Summary of Clinical Safety)

Study PSY-1005 was a multicenter, randomized, open-label, parallel-group single dose study in subjects with schizophrenia designed to evaluate the pharmacokinetics, safety, and tolerability of PP3M, and to document the relative bioavailability in comparison with a 1-mg immediate-release (IR) formulation of paliperidone.

The study consisted of 4 separate treatment panels (Panel A, B, C, and D). In each panel, a screening phase was followed by 2 single-dose treatment periods. In Period 1, subjects received an intramuscular injection of a 1-mg paliperidone IR solution followed by a 96 hour observation period. Subjects who tolerated this injection and completed all assessments were eligible to enter Period 2. In Period 2, subjects received a single dose of PP3M. Administration of PP3M in Period 2 was followed by a 364-day observation period in Panel A and Panel C; in Panel D, and if subjects in Panel B consented to participation in the extension period, the follow-up duration in Period 2 was increased by approximately an additional 26 weeks (to 544 days) in order to enable better characterization of the PK profile. Study drug administration in Period 1 and Period 2 was separated by a 7- to 21-day washout period. All patients were psychiatrically stable upon entry into the study and **remained on their current oral antipsychotic medications, which could be flexibly dosed or changed due to AEs**¹ in order to address worsening of schizophrenia symptoms, throughout the course of the study.

A total of 308 subjects with schizophrenia received a single dose of PP3M in this study (66 in Panel A, 120 in Panel B, 24 in Panel C, and 98 in Panel D). Subjects were allowed to receive concomitant antipsychotics (with the exception of risperidone, paliperidone, or other LAI antipsychotics) throughout the course of the study.

Panel A: The primary objective of Panel A was to confirm whether the PP3M (F015) formulation exhibited an appropriate release profile for a 3-monthly dosing interval as well as an acceptable local tolerability and safety profile that was comparable to the 1-month formulation. The F015 formulation has (b) (4) versus the PP1M formulation and higher suspension strength. Two manufacturing techniques (wet and dry milling) that provided different particle size distributions were tested. Only gluteal injections were allowed in Panel A.

Panel C: In Panel C (occurred prior to Panel B), the effect of lower suspension strength on the release profile of paliperidone palmitate was investigated. To support Panel B, it was decided to first conduct Panel C. The F016 formulation tested in this panel had (b) (4) as the 3-monthly F015 formulation, but a suspension strength that was equal to that of the 1-monthly F013 formulation. This formulation provided the link between the 3-monthly F015 formulation and the 1-monthly F013 formulation and allowed (b) (4) on the PK profile. Lower than expected exposure to the study agent was observed in Panels A and C due to incomplete injection in some subjects.² The sponsor states that this issue was resolved prior to initiating the Phase 3 program.

¹ Reviewer comment: Safety data is therefore difficult to evaluate in this context due to confounding from changing doses of oral antipsychotic medications.

² Incomplete injections were administered in some subjects in Panels A and C due to inadequate shaking of the Period 2 medication (PP3M) prior to injection. The sponsor states that with increased training of trial personnel prior to the initiation of Panel B and Panel D, there were no issues related to incomplete

Panel B: The primary objective of Panel B was to evaluate the single-dose PK, safety, and tolerability of PP3M (F015) over the entire expected therapeutic dose range after gluteal administration. The PK and safety profile of paliperidone palmitate after injections in the deltoid muscle was also documented to provide a choice of injection sites to subjects receiving the 3-monthly formulation.

Panel D: The primary objective of Panel D was to evaluate the single-dose PK, safety and tolerability over the entire expected therapeutic dose range after gluteal and deltoid administration to extend the findings of Panel B. In Panel D, all subjects participated in an extension period for the duration of approximately an additional 26 weeks to obtain additional assessments enabling better characterization of the PK profile. Panel D was initiated before completion of Panel B.

The conclusions of Study PSY-1005 were as follows (excerpted from study report):

- The F015 version of paliperidone palmitate may be given as a once every three month medication with similar tolerability of injection as PP1M and was chosen as the formulation to further assess the efficacy and safety of PP3M in the treatment of schizophrenia in pivotal Phase 3 studies.
- After i.m. injection of 75-525 mg-eq. paliperidone palmitate (F015) in the gluteal or deltoid muscle, paliperidone palmitate is slowly absorbed, reflected by a T_{max} of approximately 23 to 34 days and an apparent half-life of approximately 2-4 months; the half-life was similar in the gluteal and deltoid dose groups, except for the 75 mg eq. gluteal dose group where the half-life was slightly lower compared to the other dose groups.
- After a single i.m. injection of paliperidone palmitate (F015) in the gluteal or deltoid muscle, the paliperidone AUC_{∞} and C_{max} increased dose-proportionally in the 75-525 mg-eq. range.
- The LSmeans of C_{max} of paliperidone was higher after injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (27% increase over all dose levels) whereas there was no difference between both injection sites for AUC_{∞} .
- Intramuscular injections of paliperidone palmitate are well tolerated in both the gluteal and the deltoid muscle.
- After injection of paliperidone palmitate (F015) the paliperidone AUC_{∞} and C_{max} were independent of BMI, or race. Exposure (Median C_{max}) was slightly higher in males after single dose administration.
- The relative bioavailability approximated 100%, independent of dose, injection site, BMI, race or gender.
- The estimated inter-subject variability (coefficient of variation, %CV) for the AUC_{∞} and C_{max} varied between 22.0 and 34.8 and 49.1 and 99.2 respectively, for the different treatment groups.

injection of the study agent due to incomplete shaking, as observed in Panels A and C.

- After i.m. administration of paliperidone palmitate, a low incidence of low paliperidone palmitate concentrations was observed in venous samples, similar to the 1-month formulation.

6 Review of Efficacy

Please also see the review by Dr. Yang Wang of the Office of Biostatistics. In her review, she concludes that 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.”

Study RO92670PSY3012 (Study PSY-3012) Efficacy Summary

In the Double-blind Phase, PP3M was superior to placebo in delaying relapse of symptoms of schizophrenia in subjects who had achieved satisfactory symptom control during the 29-week Open-label treatment. Based on the preplanned interim analysis conducted after the 42nd relapse event, there was a statistically significant difference between the 2 treatment groups in the time to relapse of symptoms of schizophrenia in favor of PP3M. The final analysis of the relapse data confirmed the findings of the interim analysis. There was a statistically significant difference between the 2 treatment groups in the time to relapse with a longer time to relapse in subjects assigned to PP3M ($p < 0.0001$). Three times as many subjects in the Placebo group (29.0%) as in the PP3M group (8.8%) experienced a relapse event. The most common reasons for relapse were increase in PANSS total score and psychiatric hospitalization. Analyses of the efficacy of PP3M compared with placebo with regards to time to relapse of symptoms of schizophrenia was consistent after adjusting for age, sex, race, BMI or region. Analyses of secondary efficacy variables provided further evidence of the efficacy of PP3M in the maintenance treatment of subjects with schizophrenia.

6.1 Indication

Study PSY-3012 was a placebo-controlled randomized withdrawal study designed to demonstrate the superiority of PP3M over placebo in the maintenance treatment of adults 18 to 70 years who have a DSM-IV diagnosis of schizophrenia and remained clinically stable during initial treatment with PP1M over a 17-week period and PP3M over a 12-week period before randomization.

6.1.1 Methods

Title of Study: “A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3-Month Formulation for the Treatment of Subjects with Schizophrenia”

Study Centers: Colombia (5 sites), Malaysia (3 sites), Mexico (5 sites), Romania (5 sites), South Korea (3 sites), Turkey (2 sites), United States (14 sites), Ukraine (27 sites)

Study Period: 26 April 2012 to 09 April 2014

Objectives:

Primary Objective

- To evaluate the efficacy of paliperidone palmitate 3-month formulation (PP3M) compared with placebo in delaying the time to first occurrence of relapse of the symptoms of schizophrenia

Secondary Objectives

- To evaluate the improvement in the symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) associated with the use of PP3M compared with placebo
- To assess the change in the severity of illness associated with the use of PP3M as measured by the change in Clinical Global Impression-Severity (CGI-S) scale compared with placebo
- To assess the change in functional status with the use of PP3M as measured by the change in Personal and Social Performance (PSP) scale compared to placebo
- To assess the safety and tolerability of PP3M compared to placebo
- To assess the pharmacokinetics (PK) of PP3M including its relationship with demographic and dose-related variables

Design:

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study designed to determine the efficacy and safety of PP3M in the prevention of relapse of schizophrenia. The study consisted of 4 phases:

- **Screening Phase:** up to 3 weeks
- **Transition Phase:** 17-week, flexible dose, open label (PP1M)
- **Maintenance Phase:** 12-week, fixed dose, open-label (PP3M)
- **Double-blind Phase:** Randomized, double-blind, fixed dose, placebo-controlled relapse prevention phase of variable duration (PP3M versus placebo)

Screening Phase

Subjects with schizophrenia, who were either stable with safety or tolerability problems with their current medications or were in a state of acute exacerbation and who met all entry criteria at screening, were enrolled. If necessary, subjects had their current disallowed psychotropic medications tapered and discontinued during the Screening Phase. An oral tolerability test was required for subjects with no documented history of exposure to oral or LAI formulations of risperidone or paliperidone. Screening, washout, and tolerability testing could be conducted while a subject was an inpatient or an outpatient.

Transition Phase (17 weeks)

All subjects except for those switching from other LAI antipsychotics and those who were already on PP1M prior to study entry received PP1M for 120 days. These 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, both in the deltoid muscle. For stable subjects who continued on PP1M at study entry or subjects who switched from other LAIs, a full injection cycle must have elapsed between the time of the last depot injection and the first dose of PP1M was administered on Day 8. Injections on Day 36 and on Day 64 were given in either the deltoid or gluteal muscle and 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 weeks)

At the start of the 12-week Maintenance Phase (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 Double-blind Phase at Week 29.

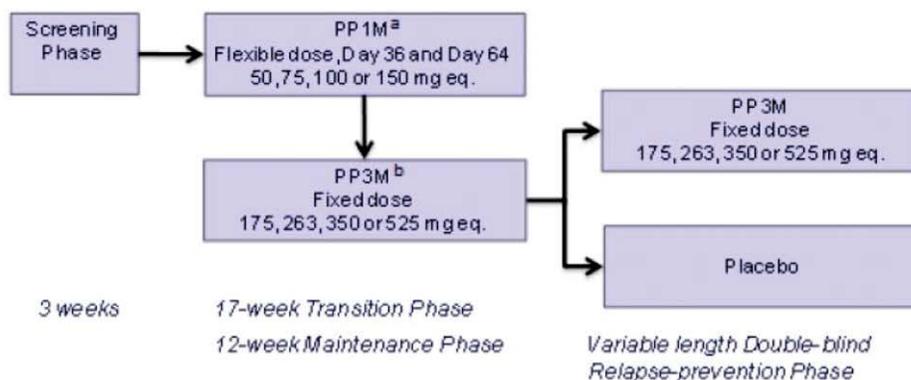
The Transition Phase and Maintenance Phase together are referred to as 'Open-label Phase' for reporting of the analysis results.

Double-blind Phase

At the start of the Double-blind Phase (Day 204/Week 29), subjects were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M or placebo. Subjects assigned to PP3M received the same dose of study agent that was administered on Day 120 of the Maintenance Phase; the dose was to remain fixed throughout the Double-blind Phase. The length of the Double-blind Phase was variable in duration. Subjects remained in the Double blind 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 is not positive.

Figure 1: Diagrammatic Representation of Study PSY-3012

Figure 1: Study R092670PSY3012 Flowchart
 (Study R092670PSY3012)



- ^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). See Table 3 for details of conversion between PP1M and PP3M doses.

Source: Study report, p. 29

Table 2: Conversions Between PP1M Dose and PP3M Doses Using 3.5-Fold Multiple

Table 3: Conversion Between PP1M Dose and PP3M Doses Using 3.5-Fold Multiple
 (Study R092670PSY3012)

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.

mg eq.=milligram equivalents; PP1M=paliperidone palmitate 1 month formulation; PP3M=paliperidone palmitate 3 month formulation

Source: Study report, p. 40

Subjects:

Inclusion Criteria

- Men and women between 18 and 70 years of age
- Diagnosis of schizophrenia (DSM-IV-TR) for at least 1 year
- Total PANSS score of <120 at screening and Baseline (Day 1)
- Had a valid reason to discontinue current antipsychotic therapy (including insufficient efficacy with current therapy, safety or tolerability issues, or subject preference for injectable medications)

Clinical Review

Christina P. Burkhart, M.D.

NDA 207946

INVEGA TRINZA (Paliperidone Palmitate Extended-Release Injectable Suspension)

- Women had to be postmenopausal for at least 2 years, surgically sterile, or practicing or agreed to practice an effective method of birth control if they were sexually active. Men had to agree to use a double-barrier method of birth control and to not donate sperm during the study and for 6 months after receiving the last dose of study agent
- BMI (kg/m^2) of ≥ 17.0
- Medically stable on the basis of a physical examination at baseline, and medical history, vital signs, 12-lead ECG, and clinical laboratory tests performed at screening
- Subjects who were taking another LAI antipsychotic (including PP1M or Risperdal CONSTA) prior to study entry had to be symptomatically stable in the judgment of the investigator.

Criteria to Enter Maintenance Phase:

- After treatment with open-label paliperidone palmitate (PP1M) during the Transition Phase, subjects had to have a PANSS total score < 70 at Visit 8 (Week 17) to enter the Maintenance Phase.

Criteria to Enter Double-Blind Phase (Subjects had to meet each of the clinical stability criteria at Visits 9, 10, and 11 [Weeks 21 through 29]):

- A score of < 70 in the PANSS total score
- Scores of ≤ 4 for PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness) and G14 (poor impulse control)

Exclusion Criteria

- Primary, active DSM-IV-TR Axis I diagnosis other than schizophrenia (e.g., dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, schizophreniform disorder, autistic disorder, primary substance-induced psychotic disorder)
- DSM-IV-TR diagnosis of active substance dependence within 6 months before screening
- Attempted suicide within 12 months before screening or were at imminent risk of suicide or violent behavior
- Involuntarily committed to psychiatric hospitalization at the time of screening
- Relevant history or current presence of any significant or unstable cardiovascular, respiratory, neurological, renal, hepatic, hematologic, endocrine, morbid obesity ($\text{BMI} > 40 \text{ kg}/\text{m}^2$), immunologic or other systemic disease, encephalopathic syndrome, mental retardation, risk factors for prolonged QT interval, torsade de pointes or sudden cardiac death
- Biochemistry, hematology, ECG or urinalysis results that were not within the laboratory's normal reference range and were deemed to be clinically significant by the investigator
- History or evidence of clinically significant hepatic disease (including aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 2 times the upper limit of normal) at screening

- History of neuroleptic malignant syndrome (NMS) or tardive dyskinesia or any malignancy within the previous 5 years, with the exception of basal cell carcinomas

Criteria for Evaluation: Efficacy

Primary

- Primary efficacy end point was the time from randomization to first relapse event in the Double-blind Phase. The date of relapse was the date of the first assessment for symptoms of relapse.

Secondary

- Change from baseline to end point in PANSS (total and subscales)
- Change from baseline to end point in CGI-S
- Change from baseline to end point in PSP

Criteria for Evaluation: Pharmacokinetics

- A single venous blood sample (4 mL) was collected for the determination of plasma concentration of paliperidone.
- An unscheduled PK sample could be collected at the discretion of the investigator or sponsor for cases of severe or serious adverse events (AEs) that could be potentially related to unexpected increases in plasma concentrations of study drug.

Criteria for Evaluation: Safety (see Section 9.7 for Time and Events Schedule)

- Laboratory measurements (chemistry, hematology, lipid assessments, fasting insulin and glucose, and urine drug screens)
- Body weight and height, waist circumference
- Vital signs, electrocardiograms (ECGs), physical examination
- AEs/Serious adverse events (SAEs)
- Extrapyramidal symptoms (EPS) were assessed using the AIMS, BARS, and SAS scales.
- Columbia Suicide Severity Rating Scale (C-SSRS) was administered to monitor suicidal ideation and behavior.
- At the end of study, the homeostatic model assessment (HOMA) was conducted to estimate changes in beta-cell function and insulin sensitivity.
- For local tolerability, there was an assessment of injection pain by the subject within 30 minutes after the injection using a visual analog scale (VAS). This subject assessment was done independently and in a blinded fashion. The investigator or sub-investigator was to assess redness, induration and swelling within 30 minutes of the injection. All injection site AEs with objective findings (eg, swelling, redness, and induration) and a severity assessment of “moderate” or “severe” were to be photographed along with a metric ruler for later review.
- An Independent Data Monitoring Committee (IDMC) was established to review the blinded safety data on an ongoing basis.

Statistical Methods:

For data analysis purposes, the Transition and the Maintenance Phase data were combined and collectively referred to as Open-label Phase. The intent-to-treat (ITT) (OL) analysis set included all subjects who received at least 1 dose of open-label study agent. This analysis set was used to summarize all efficacy and safety data for the Open-label Phase.

The ITT (MA) analysis set included all subjects who received at least 1 dose of study agent during the Maintenance Phase.

The ITT (DB) analysis set included all subjects who were randomly assigned to treatment during the Double-blind Phase and received at least 1 dose of Double-blind study agent.

The safety analysis set included all subjects who were randomly assigned to treatment during the Double-blind Phase and received at least 1 dose of double-blind study agent, and by definition was identical to the ITT (DB) analysis set.

The interim ITT (DB) analysis set included all subjects who were randomly assigned to treatment during the Double-blind Phase and received at least 1 dose of Double-blind study agent at the time of interim cut-off (i.e., when 42 relapse events were obtained). The primary analysis for efficacy was carried out on the intent-to-treat (ITT) population, defined as all subjects who receive at least 1 dose of Double-blind medication during the Double-blind Phase. The primary efficacy end point for this study was the time between subject randomization into the Double-blind Phase and the first documentation of a relapse event. 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 Double-blind Phase) were considered censored. Treatment comparison between PP3M and Placebo in the changes from baseline to end point of PANSS total score, PSP, and CGI-S during the Double-blind Phase was performed using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline (Double-blind Phase) value as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals were presented.

An interim analysis was to be conducted by the IDMC after at least 42 relapse events had occurred. If interim analysis using 2-sided log-rank test was to show a statistically significant difference ($p < 0.0101$ for exactly 42 relapse events in the interim ITT [DB] analysis set) 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 a significance level of 0.0464.

Amendments to Protocol:

The original protocol, dated 07 December 2011, was amended 4 times. Three amendments were considered substantial:

Amendment INT-1 (2/27/2012)

At the time of this amendment, 13 subjects were enrolled in the study. This amendment included the following changes:

- Procedures to initiate study agent administration in subjects currently on other depot antipsychotics prior to enrollment were clarified.
- Inclusion and exclusion criteria were changed to include revised rules for disallowed LAI antipsychotics and for washout of prohibited medications, and guidance was added on resuming antipsychotic treatment after subjects left the study.
- Patient Stated-choice Preference Survey was added to the Time and Events Schedule.
- Instructions for collection, handling, and shipping of samples for PK analysis and for screening of prohibited antipsychotics were revised, and addition of urine drug screen test strip for investigators was included.
- Blood type Rh factor was removed from the Time and Events Schedule due to logistical difficulties in implementing this testing in a global study.
- Eligibility criteria for entry into the Double-blind Phase and in the number of blood samples collected per subject were corrected.
- Task of study agent administrator was clarified, and revisions were made according to updates to protocol template.

Amendment INT-2 (7/2/2012)

At the time of this amendment, 419 subjects were enrolled in the study. This amendment included the following changes:

- Number of relapse events at interim analysis was increased based on feedback from the FDA, and the use of a more stringent error spending function based on the O'Brien-Fleming method was started.
- Telephone contacts between visits were added to monitor for potential impending relapses during the Double-blind Phase per IEC/IRB and/or investigators' feedback.
- Changes in the exclusion criteria were made to remove wording that was too restrictive or to clarify certain criteria.

Amendment INT-3 (5/13/2013)

At the time of this amendment, 476 subjects were enrolled in the study. This amendment included the following changes:

- New biomarker component was incorporated into the study to measure serum biomarkers that could predict: impending symptom exacerbation and/or relapse,

symptom stability, or correlations with systemic drug exposure of paliperidone during the Maintenance and Double-blind Phases of the study.

- DSM-5 diagnostic criteria for schizophrenia were collected after amendment was implemented.

6.1.2 Demographics

At Open-label baseline, more male (75%) than female (25%) subjects were enrolled in the study. A majority of subjects were white (59%), with a mean age of 38.4 years (range: 18 to 68 years). Based on BMI, 44% of subjects were classified as having normal body weight; 33% of subjects were overweight, and 24% were obese. At Double-blind baseline, demographic and baseline characteristics data was similar between the Placebo and PP3M groups.

Table 3: Study PSY-3012 Demographic and Baseline Characteristics for All Analysis Sets

(Study R092670-PSY-3012: ITT (OL) Analysis Set)					
	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)	
Age (yrs)					
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)
Sex, n (%)					
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)
Race, n (%)					
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)
Country, n (%)					
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)
Baseline(OL) Weight (kg)					
N	506	201	145	160	305
Mean (SD)	79.30 (16.805)	81.81 (18.716)	77.13 (15.530)	78.10 (14.973)	77.64 (15.223)
Median	78.00	79.00	75.50	77.05	76.50
Range	(43.5;140.0)	(50.0;140.0)	(43.5;119.8)	(46.7;130.0)	(43.5;130.0)
Baseline(OL) Body mass index (kg/m²)					
N	506	201	145	160	305
Category, n (%)					
Normal <25	221 (44)	85 (42)	61 (42)	75 (47)	136 (45)
Overweight 25-<30	166 (33)	51 (25)	57 (39)	58 (36)	115 (38)
Obese ≥ 30	119 (24)	65 (32)	27 (19)	27 (17)	54 (18)
Mean (SD)	26.53 (4.917)	27.09 (5.416)	26.15 (4.571)	26.18 (4.509)	26.17 (4.531)
Median	25.50	25.90	25.40	25.45	25.40
Range	(17.1;40.3)	(17.1;40.0)	(17.6;40.3)	(18.1;39.6)	(17.6;40.3)

Study report, p. 70-71

Psychiatric History

At Open-label baseline, the mean PANSS total score was 74.0 (range: 33 to 114). About 77% of subjects had been hospitalized at least once due to psychosis 24 months prior to enrollment. At Double-blind baseline, the psychiatric characteristics of subjects in the Placebo and PP3M groups were generally similar.

Table 4: Study PSY-3012 Diagnosis and Psychiatric History at Baseline for All Analysis Sets

(Study R092670-PSY-3012: ITT (OL) Analysis Set)

	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)	
Age at 1st diagnosis of schizophrenia (yrs.)					
N	505	200	145	160	305
Mean (SD)	26.2 (8.55)	25.2 (8.37)	27.7 (8.98)	26.3 (8.24)	26.9 (8.61)
Median	25.0	24.0	26.0	24.0	25.0
Range	(9;55)	(9;49)	(12;51)	(12;55)	(12;55)
No. of prior hosp. psychosis 24 months (b), n (%)					
N	454	180	128	146	274
None	150 (33)	51 (28)	51 (40)	48 (33)	99 (36)
Once	144 (32)	52 (29)	44 (34)	48 (33)	92 (34)
Twice	83 (18)	40 (22)	18 (14)	25 (17)	43 (16)
Three times	43 (9)	22 (12)	7 (5)	14 (10)	21 (8)
Four times or more	34 (7)	15 (8)	8 (6)	11 (8)	19 (7)
Baseline(OL) PANSS total					
N	506	201	145	160	305
Mean (SD)	74.0 (15.43)	76.7 (15.37)	72.3 (15.03)	72.2 (15.48)	72.3 (15.24)
Median	75.0	76.0	74.0	74.0	74.0
Range	(33;114)	(33;114)	(38;107)	(34;112)	(34;112)
Baseline(DB) PANSS total					
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)

(Study R092670-PSY-3012: ITT (OL) Analysis Set)

	ITT(OL)		ITT(DB)		Total Intent-to-Treat (D)
	Pali Palmitate (N=506)	Not Randomized to Double-Blind (N=201)	Placebo (N=145)	PP3M (N=160)	
Baseline(OL) PSP					
N	506	201	145	160	305
Mean (SD)	58.7 (12.13)	55.2 (12.38)	60.9 (11.16)	60.9 (11.70)	60.9 (11.43)
Median	60.0	56.0	62.0	62.0	62.0
Range	(21;91)	(21;91)	(33;85)	(31;91)	(31;91)
Baseline(DB) PSP					
N			145	160	305
Mean (SD)			68.6 (9.01)	68.8 (9.27)	68.7 (9.14)
Median			70.0	70.0	70.0
Range			(40;92)	(40;91)	(40;92)
Baseline(OL) CGI					
N	506	201	145	160	305
Mean (SD)	3.8 (0.89)	4.1 (0.88)	3.7 (0.92)	3.6 (0.81)	3.7 (0.86)
Median	4.0	4.0	4.0	4.0	4.0
Range	(2;6)	(2;6)	(2;6)	(2;5)	(2;6)
Baseline(DB) CGI					
N			145	160	305
Mean (SD)			2.8 (0.65)	2.7 (0.67)	2.7 (0.66)
Median			3.0	3.0	3.0
Range			(1;4)	(1;4)	(1;4)
Depot antipsychotics prior study entry, n (%)					
N	506	201	145	160	305
Y	80 (16)	27 (13)	25 (17)	28 (18)	53 (17)
N	426 (84)	174 (87)	120 (83)	132 (83)	252 (83)

Study report, p. 72-73

Prior Medications

Before study entry, 91% of the 506 ITT (OL) subjects had received 1 or more psychotropic drugs. The most commonly used (and $\geq 15\%$) classes of psychotropic medications were atypical antipsychotics (63%), typical antipsychotics (23%), depot antipsychotics (18%), and benzodiazepines (17%).

Before study entry, 283 (93%) of the 305 subjects in the ITT (DB) analysis set received psychotropic medications. The most commonly used class of psychotropic medications was the atypical antipsychotics (60%). Oral risperidone was the most common atypical antipsychotic used (34% of subjects). The percentage of subjects who received atypical

antipsychotics, typical antipsychotics, and depot antipsychotics was similar in the Placebo and PP3M groups.

Table 5: Study PSY-3012 Psychotropic Medications Received Prior to Open-Label Phase by Double-Blind Analysis Set

(Study R092670-PSY-3012: ITT (DB) Analysis Set)

Psychotropic Drug Category	Placebo (N=145)	PP3M (N=160)
Generic Term Category	n (%)	n (%)
Total no. subjects with prior psychotropic meds	133 (92)	150 (94)
Atypical antipsychotics	85 (59)	99 (62)
Risperidone oral	48 (33)	57 (36)
Quetiapine	13 (9)	15 (9)
Paliperidone	9 (6)	11 (7)
Typical antipsychotics	39 (27)	36 (23)
Haloperidol	14 (10)	8 (5)
Depot antipsychotics	27 (19)	33 (21)
Paliperidone palmitate	12 (8)	15 (9)
Benzodiazepines	18 (12)	25 (16)
Lorazepam	8 (6)	12 (8)
Anti-EPS	13 (9)	14 (9)
Trihexyphenidyl	4 (3)	8 (5)
Mood stabilizers and antiepileptics	10 (7)	8 (5)
Valproate	7 (5)	6 (4)

Study report, p.74

Benzodiazepines Use During the Study

During the Open-label Phase of the study, 119 (24%) of the 506 subjects received benzodiazepines. During the Double-blind Phase of the study, 50 (16%) of the 305 subjects received benzodiazepines. The percentage of subjects receiving benzodiazepines during the Double-blind Phase was higher in Placebo group than PP3M group (21% vs. 13%).

Table 6: Study PSY-3012 Benzodiazepines Received During the Double-Blind Phase

(Study R092670-PSY-3012: ITT (DB) Analysis Set)

Generic Term Category	Placebo	PP3M
	(N=145) n (%)	(N=160) n (%)
Total no. subjects with any benzodiazepines	30 (21)	20 (13)
Lorazepam	17 (12)	14 (9)
Clonazepam	5 (3)	5 (3)
Diazepam	4 (3)	1 (1)

Study report, p. 75

Anti-EPS and Antihistamine Use During the Study

During the Open-label Phase, 45 subjects (9%) received anti-EPS therapy and 12 subjects (2%) received antihistamine therapy. During the Double-blind Phase, anti-EPS medication was taken by a higher proportion of subjects in the PP3M group (9%) than in the Placebo group (5%). A similar percentage of subjects in the PP3M group (3%) and the Placebo group (4%) received antihistamines during the Double-blind Phase.

Table 7: Study PSY-3012 Anti-EPS and Antihistamine Use During the Double-Blind Phase

(Study R092670-PSY-3012: ITT (DB) Analysis Set)

Drug Category Generic Term Category	Placebo	PP3M
	(N=145) n (%)	(N=160) n (%)
Total no. subjects with anti-EPS or antihistamine therapy	13 (9)	18 (11)
Anti-EPS	7 (5)	14 (9)
Benzatropine	3 (2)	5 (3)
Trihexyphenidyl	4 (3)	3 (2)
Biperiden	0	6 (4)
Antihistamines	6 (4)	5 (3)
Loratadine	2 (1)	3 (2)
Diphenhydramine	2 (1)	2 (1)

Study report, p.76

Prohibited antipsychotics in plasma

Of the 305 subjects in ITT (DB) analysis set, 19 (6%) subjects tested positive for any of the prohibited antipsychotic medications in plasma at any time point during the Double-blind Phase. Subjects with clinically relevant concentrations of prohibited antipsychotic medications in plasma at one or more pre-specified time points were withdrawn from the study or were considered to have met criteria for a protocol deviation.

Protocol Deviations

For the ITT (DB) analysis set, 1 or more protocol deviations were recorded for 67 subjects (22%) of the 305 subjects at any time in the study. The most common deviations (and ≥5%) were noted in the categories of excluded concomitant therapy and “other” deviations. Based on the clinical review of the data, the sponsor concluded that these protocol deviations did not have a clinically significant impact on the findings of the study.

Table 8: Study PSY-3012 Protocol Deviations During the Study--ITT (DB)

	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Total no. subjects with any protocol deviation	32 (22)	35 (22)
Excluded concomitant therapy	16 (11)	12 (8)
Treatment deviation	3 (2)	6 (4)
Selection criteria not met	4 (3)	2 (1)
Efficacy assessment deviation	2 (1)	1 (1)
Safety assessment deviation	2 (1)	1 (1)
Subject not withdrawn as per protocol.	2 (1)	1 (1)
Other	7 (5)	18 (11)

Study report, p. 78

Reviewer comment: The protocol deviations appear relatively balanced between placebo and PP3M groups. Protocol deviations designated as “other” generally involved visit dates outside the visit windows.

The Applicant was asked for a list of protocol deviations that occurred specifically during the Double-blind Phase and supplied the table below (1/21/2015). Nine subjects in the PP3M group and 9 subjects in the placebo group received an excluded concomitant medication (usually an oral antipsychotic) during the Double-blind Phase:

Table 9: PSY-3012 Protocol Deviations that Occurred During the Double-Blind Phase

Subject Identifier for the Study	Planned Treatment Group(DB)	Date of Randomization	Protocol Deviation Coded Term	Protocol Deviation Term
63800104	PP3M	24Sep2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <haloperidol, 5 mg, oral, 03 jan 2014, reason therapy administered paranoid schizophrenia>
60013505	Placebo	05Apr2013	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study <invega, 6 mg, oral, 15 jul 2013, reason therapy administered schizophrenia>
60013804	PP3M	20Feb2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study, <quetiapine fumarate, 50 mg, oral, 25 aug 2013, reason therapy administered adverse event anxiety>
60820302	Placebo	28Mar2013	Efficacy assessment deviation	<panss/CGI-S/PSP> at visit <11> is not administered by a qualified rater
60017909	PP3M	12Sep2013	Other	Visit date outside the visit window for <additional Weeks Week 045>

Clinical Review
 Christina P. Burkhart, M.D.
 NDA 207946
 INVEGA TRINZA (Paliperidone Palmitate Extended-Release Injectable Suspension)

63800501	Placebo	21May2013	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study <triptazine, 25 mg, oral, 18 nov 2013, reason therapy administered inner tension>
63800502	Placebo	18Jun2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <quetiapine, 200 mg, oral, 07 oct 2013, reason therapy administered insomnia>
		18Jun2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <quetiapine, 800 mg, oral, 21 oct 2013, reason therapy administered treatment schizophrenia>
63800506	PP3M	22Aug2013	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study <levomepromazine, 50 mg, oral, 30 aug 2013, reason therapy administered insomnia>
60570707	PP3M	12Mar2014	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study <olanzapine, 10 mg, oral, 21 mar 2014, reason therapy administered extrapyramidal (akathisia)>
63800704	Placebo	11Jun2013	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study <haloperidol, 5 mg, oral, 30 aug 2013, reason therapy administered anxiety>
63800707	PP3M	08Jul2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <aripiprazol, 30 mg, oral, 05 oct 2013, reason therapy administered adverse event anxiety and insomnia>
60570205	Placebo	09Oct2013	Subject not withdrawn as per protocol.	Subject not withdrawn although randomization criteria not met (panss total score of <70> on visit <9>)
63802203	PP3M	04Nov2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <haloperidol, intermediate level - 0.268 ng/m, without reason and explanations>
		04Nov2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <trifluoperazine, 5 mg, oral, 26 dec 2012, reason therapy administered schizophrenia>
63801403	Placebo	14Aug2013	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study <risperon 2 mg, oral, 03 dec 2013, reason therapy administered anxiety>

Clinical Review
 Christina P. Burkhart, M.D.
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63800901		09Jul2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <haloperidol, 5 mg, oral, 15 nov 2013, reason therapy administered anxiety>
63801603	PP3M	25Sep2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <abilify (aripiprazole), 20 mg, oral, 06 may 2013 reason therapy administered insomnia>
		25Sep2013	Other	Visit date outside the visit window for <additional Weeks Week 045>
63801606	Placebo	29Oct2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <trifluoperazine, 5 mg, oral, 25 dec 2013, reason therapy administered adverse event anxiety>
63802603	PP3M	24Sep2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <risperidone, 2 mg, oral, 13 jan 2014, reason therapy administered insomnia and anxiety>
63802606	Placebo	09Oct2013	Excluded concomitant therapy	Subject used excluded medication antipsychotic during the study <risperidone, 1 mg, oral, 15 dec 2013, reason therapy administered insomnia>
63801202	PP3M	14May2013	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study <risperidone, 2 mg, oral, 17 dec 2012, reason therapy administered schizophrenia>
63801203	Placebo	22May2013	Excluded concomitant therapy	Subject used excluded medication oral antipsychotic during the study < haloperidol, 10 mg, oral, 11 aug 2013, reason therapy administered agitation>
		22May2013	Treatment deviation	Study drug is not administered at additional visit <week 053>
63801306	PP3M	13Aug2013	Other	Visit date outside the visit window for <visit 12>

Extent of Exposure

Table 10: Study PSY-3012 Number of Injections of Open-Label Study Drug

	Pali Palmitate (N=506) n (%)
Number of Injections of PP1M	506 (100)
1	8 (2)
2	35 (7)
3	30 (6)
4	75 (15)
5	358 (71)
Number of Injections of PP3M	379 (75)
1	379 (75)

Study report, p. 79

Table 11: Study PSY-3012 Dose Levels Over Time During the Transition Phase

Visit	Total n (%)	Pali Palmitate (N=506) DOSE (a), n (%)			
		50 mg eq.	75 mg eq.	100 mg eq.	150 mg eq.
Day 1 (OL)*	439 (87)	0	1 (<1)	0	438 (>99)
Week 1 (OL)	497 (98)	5 (1)	13 (3)	445 (90)	34 (7)
Week 5 (OL)	466 (92)	9 (2)	41 (9)	236 (51)	180 (39)
Week 9 (OL)	436 (86)	10 (2)	38 (9)	201 (46)	187 (43)
Week 13 (OL)	420 (83)	9 (2)	38 (9)	195 (46)	178 (42)
Final dose (TR) (OL)	506 (100)	11 (2)	42 (8)	241 (48)	212 (42)

Study report, p. 81

Table 12: Study PSY-3012 Dose Levels During the Maintenance Phase

Visit	Total n (%)	Pali Palmitate (N=379) DOSE (a), n (%)			
		175 mg eq. (b)	263 mg eq. (b)	350 mg eq. (b)	525 mg eq. (b)
Week 17 (OL)	379 (100)	9 (2)	36 (9)	185 (49)	149 (39)

(a) Within each dose level, the percentages are based on the number of subjects who had injection administered at this visit.

(b) Injection at Week 17 (OL) is PP3M, and the dose level is 3.5 times of the PP1M received at Week 13 (OL).

Study report, p. 82

Table 13: Study PSY-3012 Number of Injections of Double-Blind Study Drug

Number Of Injections	Placebo	PP3M
	(N=145) n (%)	(N=160) n (%)
1	34 (23)	31 (19)
2	68 (47)	55 (34)
3	29 (20)	49 (31)
4	12 (8)	18 (11)
5	2 (1)	6 (4)
6	0	1 (1)

Study report, p. 83

During the Double-blind phase, 107 subjects (67%) in the PP3M group received the study agent for ≥ 140 days and 15 subjects (9%) in the PP3M group received the study agent for a duration of ≥ 308 days.

Table 14: Study PSY-3012 Cumulative Frequency Distribution of Total Drug Exposure (Days) During Double-Blind Phase

Duration Days	Placebo	PP3M
	(N=145) n (%)	(N=160) n (%)
≥ 1 day	145 (100)	160 (100)
≥ 28 days	142 (98)	156 (98)
≥ 56 days	126 (87)	144 (90)
≥ 84 days	118 (81)	137 (86)
≥ 112 days	100 (69)	124 (78)
≥ 140 days	82 (57)	107 (67)
≥ 168 days	56 (39)	81 (51)
≥ 196 days	37 (26)	61 (38)
≥ 224 days	26 (18)	42 (26)
≥ 252 days	19 (13)	27 (17)
≥ 280 days	10 (7)	20 (13)
≥ 308 days	3 (2)	15 (9)

Study report, p. 84

The extent of exposure during the Double-blind phase is presented in the table below. The mean treatment duration was ~ 175 days in the PP3M group.

Table 15: Study PSY-3012 Extent of Exposure During Double-Blind Phase

	----- Placebo ----- (N=145)	----- PP3M ----- (N=160)
Treatment Duration, days (a)		
N	145	160
Category, n (%)		
≤ 28	3 (2)	4 (3)
29 - 56	16 (11)	12 (8)
57 - 84	8 (6)	7 (4)
85 - 112	18 (12)	13 (8)
113 - 140	19 (13)	18 (11)
141 - 168	30 (21)	25 (16)
169 - 196	15 (10)	21 (13)
197 - 224	10 (7)	20 (13)
225 - 252	7 (5)	14 (9)
253 - 280	9 (6)	6 (4)
281 - 308	7 (5)	5 (3)
309 - 336	0	6 (4)
337 - 364	1 (1)	2 (1)
365 - 392	0	3 (2)
393 - 420	1 (1)	2 (1)
>420	1 (1)	2 (1)
Mean (SD)	150.2 (79.08)	175.1 (90.00)
Median	146.0	169.0
Range	(16;426)	(8;463)

Study report, p. 85

A summary of the dose levels of PP3M over time and the final dose during the Double-blind Phase is detailed in the table below. Most subjects received the higher doses (350 mg eq dose or the 525 mg eq dose) of PP3M:

Table 16: Study PSY-3012 Dose Levels Over Time and Final Dose During Double-Blind Phase

Visit	Total n (%)	PP3M (N=160)			
		----- DOSE (a), n (%) -----			
		175 mg eq.	263 mg eq.	350 mg eq.	525 mg eq.
Day 1 (DB)	160 (100)	6 (4)	15 (9)	78 (49)	61 (38)
Week 12 (DB)	129 (81)	6 (5)	12 (9)	61 (47)	50 (39)
Week 24 (DB)	74 (46)	3 (4)	6 (8)	35 (47)	30 (41)
Week 36 (DB)	25 (16)	0	3 (12)	8 (32)	14 (56)
Week 48 (DB)	7 (4)	0	1 (14)	0	6 (86)
Week 60 (DB)	1 (1)	0	0	0	1 (100)

Study report, p. 85

The cumulative frequency distribution of the total drug exposure of PP3M during the combined Open-label and Double-blind Phases is provided in the table below. More than half of all subjects (59%) received at least 84 days of exposure to PP3M during the

combined Open-label and Double-blind Phases, and 28 subjects (6%) received at least 48 weeks (336 days) of exposure to PP3M during the combined phases:

Table 17: Study PSY-3012 Cumulative Frequency of Total Drug Exposure (Days) of PP3M During Open-Label and Double-Blind Phases

Duration Days	Pali Palmitate (N=506) n (%)
≥1 day	379 (75)
≥28 days	372 (74)
≥56 days	348 (69)
≥84 days	297 (59)
≥112 days	159 (31)
≥140 days	147 (29)
≥168 days	137 (27)
≥196 days	124 (25)
≥224 days	110 (22)
≥252 days	80 (16)
≥280 days	61 (12)
≥308 days	40 (8)
≥336 days	28 (6)
≥364 days	21 (4)

Study report, p. 86

6.1.3 Subject Disposition

Subject disposition and exposure to the study medication are presented separately for the Open-label phase and the Double-blind Phase. Completion and withdrawal information is presented separately for the Transition Phase, Maintenance Phase, and Double-blind Phase.

There were 506 subjects with schizophrenia enrolled and dosed in the Open-label Phase, and 305 subjects with schizophrenia randomized into the Double-blind Phase.

Table 18: Study PSY-3012 Number of Subjects in Each Analysis Set by Study Phase

(Study R092670-PSY-3012: All Subjects Analysis Set)

	Open-Label		Double-Blind(a)	
	Pali Palmitate (N=506)	Placebo (N=145)	PP3M (N=160)	Total Double-Blind (N=305)
	n (%)	n (%)	n (%)	n (%)
Intent-to-Treat(OL)	506 (100)	145 (100)	160 (100)	305 (100)
Intent-to-Treat(MA)	379 (75)	145 (100)	160 (100)	305 (100)
Intent-to-Treat(DB)	0	145 (100)	160 (100)	305 (100)
All randomized subjects	0	145 (100)	160 (100)	305 (100)
Safety	0	145 (100)	160 (100)	305 (100)

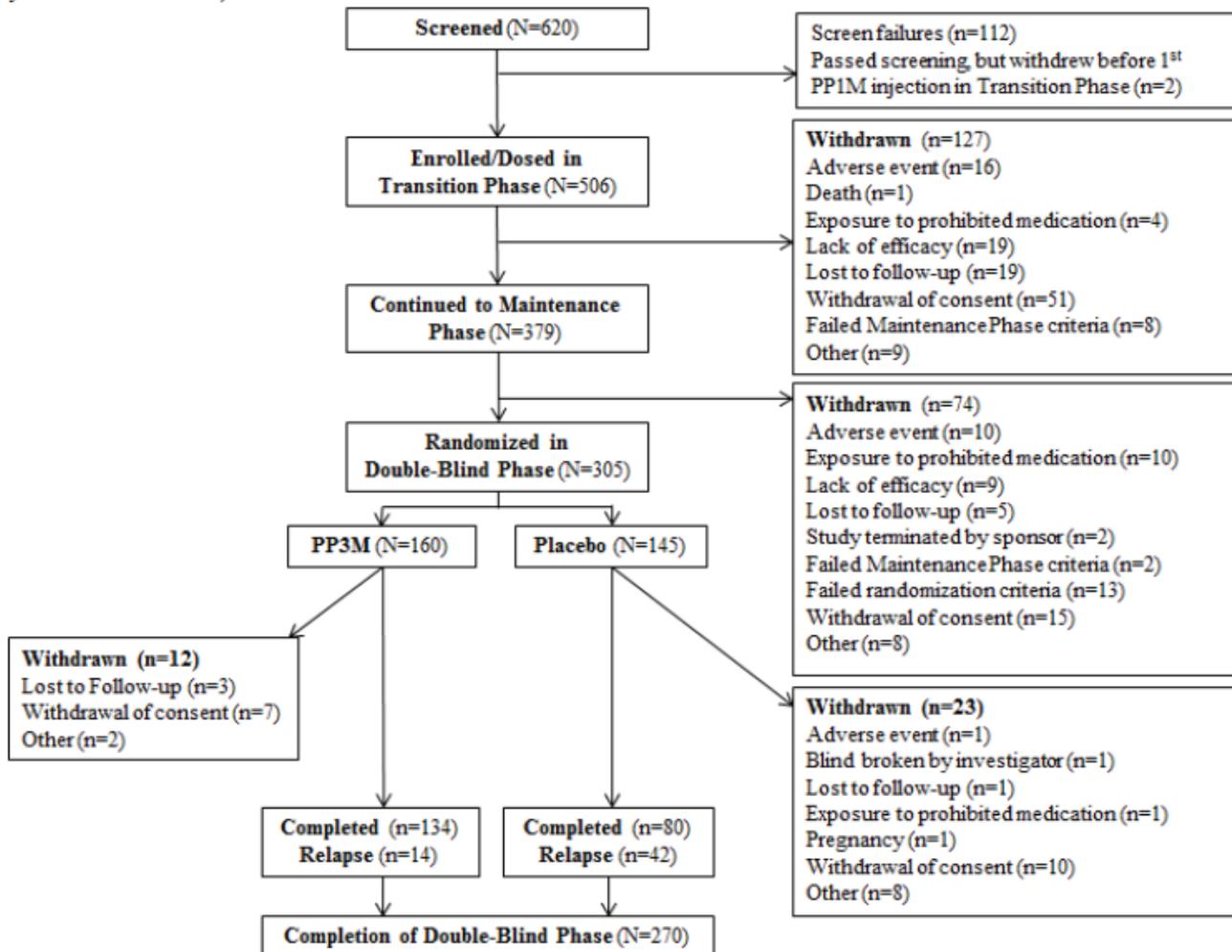
Note: Percentages calculated with the number of subjects in each group as denominator.

Study Report, p. 66

The study completion and withdrawal information across the Transition, Maintenance, and Double-blind Phases of the study are summarized in the figure below:

Figure 2: Study PSY-3012 Completion and Withdrawal Information

(Study R092670PSY3012)



Study report, p. 67

Table 19: Study PSY-3012 Completion/Withdrawal Information--Transition Phase

(Study R092670-PSY-3012: ITT (OL) Analysis Set)

	Pali Palmitate
Total Entered Transition	(N=506)
Reason For Withdrawal/Termination	n (%)
Continued to Maintenance	379 (75)
Withdrawn	127 (25)
Adverse event	16 (3)
Death	1 (<1)
Exposure to prohibited medications	4 (1)
Lack of efficacy	19 (4)
Lost to follow-up	19 (4)
Subject failed to meet criteria to Enter Maintenance Phase	8 (2)
Withdrawal of consent	51 (10)
Other	9 (2)

Study report, p.68

Table 20: Study PSY-3012 Completion/Withdrawal Information--Maintenance Phase

(Study R092670-PSY-3012: ITT (MA) Analysis Set)

	Pali Palmitate
Total Entered Maintenance	(N=379)
Reason For Withdrawal/Termination	n (%)
Continued to Double-Blind	305 (80)
Withdrawn	74 (20)
Adverse event	10 (3)
Exposure to prohibited medications	10 (3)
Lack of efficacy	9 (2)
Lost to follow-up	5 (1)
Study terminated by sponsor	2 (1)
Subject failed to meet criteria to Enter Maintenance Phase(a)	2 (1)
Subject failed to meet randomization Criteria to enter Double-blind Phase	13 (3)
Withdrawal of consent	15 (4)
Other	8 (2)

(a) Two subjects failed to meet criteria to enter the Maintenance Phase, but continued into the Maintenance Phase by mistake and received Visit 8 PP3M injection. These two subjects withdrew from the Maintenance Phase due to the reason of not meeting criteria to enter the Maintenance Phase.

Study report, p. 68

Table 21: Study PSY-3012 Completion/Withdrawal Information--Double-Blind Phase

(Study R092670-PSY-3012: ITT (DB) Analysis Set)

	Placebo (N=145)	PP3M (N=160)	Total (N=305)
Reason For Withdrawal/Termination	n (%)	n (%)	n (%)
Completed	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)
Withdrawn	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)

Study report, p. 69

6.1.4 Analysis of Primary Endpoint(s)

As specified in the Statistical Analysis Plan, one interim efficacy analysis was conducted using cumulative data up to the date when the 42nd relapse event happened (24 January 2014). Because the interim analysis demonstrated a statistically significant difference in favor of PP3M compared with placebo, with regard to the time to relapse between the 2 treatment groups, IDMC recommended stopping the trial for efficacy. The interim analysis is considered the primary analysis as prespecified in the protocol. The final analysis of data, including events subsequent to interim analysis data cutoff (24 January 2014) up to study completion (09 April 2014), is considered confirmatory.

The ITT (DB) analysis set for the interim analysis included all subjects who qualified for inclusion into the ITT (DB) analysis set (N=283) at the time of the interim analysis data cutoff (24 January 2014). The final analysis includes data from all ITT (DB) subjects enrolled in the Double-blind Phase (N=305) up to study completion (09 April 2014).

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. There was a statistically significant difference ($p < 0.001$ based on the log-rank test) between the treatment groups in the time to relapse in favor of PP3M. This difference exceeded the threshold for significance that was required to stop the study early for efficacy (i.e., $p < 0.0101$).

Table 22: Study PSY-3012 Interim Analysis: Number (%) of Relapses by Treatment Group

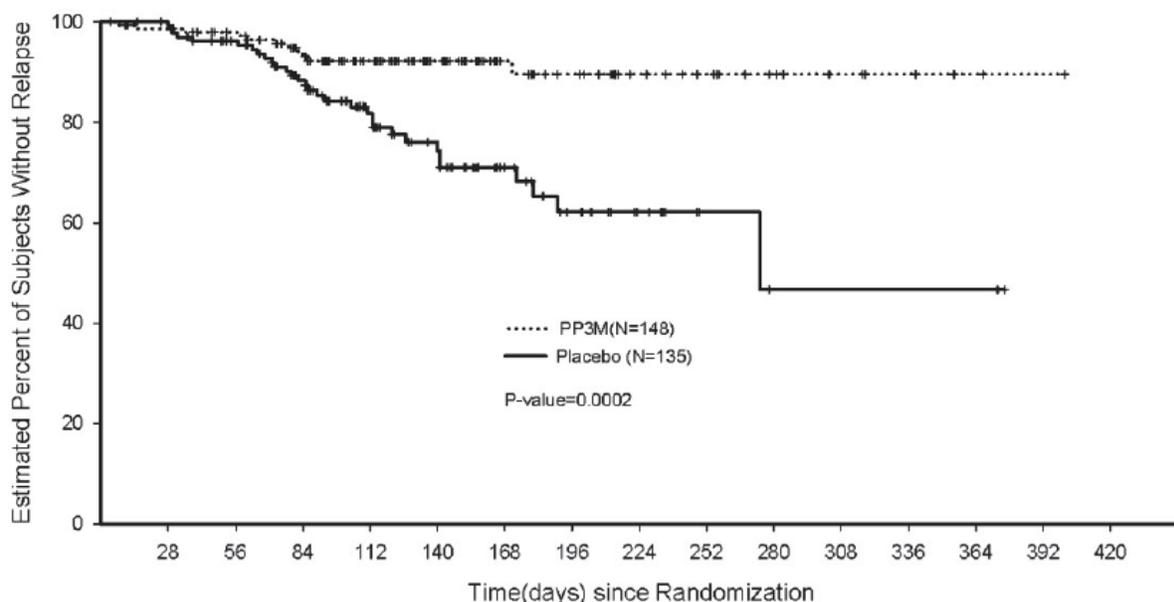
Descriptive (a)	Placebo	PP3M	P-value(b)
Number of Assessed	135	148	
Number of Censored (%)	104 (77.0)	137 (92.6)	
Number of Events (%)	31 (23.0)	11 (7.4)	

Statistical Test <0.001
 Study report, p. 88

The median time to relapse (the time at which the cumulative survival function equals 0.5, or 50%) for subjects in the placebo group (274 days) was significantly shorter than that for the PP3M group (which could not be estimated as less than 15% of the remaining patients at any time during the trial experienced a relapse).

A Kaplan-Meier plot of the time to relapse during the Double-blind Phase for the interim analysis for the 2 treatment groups is presented in the figure below. The time to first relapse for placebo-treated subjects was significantly shorter than the PP3M treated subjects (p=0.0002).

Figure 3: Study PSY-3012 Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase--Interim Analysis



Study report, p. 89

The hazard ratio for relapse (placebo/PP3M) was 3.45 (95% CI: 1.73, 6.88) indicating a 71% decrease in relapse risk with PP3M. There was a significant difference (p-value <0.001) between the treatment groups in favor of PP3M.

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 and psychiatric hospitalizations. The types and reasons for relapse events are detailed in the table below (from the original study report):

Table 23: Study PSY-3012 Frequency Distribution of Relapse Types and Reasons During the Double-Blind Phase--Interim Analysis

Type Of Recurrence Reason	Placebo	PP3M	Total
	(N=135) n (%)	(N=148) n (%)	(N=283) n (%)
Total no. subjects with Relapse	31 (23)	11 (7)	42 (15)
Psychiatric hospitalization	8 (6)	3 (2)	11 (4)
Subject had psychiatric hospitalization	8 (6)	3 (2)	11 (4)
PANSS total score	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)
Deliberate self-injury, violent behavior	1 (1)	2 (1)	3 (1)
Has subject had a suicidal ideation	1 (1)	2 (1)	3 (1)
Suicidal or homicidal ideation	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)
PANSS items (P1, P2, P3, P6, P7, G8)	5 (4)	1 (1)	6 (2)
A score of ≥ 5 after randomization	5 (4)	1 (1)	6 (2)

Study report, p. 90

On the 25 March 2015, the sponsor submitted an Erratum 1³ to the Clinical Study Report to correct errors in the Primary Efficacy Analysis-Time to Relapse (double

³ The Erratum 1 report also states that a TEAE of influenza for 1 subject in the PP3M group during the Double-blind Phase was not entered in the clinical database and hence not included in any of the TEAE summary tables in the final CSR. The event was not serious and was considered as not related to the

counting of certain events). The frequency of reasons for psychiatric hospitalizations and deliberate self-injury included subjects whose data had been double counted. For example, suicidal or homicidal ideation incidents were also counted as deliberate self-injury.

The corrections do not affect the total number of relapse events observed in either the PP3M or placebo group. The Applicant's amended table is copied below:

Table 24: Study PSY-3012 Frequency Distribution of Relapse Types and Reasons During the Double-Blind Phase--Interim Analysis (Amended)

Type Of Recurrence	Placebo (N=135)	PP3M (N=148)	Total (N=283)
Reason	n (%)	n (%)	n (%)
Total no. subjects with Relapse	31 (23)	11 (7)	42 (15)
Psychiatric hospitalization	6 8 (4 6)	2 3 (1 2)	8 11 (3 4)
Subject had psychiatric hospitalization	6 8 (4 6)	2 3 (1 2)	8 11 (3 4)
PANSS total score	26 (19)	8 (5)	34 (12)
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)
Deliberate self-injury, violent behavior	1 (1)	2 (1)	3 (1)
Has subject had a suicidal ideation	1 (1)	2 (1)	3 (1)
Suicidal or homicidal ideation	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)
PANSS items (P1, P2, P3, P6, P7, G8)	5 (4)	1 (1)	6 (2)
A score of ≥5 after randomization	5 (4)	1 (1)	6 (2)

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

Erratum 1. P.7

Based on the final analysis of the data, 42 subjects (29.0%) in the Placebo group and 14 subjects (8.8%) subjects in PP3M group experienced a relapse event during the Double-blind Phase. There was a significant difference (p<0.001 based on the log-rank test) between the 2 treatment groups in the time to relapse in favor of PP3M. The results of the final analysis (p<0.001) was consistent with that at the interim analysis (p<0.001).

study drug. The sponsor has added a footnote to all affected TEAE tables. The overall safety and efficacy conclusions of the study are not impacted by the changes.

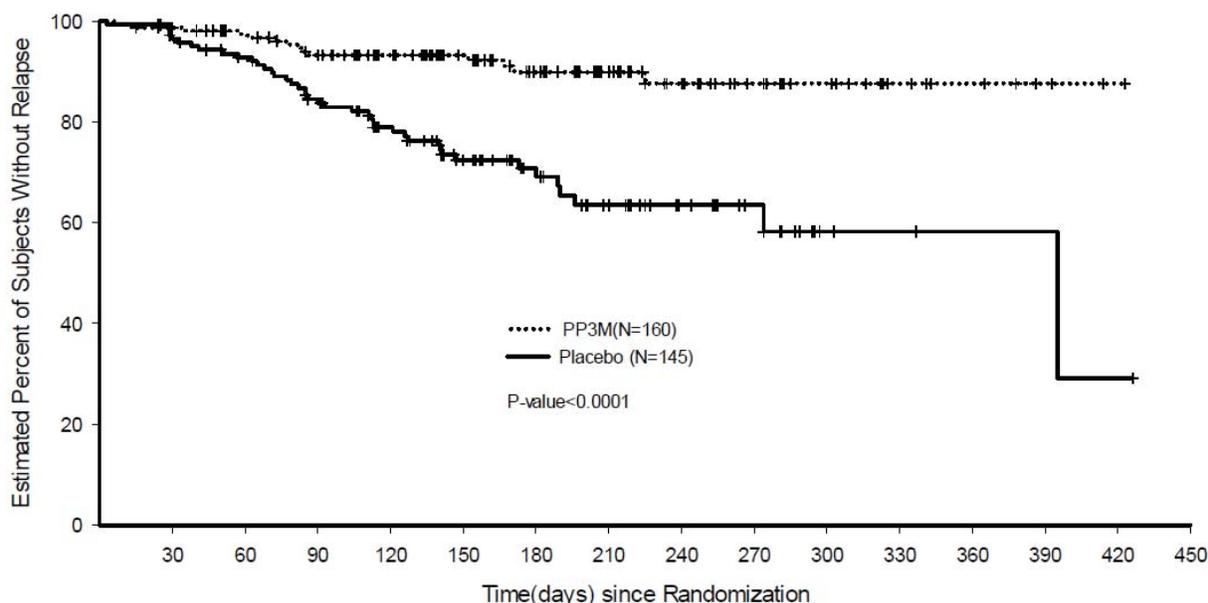
Table 25: Study PSY-3012 Final Analysis: Number (%) of Relapses by Treatment Group

Descriptive (a)	Placebo	PP3M	Total	P-value(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)	
Statistical Test				<0.001

Study report, p. 91

A Kaplan-Meier plot of the time to relapse during the Double-blind Phase for the final analysis is presented in the figure below. The time to first relapse for PP3M-treated subjects was significantly longer than that for placebo-treated subjects ($p < 0.0001$).

Figure 4: Study PSY-3012 Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase--Final Analysis



Study report, p. 92

The types and reasons for relapse events for subjects who experienced a relapse in the final ITT (DB) analysis set were similar to those specified in the interim analysis. The most common reasons for relapses were again an increase of $\geq 25\%$ in total PANSS score (23% in Placebo and 6% in PP3M) and psychiatric hospitalizations (8% in Placebo and 2% in PP3M).

6.1.5 Analysis of Secondary Endpoints(s)

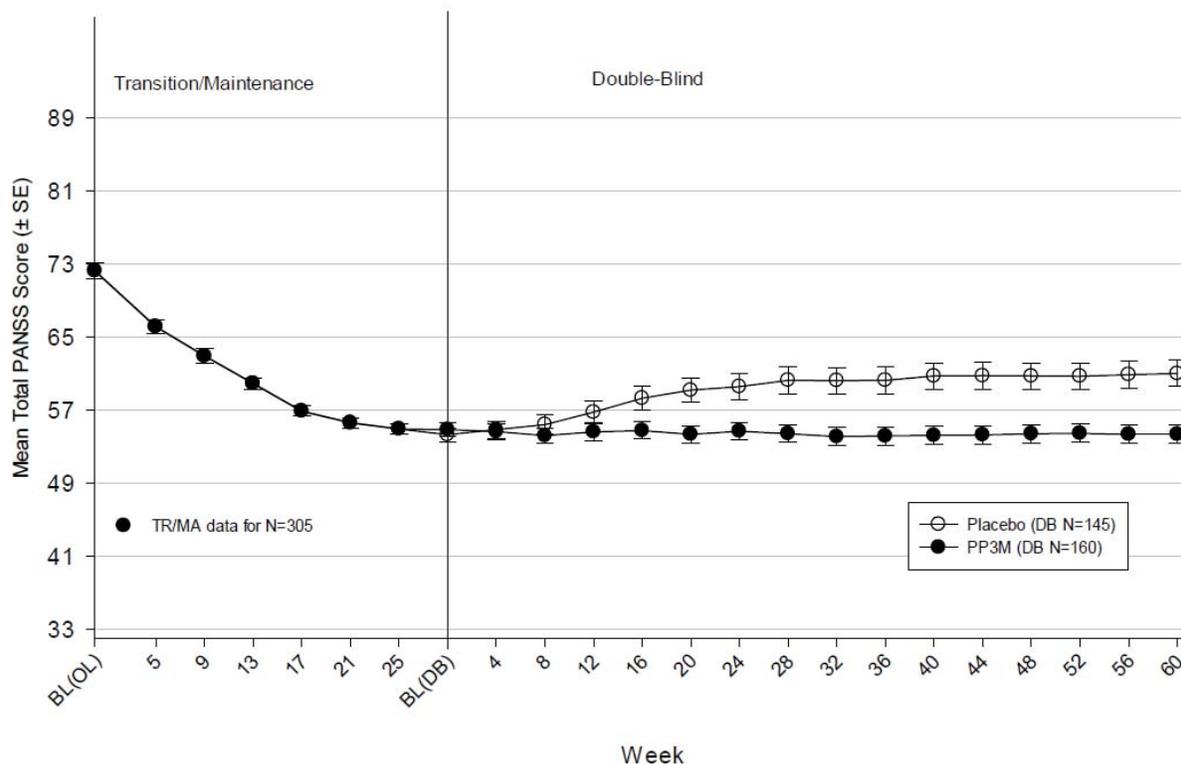
PANSS Total Score

For randomized subjects (N=305), the mean Open-label baseline PANSS total score was 72.3. The mean change at Open-label end point PANSS total score was -17.7.

The mean PANSS total scores at Double-blind baseline were 54.3 for the Placebo group and 54.8 for the PP3M group. The mean PANSS total score increased in the Placebo group (mean increase of 6.7) from Double-blind baseline to Double-blind end point, while the mean PANSS total score numerically decreased in the PP3M group (Mean: -0.5). The mean change in Placebo group at Double-blind end point was statistically significantly greater than the PP3M group ($p < 0.001$).

In the Open-label Phase, the mean PANSS total scores using LOCF imputation decreased over time. In the Double-blind Phase, for subjects in the PP3M group, the mean PANSS total scores were stable throughout the course of the study. For subjects in the Placebo group, the mean PANSS total scores increased from Double-blind baseline to around Week 28 and then continued to gradually worsen over the course of the study as demonstrated in the figure below:

Figure 5: Study PSY-3012 Arithmetic Mean PANSS Total Scores Over Time (LOCF)



Study report, p. 98

PANSS Subscale Scores and Marder Factor Scores

There was a decrease (improvement) from Double-blind baseline to Double-blind end point in the PP3M group for all PANSS subscale and factor scores, except for "anxiety/depression factor", which showed a numerical increase (0.1) at Double-blind end point. There was an increase in PANSS subscale and Marder factor scores from Double-blind baseline to Double-blind end point in the Placebo group indicating worsening of symptoms when subjects were switched to placebo.

Table 26: Study PSY-3012 PANSS Subscales/Marder Factor Scores--Change from Baseline (DB) to End Point (DB)

	Placebo (N=145)	PP3M (N=160)
Positive subscale		
Mean baseline (SD)	11.4 (2.99)	11.7 (3.20)
Mean change (SD)	2.7 (4.92)	-0.1 (2.84)
P-value(minus Placebo)(a)		<0.001
Negative subscale		
Mean baseline (SD)	16.2 (3.91)	16.4 (4.42)
Mean change (SD)	0.8 (3.76)	-0.1 (2.96)
P-value(minus Placebo)(a)		0.013
General psychopathology subscale		
Mean baseline (SD)	26.6 (4.92)	26.8 (4.98)
Mean change (SD)	3.2 (7.88)	-0.3 (4.77)
P-value(minus Placebo)(a)		<0.001
Positive symptoms factor		
Mean baseline (SD)	14.6 (3.71)	14.9 (3.72)
Mean change (SD)	2.5 (5.25)	-0.1 (2.74)
P-value(minus Placebo)(a)		<0.001
Negative symptoms factor		
Mean baseline (SD)	15.0 (3.70)	15.2 (4.28)
Mean change (SD)	0.4 (4.01)	-0.3 (3.21)
P-value(minus Placebo)(a)		0.080
Disorganized thoughts factor		
Mean baseline (SD)	13.8 (3.25)	13.8 (3.41)
Mean change (SD)	0.7 (3.38)	-0.2 (2.53)
P-value(minus Placebo)(a)		0.005
Uncontrolled hostility/excitement factor		
Mean baseline (SD)	5.2 (1.77)	5.2 (1.80)
Mean change (SD)	1.7 (3.18)	-0.0 (1.89)
P-value(minus Placebo)(a)		<0.001
Anxiety/depression factor		
Mean baseline (SD)	5.7 (2.02)	5.8 (2.10)
Mean change (SD)	1.4 (3.28)	0.1 (2.34)
P-value(minus Placebo)(a)		<0.001

Study report, p. 99

Clinical Global Impression—Severity (CGI-S)

The mean change from Double-blind baseline to Double-blind end point in the CGI-S score was 0.4 in the Placebo group and 0.1 in the PP3M group. The analysis of covariance of change from Double-blind baseline to Double-blind end point in CGI-S scores showed a significant difference ($p < 0.001$) between the two groups in favor of PP3M group.

Table 27: Study PSY-3012 Clinical Global Impression--Severity Score--Change from Baseline (DB) at End Point (DB)

	Placebo	PP3M
<u>Double-blind</u>		
End point(DB)		
Value at Baseline		
N	142	159
Mean (SD)	2.8 (0.65)	2.7 (0.68)
Value		
N	142	159
Mean (SD)	3.2 (0.96)	2.8 (0.85)
Change from Baseline		
N	142	159
Mean (SD)	0.4 (0.87)	0.1 (0.60)
Overall P-value(a) (minus Placebo)(a)	<0.001	
Diff. of LS Means (SE)		-0.3 (0.08)
95% CI		(-0.50;-0.18)

Study report, p. 102

For the 305 ITT (DB) subjects, the percentage of subjects with Double-blind baseline CGI-S scores of combined 'mild, very mild and not ill' were 90.1% for the Placebo group and 91.8% for the PP3M group. At Double-blind end point, a higher percentage of subjects in PP3M group (84.9%) retained a score of combined 'mild, very mild and not ill' as compared to Placebo group (69.0%).

Personal and Social Performance Scale (PSP)

Using the repeated measures model (MMRM), at Week 24 (DB) and Week 36 (DB), a statistically significant difference (p=0.029, p=0.014 respectively) was noted for the comparison between the PP3M and Placebo groups. At Week 48 (DB), the p-value for comparing PP3M versus Placebo was not significant (p=0.219). The applicant states that the test results at and beyond Week 48 (DB) should be interpreted with caution due to a limited number of subjects at these time points (n=22 at Week 48 [DB]).

Using an LOCF analysis, mean PSP scores were similar between the 2 treatment groups at Double-blind baseline (Placebo group 68.6; PP3M group 68.8). There was a significantly greater mean decrease (worsening) in PSP score from Double-blind baseline to Double-blind end point in the Placebo group as compared to the PP3M group (Mean -4.2 vs. -0.5; p<0.001).

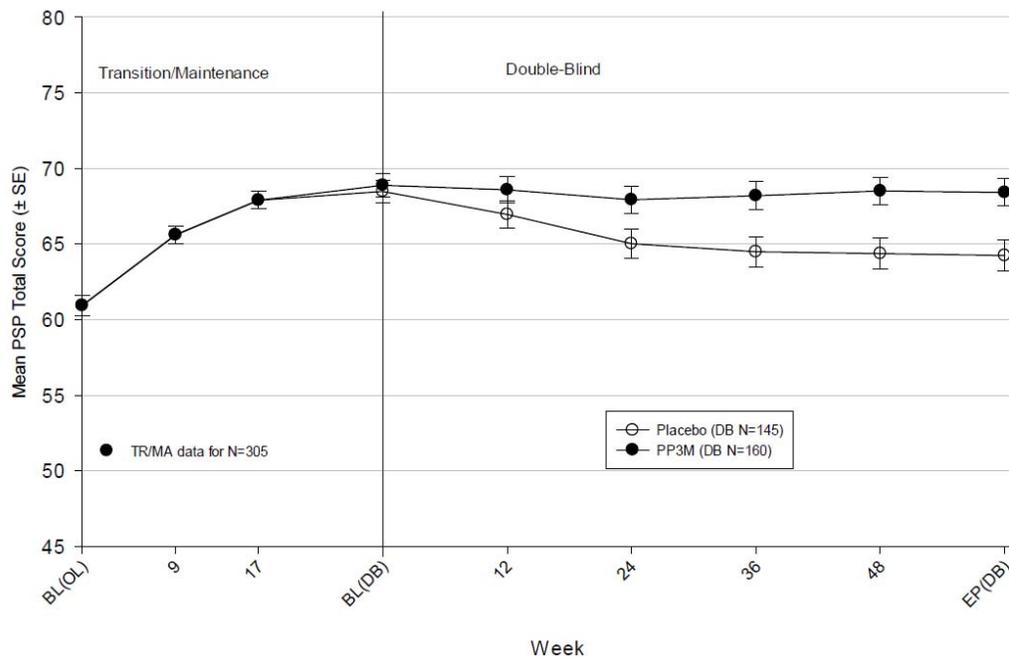
Table 28: Study PSY-3012 PSP--Change from Baseline (DB) (LOCF) at End Point (DB)

	Placebo	PP3M
Double-blind		
End point(DB)		
Value at Baseline		
N	142	157
Mean (SD)	68.5 (8.93)	68.9 (9.34)
Value		
N	142	157
Mean (SD)	64.2 (12.24)	68.4 (11.58)
Change from Baseline		
N	142	157
Mean (SD)	-4.2 (9.70)	-0.5 (6.63)
Overall P-value(a) (minus Placebo)(a)	<0.001	
Diff. of LS Means (SE)	3.8 (0.96)	
95% CI	(1.89;5.65)	

Study report, p. 107

The changes in the PSP score over time (LOCF) are presented graphically across study phases in the figure below:

Figure 6: Study PSY-3012 Arithmetic Mean PSP Score Over Time (LOCF)



Study report, p. 108

6.1.7 Subpopulations

The efficacy of PP3M compared with placebo, with regard to time to relapse of symptoms of schizophrenia, was evaluated using the Cox proportional hazard models after adjusting for the factors (one factor at a time and also using all factors together): age group (18-25, 26-50, 51-65, >65 years), sex, open-label baseline BMI category (normal: <25 kg/m², overweight: ≥25 kg/m² to <30 kg/m², obese: ≥30 kg/m²), region (US, Europe, ROW), race (White, Black, Other), and all these factors together. Results from these Cox regression analyses demonstrated that the efficacy of PP3M with regard to time to relapse of symptoms of schizophrenia was consistent regardless of age, sex, race, BMI, or region (p<0.0001 regardless of which factor was included in the model).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see full review by Dr. Rekic (Pharmacometrics). A brief summary of his conclusions can be found in Section 9.2 of this NDA review.

7 Review of Safety

Safety Summary

The safety of PP3M at doses of 175 to 525 mg eq. in the treatment of schizophrenia patients who had previously received PP1M injections over a period of at least 4 months is supported by the safety findings from 2 completed clinical studies (379 subjects in Phase 3 Study PSY-3012 and 308 subjects in Phase 1 Study PSY-1005, who received at least one dose of PP3M) and limited blinded safety data from an estimated 508 subjects in an ongoing Phase 3 study (PSY-3011). The safety profile of PP3M in these studies was generally consistent with that of PP1M. No new safety signals were detected.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety summary is based primarily on the safety findings from the study that established efficacy, Study PSY-3012. Major safety findings (deaths, SAEs, and premature discontinuations due to AEs) will also be presented for the Phase I PK study (Study PSY-1005) and the ongoing Phase 3 noninferiority trial that is being conducted for global registration (Study PSY-3011). The safety data from Study PSY-3011 is blinded. This study provides additional estimated exposure data for PP3M.

Table 29: Table of Studies Contributing Data to Summary of Clinical Safety

Study Type/ Protocol ID	Study Description	Study Treatments	No. of Subjects
Completed Phase 3 Relapse Prevention Study			
PSY-3012	Randomized, double-blind, placebo-controlled, multicenter, relapse prevention study of variable duration preceded by a 17-week, open-label transition phase ^a with PP1M and a 12-week open-label maintenance phase with PP3M	PP3M (fixed dose ^b : 175, 263, 350, or 525 mg eq./3 mos based on 3.5 times PP1M dose at end of OL transition phase) Placebo (DB phase only)	Number of Subjects Evaluable for Safety: 506 OL transition phase: 506 OL maintenance phase: 379 DB phase: PP3M: 160 Placebo: 145
Ongoing Blinded Phase 3 Noninferiority Study			
PSY-3011	Randomized, double-blind, parallel group, multicenter noninferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase ^c with PP1M	PP3M (fixed dose ^c : 175, 263, 350, or 525 mg eq./3 mos based on 3.5 times PP1M dose at end of OL stabilization phase) PP1M (fixed dose: 50, 75, 100, or 150 mg eq./4 wks based on PP1M dose at end of OL stabilization phase)	OL stabilization phase completed, n=1429 DB phase ongoing, n=1016 (blinded) Estimated 508 each on PP3M and PP1M based on 1:1 randomization ratio
Completed Phase 1 PK and Safety Study			
PSY-1005	Randomized, single-dose, open-label, parallel group, multicenter study consisting of 4 panels, with each panel including 2 single dose treatment periods (paliperidone IR in period 1 and PP3M in period 2). In each panel the single dose of PP3M was followed by a 364- to 544-day observation period for PK and safety evaluations.	PP3M: Panel A: 300 mg eq., gluteus (F015 wet or dry milled) Panel B: 75, 150, 450 mg eq., gluteus, or 300 or 450 mg eq., deltoid (F015 wet milled) Panel C: 150 mg eq., gluteus (F016 wet milled) Panel D: 175 or 525 mg eq., deltoid, or 350 or 525 mg eq., gluteus (F015 wet milled)	Number of Subjects Evaluable for Safety: 325 ^d Treated with PP3M: 308 Panel A: 66 Panel B: 120 Panel C: 24 Panel D: 98

Summary of Clinical Safety, p.7

The design and a summary of the efficacy findings of Study PSY-3012 were presented in Section 6 of this review. The design and major PK findings of Study PSY-1005 were presented in Section 5.3 of the review. It should be noted that the safety findings from Study PSY-1005 are less relevant as this was an open-label study of a single dose of PP3M against a background of oral antipsychotics (subjects were able to continue their oral antipsychotic medications). In addition, the results in Panels A and C of Study PSY-1005 were compromised by incomplete injections due to insufficient shaking prior to injection (Period 2) in some subjects. In any case, this study was designed to measure PK levels over 12-18 months and was not designed to support definitive safety conclusions. However, Study PSY-1005 does provide supportive safety information with regard to local injection site tolerability.

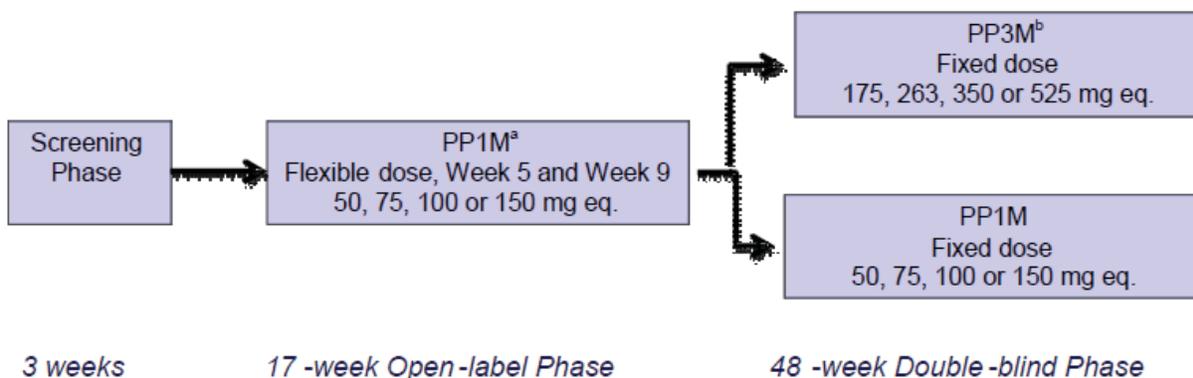
The design of the ongoing noninferiority Study PSY-3011 will be described below:

Study PSY-3011 (Ongoing Noninferiority Study)

Study PSY-3011 is a randomized, double-blind, parallel group, multicenter non-inferiority study, designed to determine if the efficacy of PP3M is non-inferior to the efficacy of PP1M as maintenance treatment in adults with schizophrenia who are initially treated for an acute exacerbation with PP1M. The study is currently ongoing, and all subjects have completed the initial open-label treatment phase. A total of 1,429 subjects aged 18 to 70 years with a DSM-IV-TR diagnosis of schizophrenia were enrolled into the Open-label Phase and 1,016 were randomized into the double-blind treatment phase.

The study consists of 3 phases: a screening/washout/tolerability phase (up to 21 days); a 17-week partly flexible dose open-label stabilization phase and a 48-week fixed dose, randomized, Double-Blind Phase. Subjects must have had a total PANSS score between 70 and 120 at screening. If applicable, subjects had their current disallowed psychotropic medications tapered off and discontinued during the Screening Phase. Subjects treated with PP1M or another LAI antipsychotic within 4 weeks before screening were excluded from enrollment in this study.

Figure 7: Design of Phase 3 Noninferiority Study Psy-3011



Summary of Clinical Safety, p.12

All subjects received PP1M for 17 weeks in the Open-label Phase. Subjects received the first PP1M injection of 150 mg eq. on Day 1 and the second injection of 100 mg eq. on Day 8, both in the deltoid muscle. Injections on Day 36 (Week 5) and Day 64 (Week 9) could be given in either the deltoid or gluteal muscle and were flexibly dosed (50 to 150 mg eq.). At Day 92 (Week 13), subjects received the dose of PP1M that was administered at Day 64.

Subjects who satisfied all of the following clinical stability criteria at both Weeks 14 and 17 of the Open-label phase were eligible to enter the Double-blind treatment phase:

- A score of <70 in the PANSS total score

- Scores of ≤ 4 for PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness) and G14 (poor impulse control)
- Reduction in Clinical Global Impression – Severity (CGI-S) score from open-label baseline of ≥ 1 at Weeks 14 and 17

Upon entry into the Double-blind Phase, subjects were randomly assigned in a 1:1 ratio to receive fixed-dose, intramuscular injections of either PP3M (175, 263, 350, or 525 mg eq.) or PP1M (50, 75, 100, or 150 mg eq.). Subjects in the PP3M treatment group received a 3.5-fold multiple of the PP1M dose at Week 13. The same PP3M dose was administered throughout the double-blind treatment period; subjects also received matched placebo injections monthly when not receiving active medication in order to maintain the blind. Subjects in the PP1M treatment group received the same PP1M dose as that administered at Week 13. The same PP1M dose was administered throughout the double-blind treatment period. Subjects remained in the Double-blind Phase until they experienced a relapse event (based on the prospectively defined criteria), or until they met the discontinuation/withdrawal criteria, or until Week 61, whichever date was the earliest.

7.1.2 Categorization of Adverse Events

Medical Dictionary for Regulatory Activities Terminology (MedDRA) (Version 16.0 for PSYPSY-3012; Version 16.1 for PSY-1005 and PSY-3011) was used to obtain the adverse event (AE) preferred terms for this analysis.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of safety data from these studies was performed due to the differences in study design.

7.2 Adequacy of Safety Assessments

See Section 9.7 for Time and Events Schedule. Safety evaluations during the Phase 3 studies included adverse events, clinical laboratory tests (chemistry, hematology, lipid assessments, fasting insulin and glucose, and urine drug screens), electrocardiogram (ECG), vital signs (pulse, blood pressure), weight, height, body mass index (BMI), and physical examination. Serious adverse events were routinely collected for a period up to the End-of-Study Visit or for up to 3 months after the last dose of study drug, whichever was later. Extrapyrimal Symptoms (EPS) were assessed using the EPS rating scales: AIMS (Abnormal Involuntary Movement Scale), BARS (Barnes Akathisia Rating Scale), and SAS (Simpson Angus Scale). The Columbia-Suicide Severity Rating Scale (C-SSRS) was administered to assess potential suicidal ideation and behavior. Injection site assessments included assessment of injection pain by the subject within 30 minutes

after the injection using a self-administered pain Visual Analog Scale (VAS). The investigator or sub-investigator assessed redness, induration and swelling within 30 minutes of the injection. All injection site adverse events with objective findings (e.g., swelling, redness, and induration) and a severity assessment of “moderate” or “severe” were to be photographed along with a metric ruler for later review.

Reviewer comment: The safety assessments appear adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The combined exposure to PP3M in Study PSY-3012 was 160.18 patient-years, based on 379 subjects who received at least one dose of PP3M. A total of 28 subjects received at least 48 weeks (336 days) of exposure to PP3M during the combined phases of Study PSY-3012. A total of 687 subjects (379 from PSY-3012 and 308 from PSY-1005) have been exposed to at least one dose of PP3M in the completed trials. An estimated 508 subjects received PP3M in the Double-blind Phase of the ongoing study PSY-3011 as of the clinical cutoff date of 31 May 2014. A total of 241 subjects had received at least 48 weeks (336 days) of exposure to PP1M and PP3M as of the 31 May 2014 cutoff date, leading to an estimate of 120 subjects with at least 48 weeks exposure to PP3M in Study PSY-3011. Therefore, based on the 3 studies, the Applicant states that 1,195 subjects have received at least one injection of PP3M, and that approximately 148 subjects have received at least 48 weeks of exposure.

There has also been extensive exposure to PP1M. Based on the (b) (4) syringes of PP1M distributed worldwide from launch to 30 June 2014, the estimated exposure is 7,332,275 person-months or 611,023 person years.

Reviewer comment: The exposure appears adequate with the addition of the exposure data from PSY-3011.

7.2.2 Explorations for Dose Response

These trials were not designed to assess dose response. According to the applicant, the design of the pivotal study (Study PSY-3012) “was not intended to support a formal evaluation of the dose response of PP3M for specific safety findings (e.g. EPS-related AEs, weight gain) or tolerability. Subjects were not randomly assigned to distinct dose levels of PP3M upon entering the Double-blind Phase; rather, subjects who completed the Transition Phase at a particular dose of PP1M were converted to the corresponding dose of PP3M prior to randomization. This is consistent with the proposed dosing recommendations of the product in clinical practice (i.e. conversion to PP3M after 4 or more months of treatment with PP1M). Any conclusion about a differential effect of PP3M dose on reporting rate of adverse events in the Double-blind Phase is therefore

confounded by the clinical response and tolerability of PP1M for individual subjects in the Transition Phase.”

7.2.3 Special Animal and/or In Vitro Testing

Please see Section 4.3 for a brief discussion of local tolerability studies that were conducted with the 3-month injectable formulation (F015) in the minipig and Dr. Elzbieta Chalecka-Franaszek’s (Pharm/Tox) review for full details.

7.2.4 Routine Clinical Testing

All tests reasonably applicable were conducted to assess the safety of the PP3M formulation in the treatment of schizophrenia in adults. See Sections 9.7 for a Schedule of Assessments for details on the timing and extent of the routine clinical testing for the pivotal clinical trial.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant adequately attempted to assess all potential adverse events that might be associated with this drug class.

7.3 Major Safety Results

Study PSY-3012

Table 30: Study PSY-3012 Overall Summary of TEAEs--Open-Label and Double-Blind Phases

	-- Open Label -		-Double-Blind Safety	
	Pali Palmitate		Placebo	PP3M
	(N=506)	(N=145)	(N=160)	
	n (%)	n (%)	n (%)	
TEAE	330 (65.2)	84 (57.9)	99 (61.9)	
Possibly related TEAE ^a	225 (44.5)	27 (18.6)	54 (33.8)	
TEAE leading to death	1 (0.2)	0	0	
1 or more serious TEAE	33 (6.5)	15 (10.3)	4 (2.5)	
TEAE leading to drug withdrawn	26 (5.1)	1 (0.7)	0	

Summary of Clinical Safety, p. 22

7.3.1 Deaths

There were 7 deaths reported in studies conducted as part of the PP3M clinical program. There was 1 death (malignant melanoma) in Panel B of Phase 1 Study PSY-1005. Pivotal Study PSY-3012 reported 1 death in the Open-Label Transition Phase.

This patient never received an injection of PP3M. There were no deaths in the Double-blind Phase of Study PSY-3012. Ongoing blinded Study PSY-3011 has reported 5 deaths as of the clinical cutoff date of 31 May 2014. Two of the 5 patients who died in Study PSY-3011 never received PP3M. The data for treatment group (PP1M versus PP3M) is still blinded for the other 3 deaths (2 suicides and 1 death secondary to bacterial meningitis). Review of the data demonstrates that a relationship to PP3M is unlikely. The following are brief narratives of the deaths by individual study:

Phase 1 Study PSY-1005

Subject 603700, a 54-year-old male, died due to metastatic melanoma approximately 7 months after receiving the injection of PP3M. The event was considered by the investigator to be not related to the study agent.

Pivotal Study PSY-3012

Study PSY-3012 reported 1 death in the Open-Label Transition Phase:

Subject 60017105, a 63-year old female, was enrolled in the Open-label Phase of the study. The subject had a medical history that included bronchial asthma, constipation, EPS, hypothyroidism; prior to the study, she was treated with haloperidol, which was stopped several months before event. Concomitant medications at the time of the event included omeprazole for gastrointestinal reflux disease, bisacodyl for constipation, and levothyroxine sodium for hypothyroidism. She developed toxic megacolon on Day 112 following the first injection of PP1M in the Transition Phase. This led to septic shock and multi-organ failure while in the hospital. The subject died due to toxic megacolon; her family refused autopsy. The investigator did not consider this event to be related to the study agent

Reviewer comment: Neither death in the completed studies for PP3M was related to PP3M.

Ongoing Blinded Study PSY-3011

As of the clinical cutoff date of 31 May 2014, 5 deaths were reported, as shown in the table below. The first two subjects in the table never received PP3M.

Table 31: Ongoing Blinded Study PSY-3011 Deaths (as of May 31, 2014)

Subject Number	AEs Leading to Death	Reported Term	Disposition Date	Relationship to Drug	Phase
40010408	Arteriosclerosis	Arteriosclerotic Cardiovascular Disease	(b) (6)	Doubtful	Open Label
40820401	Cardiac Arrest	Sudden Cardiac Arrest	(b) (6)	Doubtful	End Of Study ^b
40340105	Suicide Attempt	Suicide Attempt	(b) (6)	Not Related	Double Blind
43510111	Pyrexia	Fever	(b) (6)	Not Related	Double Blind
40860108	Toxicity To Various Agents	Drug Intoxication	(b) (6)	NA	Double Blind

^b The subject was withdrawn from the study as lost to follow-up before she was found dead, and her death was therefore recorded in the database as "End-of-Study Visit." This event should be considered as having occurred in the Open-Label Phase. A query has been issued to follow-up on this discrepancy.

Summary of Clinical Safety, p. 28

Subject 40010408, a 53-year-old male from the US with a history of hypertension, was enrolled in Open Label phase of the study and received 1 injection of PP1M 100 mg eq. Concomitant medications included hydrochlorothiazide and benazepril for hypertension and omeprazole for gastroesophageal reflux disease. On an unspecified date at Visit 2, an ECG showed left anterior hemi-block. The subject was found dead at home approximately 2.5 weeks after the PP1M injection. According to coroner's report, the subject's death was due to arteriosclerotic cardiovascular disease and the manner of the death was natural. The time interval between onset date of arteriosclerotic cardiovascular disease and death was not reported. The investigator considered the causality between arteriosclerotic cardiovascular disease and study drug as doubtful. (Reviewer comment: This subject never received PP3M.)

Subject 40820401, a 34-year-old female from South Korea, received PP1M 150 mg eq. in the Open Label phase of the study. Concomitant medications included benztropine, risperidone, and diazepam for anxiety. After the subject did not report to the hospital for her third scheduled injection, she was found dead without any evidence of injury or suicidal attempts. The subject had no history of suicide attempts, overdose, or cardiac problems. Approximately a week before her death, the subject's electrocardiogram was interpreted as normal. Based on the CIOMS, "The subject's autopsy was performed on an unspecified date and the cause of death was sudden cardiac arrest (as informed by

the subject's father)." The investigator considered the causality between sudden cardiac arrest and paliperidone palmitate as doubtful. The subject was withdrawn from the study as lost to follow-up before she was found dead, and her death was therefore reported as "End-of-Study Visit". A query has been issued to follow-up on this discrepancy. (Reviewer comment: This subject never received PP3M.)

Subject 40340105, a 34-year-old male from Spain, was randomized to treatment in the Double-blind Phase of the study. Concomitant medications were not reported. Approximately 11 days after double-blind treatment was initiated, the subject met with the investigator, where "no impairment was detected" and the family informed the investigator that the subject "was better". The following day, the subject committed suicide by ingesting clozapine that he took from another patient. The subject was hospitalized on the same day and died in the hospital. The final diagnosis included massive subarachnoid hemorrhage, drug intoxication, left lung pneumonia and encephalic death. The investigator assessed the causality between suicide attempt and the study drug as not related. The blind has not been broken for this case.

Subject 43510111, a 37-year-old male from Portugal, was randomized to double-blind treatment in the study. The subject was on no concomitant medications at the time of his death. The subject experienced fever of moderate intensity approximately 1 month after his most recent injection (Visit 16, 9th injection of Double-blind Phase), was admitted to a hospital 2 days later, and died of fever the same day. It was later determined that the cause of death was bacterial meningitis. The investigator considered the causality between fever and study agent as not related. The blind has not been broken for this case.

Subject 40860108, a 24-year-old male from China, was randomized to treatment in the Double-blind Phase of the study. The subject was on no concomitant medications at the time of his death. The subject died of drug intoxication 3 days after receiving his Visit 13 injection of the study agent (6th injection of double-blind phase). At Visit 13, the C-SSRS was negative. The subject's father stated that the cause of subject's death was intoxication after "drinking an agricultural chemical". An autopsy was not performed. The investigator provided no causality assessment. The company causality was assessed as doubtful. The blind has not been broken for this case.

Reviewer Comment:

The Applicant states that "it should be noted that the subject population in these clinical studies is characterized by the presence of severe schizophrenia symptoms, multiple medical and psychiatric comorbidities, high levels of tobacco and other substance use, and that similar types of fatal events would generally be expected in a cohort of patients with schizophrenia not participating in a clinical trial." The Applicant did not identify any new safety signal based on these deaths that could be definitively attributed to paliperidone palmitate, as part of either the PP1M or PP3M formulation. This assessment seems reasonable.

7.3.2 Nonfatal Serious Adverse Events

This section will focus on SAEs associated with administration of PP3M.

Study PSY-3012

Open-label Phase: Treatment-emergent SAEs were mainly observed in the psychiatric disorders SOC (27 subjects [5.3%]), and the only treatment-emergent SAE reported in at least 2% of subjects was schizophrenia (2.4%).

Maintenance Phase: Treatment-emergent SAEs after administration of PP3M during the Maintenance Phase were also mainly observed in the psychiatric disorders SOC, and the only treatment-emergent SAE reported in at least 1% of subjects was schizophrenia (1.1%).

Table 32: PSY-3012 Treatment-Emergent SAEs During the Maintenance Phase

Body System Or Organ Class Dictionary-Derived Term	Pali Palmitate (N=379) n (%)
Total no. subjects with serious AEs	12 (3.2)
Psychiatric disorders	9 (2.4)
Schizophrenia	4 (1.1)
Psychotic disorder	3 (0.8)
Delusion	1 (0.3)
Hallucination, auditory	1 (0.3)
Hallucination, visual	1 (0.3)
Suicidal ideation	1 (0.3)
Gastrointestinal disorders	1 (0.3)
Gastritis erosive	1 (0.3)
Infections and infestations	1 (0.3)
Pyelonephritis chronic	1 (0.3)
Renal and urinary disorders	1 (0.3)
Calculus urinary	1 (0.3)
Vascular disorders	1 (0.3)
Venous thrombosis limb	1 (0.3)

Study report, p. 121

The Applicant notes one event of potential clinical interest:

Subject 63801702: This subject was a 57-year-old male who experienced a venous thrombosis in the right leg, reported on Day 201 of the study and judged by the investigator as possible related to the study agent. The subject was hospitalized and

recovered within 15 days. The subject received multiple deltoid injections of PP1M in the Transition Phase, and the last injection before the reported SAE occurred was on Day 126, when he was administered PP3M 350 mg eq. in the right deltoid as open-label study drug in the Maintenance Phase. He continued in the Double-blind Phase of the study after recovering from the SAE, and received 2 additional deltoid injections of double-blind study drug. No further vascular events were reported.

Double-Blind Phase:

More subjects in the placebo group than in the PP3M group experienced treatment-emergent SAEs (10.3% vs. 2.5%), as well as SAEs in the psychiatric disorders SOC (9.0% vs. 2.5%). The only treatment-emergent SAEs reported by more than one subject in either treatment group were schizophrenia reported in 11 subjects (7.6%) in the placebo group and suicide attempt reported in 2 subjects (1.3%) in the PP3M group.

Table 33: PSY-3012 Treatment-Emergent SAEs During the Double-Blind Phase

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Total no. subjects with serious AEs	15 (10.3)	4 (2.5)
Psychiatric disorders	13 (9.0)	4 (2.5)
Suicide attempt	0	2 (1.3)
Schizophrenia	11 (7.6)	1 (0.6)
Schizophrenia, paranoid type	0	1 (0.6)
Anxiety	1 (0.7)	0
Suicidal ideation	1 (0.7)	0
Infections and infestations	1 (0.7)	0
Cellulitis	1 (0.7)	0
Investigations	1 (0.7)	0
Transaminases increased	1 (0.7)	0

Summary of Clinical Safety, p. 31

Study PSY-3011

Blinded summaries of treatment-emergent SAEs reported in this ongoing study as of the cutoff date of 31 May 2014 were submitted to this NDA. Only the SAEs for the Double-blind Phase (PP1M or PP3M administered) will be presented in the table below as only PP1M was administered during the Open-label Phase. Treatment-emergent SAEs in the Double-blind Phase of Study PSY-3011 were mainly observed in the psychiatric disorders SOC (4.4%), and the only treatment-emergent SAE reported in at least 1% of subjects was schizophrenia (2.3%):

Table 34: PSY-3011 Treatment-Emergent SAEs in Double-Blind Phase

Body System Or Organ Class Dictionary-Derived Term	Blinded Double-Blind Treatment (N=1016) n (%)
Total no. subjects with serious AEs	61 (6.0)
Psychiatric disorders	45 (4.4)
Schizophrenia	23 (2.3)
Psychiatric symptom	4 (0.4)
Psychotic disorder	4 (0.4)
Anxiety	3 (0.3)
Delusion	3 (0.3)
Suicide attempt	3 (0.3)
Agitation	1 (0.1)
Depression	1 (0.1)
Hallucination	1 (0.1)
Persecutory delusion	1 (0.1)
Schizophrenia, paranoid type	1 (0.1)
Substance-induced psychotic disorder	1 (0.1)
Injury, poisoning and procedural complications	4 (0.4)
Alcohol poisoning	1 (0.1)
Intentional overdose	1 (0.1)
Meniscus injury	1 (0.1)
Toxicity to various agents	1 (0.1)
Gastrointestinal disorders	3 (0.3)
Colitis ulcerative	1 (0.1)
Gastrointestinal disorder	1 (0.1)
Haemorrhoids	1 (0.1)
Blood and lymphatic system disorders	2 (0.2)
Pancytopenia	1 (0.1)
Thrombocytopenia	1 (0.1)
General disorders and administration site conditions	2 (0.2)
Chest pain	1 (0.1)
Pyrexia	1 (0.1)

Body System Or Organ Class Dictionary-Derived Term	Blinded Double-Blind Treatment (N=1016) n (%)
Nervous system disorders	2 (0.2)
Syncope	1 (0.1)
Viiith nerve paralysis	1 (0.1)
Ear and labyrinth disorders	1 (0.1)
Vertigo	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)
Diabetes mellitus	1 (0.1)
Renal and urinary disorders	1 (0.1)
Calculus ureteric	1 (0.1)
Reproductive system and breast disorders	1 (0.1)
Menstrual disorder	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)
Xanthelasma	1 (0.1)

Summary of Clinical Safety, p.225-226

Study PSY-1005

It should be again noted that Study PSY-1005 was an open-label study of a single dose of PP3M against a background of oral antipsychotics so conclusions about the safety of PP3M are limited in this setting.

One or more treatment-emergent SAEs were reported in 9 subjects in Panel A, 14 subjects in Panel B, 1 subject in Panel C, and 11 subjects in Panel D. Most SAEs were in the psychiatric disorders SOC. All treatment-emergent SAEs were considered by the investigator as not related or doubtfully related to the study drug, except for 1 case of dystonia.

Panel A: These SAEs included suicidal ideation (3), agitation (2), depression (2), and psychotic disorder (2), schizophrenia (1), paranoia (1), gastroenteritis (1), type 2 diabetes mellitus (1), diabetic ketoacidosis (1), and drug abuser (1).

Panel B: These SAEs included psychotic disorder (4), schizophrenia (4), major depression (1), aggression (1), hyponatremia (1), dystonia (1), metastatic malignant melanoma (1), psychomotor hyperactivity (1), ectopic pregnancy (1), and pleurisy (1).

Panel C: One treatment-emergent SAE of suicide attempt was reported in 1 subject.

Panel D: These SAEs included psychotic disorder (2), schizophrenia (2), abnormal behavior (1), acute psychosis (1), substance-induced psychotic disorder (1), depression (1), back pain (1), gastric ulcer hemorrhage (1), and respiratory failure (1).

7.3.3 Dropouts and/or Discontinuations

Study PSY-3012

TEAEs leading to discontinuation after administration of PP3M during the Maintenance Phase were primarily in the psychiatric disorders SOC (8 subjects [2.1%]). During the Double-blind Phase, only 1 subject in the placebo group discontinued treatment due to the event of transaminases increased. No subjects in the PP3M group discontinued due to a TEAE during the Double-Blind Phase.

Table 35: Study PSY-3012 TEAEs Leading to Study Drug Discontinuation During the Maintenance Phase

Body System Or Organ Class Dictionary-Derived Term	Pali Palmitate (N=379) n (%)
Total no. subjects with drug withdrawn due to AE	10 (2.6)
Psychiatric disorders	8 (2.1)
Psychotic disorder	3 (0.8)
Schizophrenia	2 (0.5)
Bruxism	1 (0.3)
Delusion	1 (0.3)
Obsessive thoughts	1 (0.3)
Paranoia	1 (0.3)
Restlessness	1 (0.3)
Gastrointestinal disorders	1 (0.3)
Gastritis erosive	1 (0.3)
Investigations	1 (0.3)
Electrocardiogram QT prolonged	1 (0.3)

Summary of Clinical Safety, p.124

Study PSY-3011

TEAEs leading to discontinuation were reported for 24 subjects (2.4%) in the Double-blind Phase. Most events belonged to the psychiatric disorders SOC in both study phases (1.0%). No individual events leading to discontinuation were reported at the rates of 1% or above. Suicide attempts led to 2 discontinuations in the Double-blind Phase; suicidal ideation resulted in 1 discontinuation in the Double-blind Phase. Discontinuations due to EPS-related TEAEs in the Double-blind Phase included akathisia in 2 subjects (0.2%) and tardive dyskinesia in 1 subject (0.1%).⁴ One subject (Subject 40016701) discontinued the Double-blind phase due to cerebrovascular

⁴ Tardive dyskinesia in this subject (Subject 40816903) was reported at the end of study. It was judged by the investigator as very likely related to the study agent, and was not categorized as a serious adverse event. According to the Applicant, this TEAE would be better classified as dyskinesia, since the duration of the abnormal movements did not reach the accepted threshold for tardive dyskinesia. Specifically, the

accident, which did not lead to hospitalization, was not a SAE, and was judged by the investigator as not related to the study agent. Blinded summaries of TEAEs leading to discontinuation during the Double-blind Phase in this ongoing study as of the clinical cutoff date of 31 May 2014 are summarized in the table below:

Table 36: PSY-3011 TEAEs Leading to Study Drug Discontinuation During the Double-blind Phase as of May 31, 2014

Body System Or Organ Class Dictionary-Derived Term	Blinded Double-Blind Treatment (N=1016) n (%)
Total no. subjects with drug withdrawn due to AE	24 (2.4)
Psychiatric disorders	10 (1.0)
Delusion	2 (0.2)
Schizophrenia	2 (0.2)
Suicide attempt	2 (0.2)
Anxiety	1 (0.1)
Hallucination	1 (0.1)
Hallucination, auditory	1 (0.1)
Sleep disorder	1 (0.1)
Suicidal ideation	1 (0.1)
Nervous system disorders	5 (0.5)
Akathisia	2 (0.2)
Cerebrovascular accident	1 (0.1)
Somnolence	1 (0.1)
Tardive dyskinesia	1 (0.1)
Reproductive system and breast disorders	4 (0.4)
Galactorrhoea	2 (0.2)
Amenorrhoea	1 (0.1)
Lactation disorder	1 (0.1)
Investigations	2 (0.2)
Blood glucose increased	1 (0.1)
Weight increased	1 (0.1)
Blood and lymphatic system disorders	1 (0.1)
Pancytopenia	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)
Diabetes mellitus	1 (0.1)
Pregnancy, puerperium and perinatal conditions	1 (0.1)
Pregnancy	1 (0.1)

subject had a 0 rating on the AIMS scale 2 months prior to the event, no reported problems 1 month prior to the event, and the symptoms had resolved by the 3-month follow up (after discontinuing study medication). Tardive dyskinesia was not reported as an adverse event in Study PSY-3012 or in Study PSY-1005.

Summary of Clinical Safety, p.221

Study PSY-1005

Three subjects withdrew from Panel A due to TEAEs of anxiety, suicidal ideation, and hypertension. Three subjects withdrew from Panel B due to TEAEs of psychotic disorder, metastatic malignant melanoma, muscle spasticity and dysphemia. One subject withdrew from Panel D due to TEAE of of psychotic disorder. No subjects withdrew from Panel C of the study due to TEAEs.

7.3.4 Significant Adverse Events

Most of the TEAEs during the Double-blind Phase were mild or moderate in severity. In the Placebo group, the TEAEs that were rated as severe were schizophrenia (4) and influenza (1). In the PP3M group, the TEAEs that were rated as severe were anxiety (1), agitation (1), schizophrenia (1), suicide attempt (1), aggression (1), and paranoid type schizophrenia (1).

Table 37: PSY-3012 PP3M Severe TEAEs during Double-Blind Phase

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=145)					PP3M (N=160)				
	Total n (%)	Severity <a>				Total n (%)	Severity <a>			
		NS	Mild	Mod	Sev		NS	Mild	Mod	Sev
Total no. subjects with adverse events	84 (57.9)					99 (61.9)				
Psychiatric disorders	46 (31.7)	0	20	22	4	30 (18.8)	0	20	6	4
Anxiety	16 (11.0)	0	11	5	0	13 (8.1)	0	11	1	1
Insomnia	17 (11.7)	0	9	8	0	11 (6.9)	0	10	1	0
Agitation	3 (2.1)	0	2	1	0	2 (1.3)	0	0	1	1
Schizophrenia	15 (10.3)	0	3	8	4	2 (1.3)	0	1	0	1
Suicide attempt	0	0	0	0	0	2 (1.3)	0	0	1	1
Aggression	0	0	0	0	0	1 (0.6)	0	0	0	1
Apathy	0	0	0	0	0	1 (0.6)	0	1	0	0
Psychotic disorder	0	0	0	0	0	1 (0.6)	0	0	1	0
Restlessness	2 (1.4)	0	2	0	0	1 (0.6)	0	1	0	0
Schizophrenia, paranoid type	0	0	0	0	0	1 (0.6)	0	0	0	1
Tearfulness	0	0	0	0	0	1 (0.6)	0	0	1	0
Depression	1 (0.7)	0	1	0	0	0	0	0	0	0
Fear	1 (0.7)	0	0	1	0	0	0	0	0	0
Hallucination, auditory	1 (0.7)	0	1	0	0	0	0	0	0	0
Negative thoughts	1 (0.7)	0	0	1	0	0	0	0	0	0
Suicidal ideation	3 (2.1)	0	2	1	0	0	0	0	0	0
Tension	1 (0.7)	0	0	1	0	0	0	0	0	0

Note: Incidence is based on the number of subjects, not the number of events
 Study report, p.1336

7.3.5 Submission Specific Primary Safety Concerns

Selected adverse events of interest were examined separately for Study PSY-3012.⁵ These adverse events of special interest included frequently reported adverse events

⁵ This review will focus only on adverse events of special interest that occurred during the Maintenance Phase and Double-blind Phase of Study PSY-3012 as PP3M was administered only during these periods.

described in subjects receiving PP1M as well as less frequent, clinically important events that have been reported with the use of various antipsychotics. These adverse events of interest are detailed in the table below:

Table 38: PSY-3012 Adverse Events of Special Interest

Category	Adverse Event of Interest
Psychiatric and CNS-related AEs	Suicidality Aggression or Agitation Somnolence and Sedation Seizures/Convulsions EPS Neuroleptic Malignant Syndrome
Events Related to Cardiovascular and Cerebrovascular Safety	Tachycardia Cardiac arrhythmias Orthostatic hypotension Adverse events suggestive of proarrhythmic potential Ischemia-related events
Endocrine and Metabolic Effects	Prolactin-related AEs Diabetes Mellitus and Hyperglycemia-Related AEs AEs Related to Weight Gain
Injection Site-Related Events	Injection site reactions Post-injection events of clinical relevance
Overdose-Related Events	Plasma Concentration of Paliperidone Exceeding 125 ng/mL

No subject in Study PSY-3012 had the following adverse events of special interest: seizures/convulsions, ischemia, rhabdomyolysis, or overdose. Overall, the types and rates of clinically significant adverse events in subjects treated with PP3M in the Double-blind Phase of this study were consistent with the safety profile of PP1M.

Suicidality

During the Double-blind Phase, suicidality-related TEAEs occurred in 3 subjects (2.1%) in the placebo group (suicidal ideation), and in 2 subjects (1.3%) in the PP3M group (suicide attempt). Based on C-SSRS findings, during the Double-blind phase, a higher percentage of subjects in the PP3M group than in the placebo group shifted from the categories of suicidal ideation and suicidal behavior at screening to the category of no event over time.

Table 39: PSY-3012 Most Severe Post Baseline (DB) Potentially Suicide-Related Category vs. Screening Based on C-SSRS During Double-Blind Phase

	--- Most Severe Post Baseline (DB) Potentially Suicide-Related Category ---			
	No Event	Suicidal Ideation	Suicidal Behavior	Total
Placebo				
SCREENING				
No event	117 (82.4)	4 (2.8)	0	121 (85.2)
Suicidal ideation	6 (4.2)	0	0	6 (4.2)
Suicidal behavior	14 (9.9)	1 (0.7)	0	15 (10.6)
-----	-----	-----	-----	-----
Total	137 (96.5)	5 (3.5)	0	142 (100)
PP3M				
SCREENING				
No event	129 (81.1)	2 (1.3)	1 (0.6)	132 (83.0)
Suicidal ideation	9 (5.7)	0	0	9 (5.7)
Suicidal behavior	17 (10.7)	1 (0.6)	0	18 (11.3)
-----	-----	-----	-----	-----
Total	155 (97.5)	3 (1.9)	1 (0.6)	159 (100)

Study report, p. 175

Aggression or Agitation

During the Double-blind Phase, the incidence of TEAEs related to agitation was numerically higher in the placebo group than in the PP3M group (2.1% vs. 1.3%). One event related to aggression occurred in 1 subject (0.6%) in the PP3M group.

Somnolence and Sedation

During the Double-blind Phase, somnolence (mild) occurred in 1 subject (0.6%) in the PP3M group.

EPS-Related Adverse Events

During Maintenance Phase, the most commonly occurring treatment-emergent EPS-related AEs after administration of PP3M were those grouped under Hyperkinesia (1.6%) and Parkinsonism (1.3%).

Table 40: PSY-3012 Treatment-Emergent EPS-Related AEs During the Maintenance Phase

Extrapyramidal Symptom Group Dictionary-Derived Term	Pali Palmitate (N=379) n (%)
Total no. subjects with adverse events	12 (3.2)
Hyperkinesia	6 (1.6)
Restlessness	4 (1.1)
Akathisia	2 (0.5)
Parkinsonism	5 (1.3)
Musculoskeletal stiffness	2 (0.5)
Drooling	1 (0.3)
Muscle rigidity	1 (0.3)
Parkinsonism	1 (0.3)
Dyskinesia	1 (0.3)
Dyskinesia	1 (0.3)
Dystonia	1 (0.3)
Dystonia	1 (0.3)
Tremor	1 (0.3)
Tremor	1 (0.3)

Study report, p. 128

During the Double-blind Phase, the incidence of EPS-related AEs was higher in the PP3M group than in the placebo group (8.1% vs. 3.4%). The most commonly occurring events in this category were those grouped under Hyperkinesia (5.0%) and Parkinsonism (3.8%) in the PP3M group. None of the treatment-emergent EPS-related AEs was reported as an SAE or resulted in study drug discontinuation. The rates of EPS-related adverse events in subjects at the 525 mg eq. Double-Blind dose level were not higher than those reported for the subjects at lower Double-Blind dose levels.

Table 41: PSY-3012 Treatment-Emergent EPS-Related AEs During the Double-Blind Phase

	Placebo (N=145)	PP3M (N=160)
Dictionary-Derived Term	n (%)	n (%)
Total no. subjects with adverse events	5 (3.4)	13 (8.1)
Hyperkinesia	3 (2.1)	8 (5.0)
Akathisia	1 (0.7)	7 (4.4)
Restlessness	2 (1.4)	1 (0.6)
Parkinsonism	0	6 (3.8)
Muscle tightness	0	2 (1.3)
Cogwheel rigidity	0	1 (0.6)
Extrapyramidal disorder	0	1 (0.6)
Hypokinesia	0	1 (0.6)
Muscle rigidity	0	1 (0.6)
Musculoskeletal stiffness	0	1 (0.6)
Parkinsonism	0	1 (0.6)
Tremor	0	2 (1.3)
Tremor	0	2 (1.3)
Dyskinesia	2 (1.4)	1 (0.6)
Dyskinesia	2 (1.4)	1 (0.6)
Dystonia	0	1 (0.6)
Dystonia	0	1 (0.6)

Study report, p. 129

Reviewer comment: The percentage of subjects who experienced akathisia in the PP3M treatment group (Double-blind Phase) was similar to the percentage of subjects who experienced akathisia with PP1M in the registration trials.

Extrapyramidal Symptom Rating Scales

Median global clinical scores on the BARS and SAS and total AIMS scores showed no clinically meaningful change from Double-blind baseline to end point for either the PP3M or placebo treatment group. The incidences at which akathisia was rated as absent in placebo and PP3M groups was similar (95.1% and 95.0%). However, a numerically higher percentage of subjects in the PP3M group compared to the placebo group were rated as having mild (2.5% vs. 0.7%) or moderate (1.3% vs. 0.7%) akathisia.

Table 42: PSY-3012 Barnes Akathisia Rating Scale (BARS) Global Clinical Rating Score--Frequency Distribution at Baseline (DB) and End Point (DB)

	---- Placebo --- (N=145)		----- PP3M ----- (N=160)	
	n	%	n	%
Global Clinical Rating of Akathisia				
<u>Baseline(DB)</u>				
Absent	136	95.8	150	94.3
Questionable	3	2.1	3	1.9
Mild Akathisia	2	1.4	5	3.1
Moderate Akathisia	1	0.7	1	0.6
Marked Akathisia	0	0.0	0	0.0
Severe Akathisia	0	0.0	0	0.0
<u>End Point(DB)</u>				
Absent	135	95.1	151	95.0
Questionable	5	3.5	2	1.3
Mild Akathisia	1	0.7	4	2.5
Moderate Akathisia	1	0.7	2	1.3
Marked Akathisia	0	0.0	0	0.0
Severe Akathisia	0	0.0	0	0.0

Study report, p.131

EPS Based on Rating Scales and Use of Anticholinergic Medication

Anti-EPS or antihistamine medication was received by a higher proportion of subjects in the PP3M group than in the placebo group (11% vs. 9%) during the Double-blind Phase.

Table 43: PSY-3012 Anti-EPS and Antihistamine Drug Therapy Received During the Double-Blind Phase

	Placebo (N=145)	PP3M (N=160)
Drug Category	n (%)	n (%)
Generic Term Category		
Total no. subjects with anti-EPS or antihistamine therapy	13 (9)	18 (11)
Anti-EPS	7 (5)	14 (9)
Benzatropine	3 (2)	5 (3)
Trihexyphenidyl	4 (3)	3 (2)
Biperiden	0	6 (4)
Antihistamines	6 (4)	5 (3)
Loratadine	2 (1)	3 (2)
Diphenhydramine	2 (1)	2 (1)
Antihistamines	0	1 (1)
Chlorphenamine	1 (1)	0
Hydroxyzine	1 (1)	0
Oxatomide	1 (1)	0

Study Report, p. 76

Neuroleptic Malignant Syndrome

There were no reported adverse events of NMS in either of the completed studies or in the ongoing Study PSY-3011 as of the cutoff date of 31 May 2014. For Study PSY-3012, TEAEs suggestive of distinct symptoms that could be part of the NMS presentation were also considered in the Applicant's clinical review. No cases of NMS were identified by the clinical reviewers.

Events Related to Cardiovascular and Cerebrovascular Safety

There were no reports of "sudden death", no cerebrovascular or ischemia-related events, no cases of ventricular tachycardia, ventricular fibrillation and flutter, seizures, or torsade de pointes. Syncope was reported in 1 case in the Open-label Phase in the subject who later died of toxic megacolon (Subject 60017105).

One subject (0.7%) in the placebo group and 1 subject (0.6%) in the PP3M group in the Double-blind Phase had TEAEs related to tachycardia. None of the TEAEs related to tachycardia was reported as a SAE or resulted in study drug discontinuation.

Endocrine and Metabolic Effects

Prolactin-Related Adverse Events

In general, observed increases in serum prolactin concentrations were mostly asymptomatic and infrequently associated with potentially prolactin-related adverse event reports.

During the Maintenance Phase, the incidence of Prolactin-related adverse events was low:

Table 44: PSY-3012 Treatment-Emergent Potentially Prolactin-Related AEs During the Maintenance Phase

Sex	Pali Palmitate (N=379)
Dictionary-Derived Term	n (%)
Both (N)	379
Total no. subjects with adverse events	3 (0.8)
Galactorrhoea	1 (0.3)
Gynaecomastia	1 (0.3)
Sexual Dysfunction	1 (0.3)
 Male (N)	 285
Total no. subjects with adverse events	2 (0.7)
Erectile Dysfunction	2 (0.7)
 Female (N)	 94
Total no. subjects with adverse events	2 (2.1)
Amenorrhoea	2 (2.1)

Study report, p.1362

During the Double-blind Phase, 1 female subject (2.4%) in the PP3M group experienced a TEAE of amenorrhea, which was not serious and did not lead to discontinuation of treatment.

Diabetes Mellitus and Hyperglycemia-Related Adverse Events

During the Maintenance Phase, only 1 subject (0.3%) experienced a treatment-emergent hyperglycemia-related AE (Type 2 diabetes mellitus). During the Double-blind Phase, hyperglycemia-related AEs occurred at a higher frequency in the placebo group compared with the PP3M group (8 subjects [5.5%] vs. 4 subjects [2.5%]). None of these events was serious or led to discontinuation of treatment.

Table 45: PSY-3012 Treatment-Emergent Diabetes Mellitus and Hyperglycemia-Related AEs During the Double-Blind Phase

	Placebo (N=145)	PP3M (N=160)
Glucose Group		
Dictionary-Derived Term	n (%)	n (%)
Total no. subjects with adverse events	8 (5.5)	4 (2.5)
Glucose related	8 (5.5)	4 (2.5)
Blood glucose increased	3 (2.1)	3 (1.9)
Diabetes mellitus	0	1 (0.6)
Hyperglycaemia	4 (2.8)	0
Insulin resistance	1 (0.7)	0
Urine ketone body present	1 (0.7)	0

Study report, p.140

Weight Gain Related TEAEs

Five subjects (3.4%) in the Placebo group and 15 subjects (9.4%) in the PP3M group in the Double-blind Phase had TEAEs related to weight gain. The TEAE of weight increased (14 subjects [8.8%]) was the most frequently reported TEAE related to weight gain in the PP3M group. None of the TEAEs related to weight gain was reported as an SAE or resulted in study drug discontinuation.

Injection Site-Related Events

Adverse effects associated with i.m. injection of PP1M and/or PP3M were evaluated based on (1) reported adverse events and (2) separate rating scales for investigator assessment of the injection site redness, swelling, and induration and subject ratings of pain of current injection. The investigator or designee who was blinded to the treatment assignment evaluated the injection site within 30 minutes of each injection for redness, swelling, and induration on a 4-point scale (0=absent; 1=mild; 2=moderate; 3=severe) and evaluated the site of the last injection at the EOS visit. Injection site pain was assessed by subjects using a VAS within 30 minutes after each injection.

Study PSY-3012

The table below details the injection site locations during the Open-label Phase (Week 17 when PP3M was first administered).The proportion of subjects with injections in the gluteal region was higher than in the deltoid region:

Table 46: PSY-3012 Injection Site Locations During Open-Label Phase (Week 17)

Open-Label Visit	Pali Palmitate n (%)
Injection Site	
Week 17 (OL)	379
Deltoid	169 (45)
Gluteus	210 (55)

Study report, p. 2122

The table below details the injection site locations during the Double-blind Phase. In general, more subjects received injections in the gluteus:

Table 47: PSY-3012 Injection Site Locations of Study Drug Over Time During the Double-Blind Phase

Double-Blind Visit	Placebo	PP3M
Injection Site	(N=145)	(N=160)
	n (%)	n (%)
Day 1 (DB)	145	160
Deltoid	71 (49)	70 (44)
Gluteus	74 (51)	90 (56)
Week 12 (DB)	111	129
Deltoid	46 (41)	51 (40)
Gluteus	65 (59)	78 (60)
Week 24 (DB)	43	74
Deltoid	19 (44)	28 (38)
Gluteus	24 (56)	46 (62)
Week 36 (DB)	14	25
Deltoid	6 (43)	12 (48)
Gluteus	8 (57)	13 (52)
Week 48 (DB)	2	7
Deltoid	2 (100)	5 (71)
Gluteus	0	2 (29)
Week 60 (DB)	0	1
Deltoid	0	1 (100)

Study report, p. 2123

Injection site reaction evaluations immediately after administration of the first dose of PP3M in the Maintenance Phase were done at Week 17 during the Open-label Phase. According to the Applicant, induration, redness, and swelling were observed in no more than 2% of subjects and were mild in nature.

Week 17 in the Open-label Phase was the only time point where injection site pain after administration of PP3M in the Open-label Phase was evaluated. Week 29 was the first time point where injection site pain from administration of PP3M/Placebo in the Double-blind Phase was evaluated. Subjects' injection site pain ratings during the Open-label Phase are detailed in the table below:

Table 48: PSY-3012 Subject Evaluation of Injection Site Pain Over Time During the Open-Label Phase

	N	Mean	Med	Min	Max
Injection pain					
<u>Pali Palmitate</u>					
Baseline(OL)	439	18.5	11.0	0	98
Week 1(OL)	469	15.8	11.0	0	97
Week 5(OL)	457	14.4	8.0	0	88
Week 9(OL)	434	14.1	8.0	0	92
Week 13(OL)	419	14.1	8.0	0	86
Week 17(OL)	379	16.0	9.0	0	95
Week 29(OL)	305	14.4	7.0	0	93
End Point(OL)	497	15.3	8.0	0	93

Study report, p. 1689

During the Double-blind Phase, local injection site tolerability was good. Redness and swelling were observed in no more than 2% of subjects in both groups and were mild in nature. The level of redness was generally similar between the placebo and PP3M groups (i.e., redness being absent in 100% and 99% of subjects, respectively) at any post-baseline time point. The occurrence of swelling was similar between the placebo and PP3M groups (absent in 99% in each group). Induration was absent during entire Double-blind Phase for both groups.

Table 49: PSY-3012 Investigator Evaluation of Injection Site INDURATION Over Time During the Double-Blind Phase

	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Induration		
Baseline(DB)	145	160
Absent	145 (100)	160 (100)
Mild	0	0
Week 12(DB)	136	151
Absent	136 (100)	151 (100)
Mild	0	0
Week 24(DB)	82	110
Absent	82 (100)	110 (100)
Mild	0	0
Week 36(DB)	29	46
Absent	29 (100)	46 (100)
Mild	0	0
Week 48(DB)	4	16
Absent	4 (100)	16 (100)
Mild	0	0
Week 60(DB)	0	4
Absent	0	4 (100)
Mild	0	0
End point(DB)	137	151
Absent	137 (100)	151 (100)
Mild	0	0

Study report, p. 170

Table 50: PSY-3012 Investigator Evaluation of Injection Site REDNESS Over Time During the Double-Blind Phase

Redness	Placebo	PP3M
Baseline(DB)	145	160
Absent	145 (100)	158 (99)
Mild	0	2 (1)
Week 12(DB)	136	151
Absent	135 (99)	150 (99)
Mild	1 (1)	1 (1)
Week 24(DB)	82	110
Absent	81 (99)	109 (99)
Mild	1 (1)	1 (1)
Week 36(DB)	29	46
Absent	29 (100)	45 (98)
Mild	0	1 (2)
Week 48(DB)	4	16
Absent	4 (100)	16 (100)
Mild	0	0
Week 60(DB)	0	4
Absent	0	4 (100)
Mild	0	0
End point(DB)	137	151
Absent	137 (100)	151 (100)
Mild	0	0

Study report, p. 170-171

Table 51: PSY-3012 Investigator Evaluation of Injection Site SWELLING Over Time During the Double-Blind Phase

Swelling	Placebo	PP3M
Baseline(DB)	145	160
Absent	144 (99)	159 (99)
Mild	1 (1)	1 (1)
Week 12(DB)	136	151
Absent	136 (100)	150 (99)
Mild	0	1 (1)
Week 24(DB)	82	110
Absent	82 (100)	110 (100)
Mild	0	0
Week 36(DB)	29	46
Absent	29 (100)	46 (100)
Mild	0	0
Week 48(DB)	4	16
Absent	4 (100)	16 (100)
Mild	0	0
Week 60(DB)	0	4
Absent	0	4 (100)
Mild	0	0
End point(DB)	137	151
Absent	137 (100)	151 (100)
Mild	0	0

Study report, p. 171-172

The subjects' mean evaluations of the intensity of the pain of the current injection remained similar from the Double-blind baseline to Double-blind end point in the placebo group (from 12.9 to 13.0), but showed a slight decrease in the PP3M group (from 15.8 to 15.1).

Table 52: PSY-3012 Subject Evaluation of Injection Site Pain Over Time During the Double-Blind Phase

	N	Mean	Med	Min	Max
Injection pain					
Placebo					
Baseline(DB)	145	12.9	7.0	0	79
Week 12(DB)	111	14.5	9.0	0	72
Week 24(DB)	43	12.4	7.0	0	39
Week 36(DB)	14	14.6	12.5	0	53
Week 48(DB)	2	15.5	15.5	1	30
End point(DB)	111	13.0	9.0	0	65
PP3M					
Baseline(DB)	160	15.8	7.5	0	93
Week 12(DB)	129	15.3	9.0	0	86
Week 24(DB)	74	14.1	7.5	0	75
Week 36(DB)	25	12.0	5.0	0	79
Week 48(DB)	7	9.7	7.0	0	32
Week 60(DB)	1	17.0	17.0	17	17
End point(DB)	129	15.1	9.0	0	86

Study report, p. 1690

The subjects' evaluations of the intensity of the pain of the current injection by Double-blind dose level subgroup in subjects assigned to PP3M did not show any dose-dependent trend. At Double-blind end point, the subjective ratings had decreased in the 175/263 mg eq. and the 525 mg eq. dose level subgroups (from 16.3 to 13.6 and from 16.7 to 14.6, respectively), and increased in the 350 mg eq. subgroup (from 14.9 to 15.9). In addition, there was no evidence of a dose effect with regards to the investigators' evaluations of injection site over time. Across dose level subgroups, all of the parameters evaluated (induration, pain, redness, and swelling) were rated as absent in 98% to 100% of the cases, and the remainder of the cases were rated as mild.

In the Double-blind Phase, 6 subjects (3.8%) in the PP3M group and none in the placebo group had TEAEs related to injection site reaction. Injection site pain (1.3%) was the only type of TEAE reported at the rate of 1% or above. None of these events was reported as serious or resulted in study drug discontinuation.

Per study protocol, all injection site adverse events with objective findings (eg, swelling, redness, and induration) and a severity assessment of "moderate" or "severe" were to be photographed along with a metric ruler for later review. No photographs were taken or biopsies performed. The Applicant states that although injections with PP3M were generally more painful than matched placebo, there were improvements over the course

of the study in both investigators' and the subjects' ratings of the injection sites. Overall, good local injection site tolerability was demonstrated.

Study PSY-1005

Study PSY-1005 provided key supportive safety information with regard to local injection site tolerability. According to the Applicant, the study demonstrated that PP3M injections were well tolerated at all doses tested in all the four panels.

Of the 308 subjects who received a single PP3M injection in this study, 24 (7.8%) reported events related to injection site reactions. The only TEAE reported at the rates exceeding 2% was pain in extremity (2.9%) and injection site pain (2.6%).

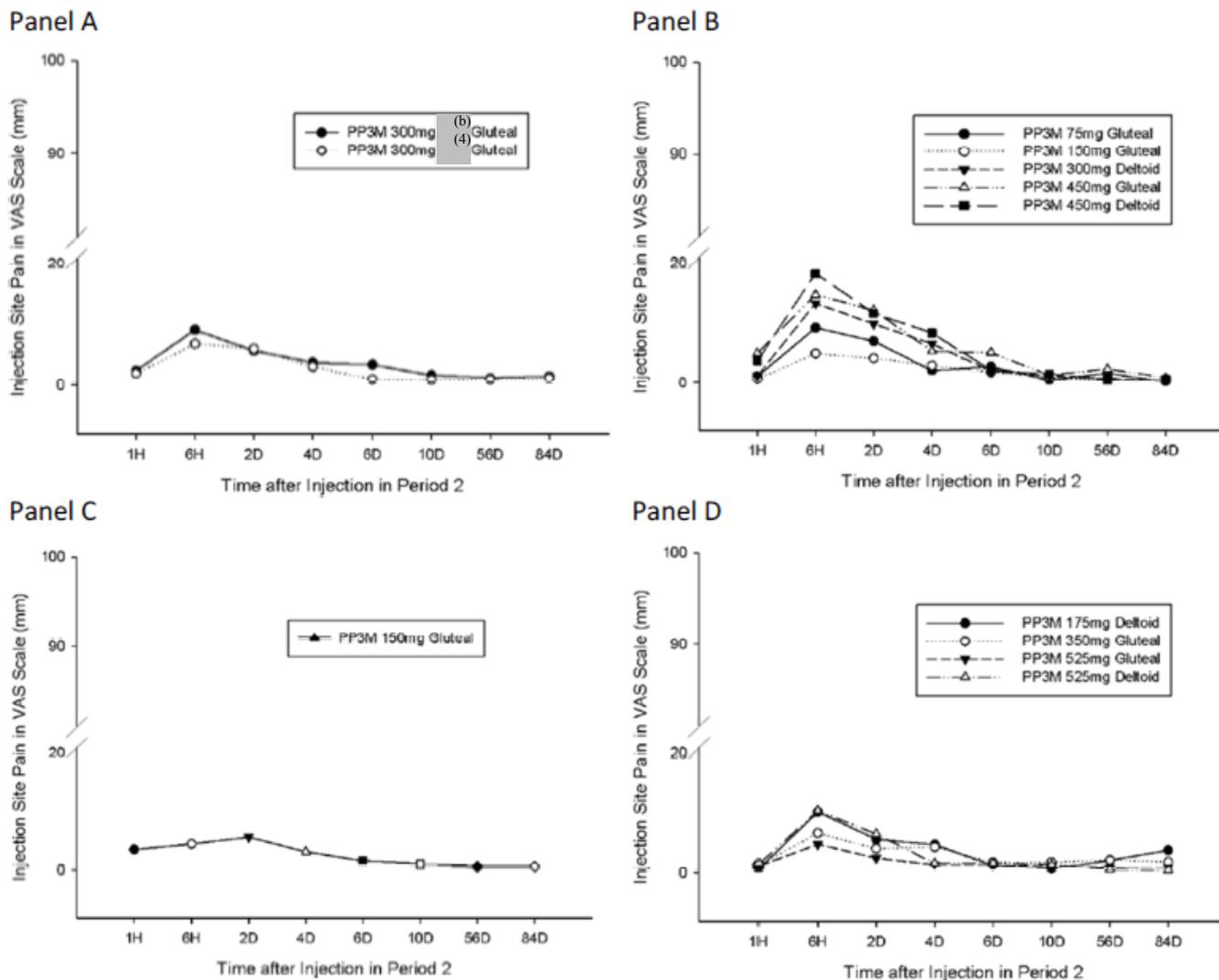
Table 53: PSY-1005 Treatment-Emergent Injection Site-Related AEs

	PP3M
Subjects treated	308
Subjects with 1 or more AEs	24 (7.8%)
Pain in extremity	9 (2.9%)
Injection site pain	8 (2.6%)
Injection site induration	6 (1.9%)
Injection site erythema	2 (0.6%)
Injection site swelling	2 (0.6%)
Injection site warmth	2 (0.6%)
Injection site irritation	1 (0.3%)
Injection site mass	1 (0.3%)
Injection site nodule	1 (0.3%)
Injection site pruritus	1 (0.3%)
Injection site rash	1 (0.3%)

Summary of Clinical Safety, p.55

According to the subjects' evaluations, the residual injection pain peaked at 1 or 6 hours, and trended downward 3 days after the injection. Deltoid injections were numerically more painful than gluteal injections. Injection site pain ratings for each of the study panels (based on VAS scale) are shown in the figure below. There was no clinically relevant difference in tolerability of the 525 mg eq. deltoid injection, compared to other doses across injection sites.

Figure 8: PSY-1005 Injection Site Pain Ratings Based on VAS Scale



Summary of Clinical Safety, p.56

Plasma Concentration of Paliperidone Exceeding 125ng/mL

An additional analysis was performed to assess the potential for TEAEs to be associated with increased plasma exposure among subjects receiving paliperidone palmitate in Studies PSY-1005 and PSY-3012.⁶ Subjects who had paliperidone plasma concentration of at least 125ng/mL were identified, and case reviews were performed for all safety assessments.

⁶ The Applicant notes that only limited information could be gained from Study PSY-3012 due to the sparse PK sampling.

Clinical Review

Christina P. Burkhart, M.D.

NDA 207946

INVEGA TRINZA (Paliperidone Palmitate Extended-Release Injectable Suspension)

A total of 17 subjects were identified, including 6 subjects in Study PSY-1005 and 11 subjects in Study PSY-3012. In total, 3.7% and 2.2% of the subjects had a $C_{max} > 125$ ng/mL after the fourth injection of PP3M 525 mg eq. in the deltoid and gluteal sites, respectively. According to the Applicant, the clinical review of the identified cases revealed no clinically relevant safety findings associated with the high plasma concentrations of paliperidone.

Table 54: PSY-3012 List of Subjects with Paliperidone Plasma Concentrations Higher than 125 ng/mL Checked for AEs After or Just Before the Observed High Concentration

CRF ID	AE ^a (start day – stop day)	Grade / SAE	Severity	Relationship	Last received treatment	Scheduled sampling day	plasma concentration (ng/mL) mean (min-max)
60011507	Weight increased (Day 65 – NR)	NA/N	Moderate	Very likely	PP3M, 525 mg eq.	Day 148	142 53.8 (8.53-167)
	Dry mouth (Day 106 – NR)	NA/N	Mild	Probable	PP3M, 525 mg eq.	Day 568	137 70.9 (40.5-137)
	Dental Caries ^b (Day 311 – Day 311)	NA/N	Mild	Not related			
60013809	Weight increased (Day 88 – NR)	NA/N	Severe	Probable	PP1M, 150 mg eq.	Day 99	136 39.1 (8.83-136)
	Upper respiratory tract infection (Day 146 – Day 152)	NA/N	Moderate	Not related	PP3M, 525 mg eq.	Day 148	137 53.8 (8.53-167)
60017109	Weight decreased (Day 148 – NR)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 232	165 51.8 (10.4-123)
60017110	Weight increased (Day 202 – NR)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 232	139 51.8 (10.4-123)
	Insomnia (Day 244 – NR)	NA/N	Mild	Possible			
	Anxiety (Day 253 – NR)	NA/N	Mild	Possible			
60017817	Insomnia (Day 141 – Day 178)	NA/N	Mild	Not related	PP3M, 525 mg eq.	Day 148	125 53.8 (8.53-167)
60017820	-	-	-	-	PP3M, 525 mg eq.	Day 176	176 45.6 (2.95-176)
60522206	Insomnia (Day 3 – NR)	NA/N	Moderate	Not related	PP3M, 525 mg eq.	Day 232	137 51.8 (10.4-123)
	Influenza (Day 227 – 262)	NA/N	Mild	Not related			
	Influenza (Day 265 – 274)	NA/N	Moderate	Not related			
	Influenza (Day 283 – 293)	NA/N	Mild	Not related			
	Bronchitis (Day 310 – 316)	NA/N	Mild	Not related			

CRF ID	AE ^a (start day – stop day)	Grade / SAE	Severity	Relationship	Last received treatment	Scheduled sampling day	plasma concentration (ng/mL) mean (min-max)
60522302	Blood pressure increased (Day 293 – Day 300)	NA/N	Mild	Not related	PP3M, 525 mg eq.	Day 148	152 53.8 (8.53–167)
	Hypertension (Day 300 – NR)	NA/N	Mild	Not related			
63800708	-	-	-	-	Placebo, 0 mg	Day 316	131 12.2 (BQL-131)
63801202	Anxiety (Day 340 – Day 341)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 148	167 53.8 (8.53–167)
					PP3M, 525 mg eq.	Day 176	139 45.6 (2.95-176)
63802504	Weight increased (Day 155 – NR)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 148	160 53.8 (8.53–167)
	Insomnia (Day 209 – Day 215)	NA/N	Mild	Possible			
	Insomnia (Day 245 – Day 264)	NA/N	Moderate	Possible			
	Hyperglycaemia (Day 295 – NR)	NA/N	Mild	Not related			

BQL = Below quantification limit, NA = Not available, NR = Not recovered

a AEs occurring after first occurrence of paliperidone plasma concentration ≥ 125 ng/mL, or AEs occurring before first occurrence of paliperidone plasma concentration ≥ 125 ng/mL and resolving thereafter or any unresolved AEs.

b This AE was resolved before the scheduled sampling day 568.

Study Report, p. 299-300

Dr. Dinko Rekid (Pharmacometrics) has also addressed these unexplained high concentrations observed in patients. He states that, in some cases, probable analytical error and natural between subject variability were responsible for the high observations. Please see Dr. Rekid's full review for further details.

Subjects with Detectable Plasma Concentrations of Paliperidone Palmitate

In Study PSY-1005, quantifiable paliperidone palmitate plasma concentrations were detected in isolated cases (3 samples in Panel A and 22 samples in panel D):

Panel A:

- Quantifiable paliperidone palmitate plasma concentration (0.265ng/mL at Day 2) was detected in only 1 plasma sample (0.4%) after a single i.m. injection of 300 mg eq. paliperidone palmitate (F015) manufactured by (b) (4)
- Quantifiable paliperidone palmitate plasma concentrations (0.263 and 0.472 ng/mL, both at 1 hour postdose) were detected in only 2 plasma samples (1%) after a single i.m. injection of 300 mg eq. paliperidone palmitate (F015) manufactured by (b) (4)

Panel B and C:

- None of the samples collected in Period 2 had a quantifiable paliperidone palmitate concentration.

Panel D:

- Quantifiable paliperidone palmitate plasma concentration was detected in 7 subjects and 22 samples (3.7%). Two of these subjects (6 samples) were in the 525 mg eq. deltoid treatment group and five of these subjects (16 samples) were in the 525 mg eq. gluteal treatment group. Concentrations of paliperidone palmitate were detected between 1 hour and 120 hours (both treatment groups) and ranged between 0.270ng/mL and 19.2ng/mL for the 525 mg eq. deltoid treatment group and between 0.229ng/mL and 4.13ng/mL for the 525 mg eq. gluteal treatment group.

The Applicant states that no additional safety concerns were associated with these findings.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study PSY-3012

Maintenance Phase (Open-Label PP3M Administration)

The TEAEs that occurred most frequently in the Open-Label Phase (PP1M and PP3M) were in the psychiatric disorders SOC (29.1%). The most frequently reported TEAEs (in at least 5% of the subjects) were weight increased (10.1%), insomnia (9.9%), anxiety (8.7%), injection site pain (8.7%), and headache (6.5%).

The TEAEs that occurred most frequently in the Maintenance Phase after administration of PP3M were also in the psychiatric disorders SOC (16.1%). The most frequently reported TEAE (in at least 5% of the subjects) during the Maintenance Phase was anxiety (5.8%).

Table 55: Study PSY-3012 TEAEs in at Least 2% of Subjects During Maintenance Phase

Body System Or Organ Class Dictionary-Derived Term	Pali Palmitate (N=379) n (%)
Total no. subjects with adverse events	162 (42.7)
Psychiatric disorders	61 (16.1)
Anxiety	22 (5.8)
Insomnia	18 (4.7)
Nervous system disorders	29 (7.7)
Headache	11 (2.9)
Investigations	25 (6.6)
Weight increased	17 (4.5)

Summary of Clinical Safety, p. 24

Double-Blind Phase

Only adverse events that either newly appeared or worsened in severity after initiation of double-blind medication were considered as treatment-emergent adverse events (TEAEs) in the Double-blind Phase.

The TEAEs that occurred more frequently in the PP3M group than in the placebo group (at least 3% difference between groups) were nasopharyngitis, weight increased, headache, and akathisia.

Table 56: Study PSY-3012 TEAEs in at Least 2% of Subjects in Either Treatment Group During the Double-Blind Phase

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Total no. subjects with adverse events	84 (57.9)	99 (61.9)
Psychiatric disorders	46 (31.7)	30 (18.8)
Anxiety	16 (11.0)	13 (8.1)
Insomnia	17 (11.7)	11 (6.9)
Agitation	3 (2.1)	2 (1.3)
Schizophrenia	15 (10.3)	2 (1.3)
Suicidal ideation	3 (2.1)	0
Infections and infestations	16 (11.0)	28 (17.5)
Nasopharyngitis	2 (1.4)	9 (5.6)
Upper respiratory tract infection	3 (2.1)	6 (3.8)
Urinary tract infection	2 (1.4)	5 (3.1)
Influenza	3 (2.1)	3 (1.9)
Investigations	25 (17.2)	27 (16.9)
Weight increased	5 (3.4)	14 (8.8)
Blood glucose increased	3 (2.1)	3 (1.9)
Weight decreased	11 (7.6)	2 (1.3)
Nervous system disorders	10 (6.9)	25 (15.6)
Headache	6 (4.1)	14 (8.8)
Akathisia	1 (0.7)	7 (4.4)
General disorders and administration site conditions	6 (4.1)	11 (6.9)
Irritability	3 (2.1)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	5 (3.4)	6 (3.8)
Cough	3 (2.1)	5 (3.1)
Metabolism and nutrition disorders	8 (5.5)	5 (3.1)
Decreased appetite	3 (2.1)	1 (0.6)
Hyperglycaemia	4 (2.8)	0

Summary of Clinical Safety, p. 25

Study PSY-3012 was not designed to assess dose response. However, the total rate of adverse event reporting was very similar across PP3M dose level subgroups (61.5% to 62.3%) in the Double-blind Phase.

Study PSY-3011 (Blinded data)

Open-Label Phase (PP1M)

TEAEs occurred most frequently in the psychiatric disorders SOC (326 subjects [22.8%]). The most frequently reported TEAEs (in at least 5% of the subjects) were injection site pain (9%), insomnia (7.0%), akathisia (5.9%), and anxiety (5.5%).

Double-Blind Phase (Blinded data: PP1M and PP3M)

TEAEs occurred most frequently in the Investigations SOC (24.1%), with the most common TEAE of weight increased in 184 subjects (18.1%). The only other TEAE reported in at least 5% of the subjects was nasopharyngitis (6.6%). Other TEAEs occurring in at least 2% of subjects during the Double-blind phase were mostly in the psychiatric and nervous system disorders SOCs. TEAEs occurring in at least 2% of subjects during the Double-blind phase included anxiety (4.4%), headache (3.8%), akathisia (3.1%), insomnia (3.1%), schizophrenia (3.1%), weight decreased (2.1%) and injection site pain (2.0%).

Table 57: Study PSY-3011 TEAEs During the Double-Blind Phase (Cut-Off Date of 5/31/14)

Body System Or Organ Class Dictionary-Derived Term	Blinded Double-Blind Treatment (N=1016) n (%)
Total no. subjects with adverse events	608 (59.8)
Investigations	245 (24.1)
Weight increased	184 (18.1)
Weight decreased	21 (2.1)
Alanine aminotransferase increased	13 (1.3)
Blood glucose increased	13 (1.3)
Gamma-glutamyltransferase increased	8 (0.8)
Blood insulin increased	5 (0.5)
Alanine aminotransferase abnormal	4 (0.4)
Aspartate aminotransferase increased	4 (0.4)
Blood triglycerides increased	4 (0.4)
Insulin c-peptide increased	4 (0.4)
Waist circumference increased	4 (0.4)
Blood pressure increased	3 (0.3)
Body mass index increased	3 (0.3)
Blood cholesterol increased	2 (0.2)
Blood insulin decreased	2 (0.2)
Electrocardiogram abnormal	2 (0.2)
Electrocardiogram qt prolonged	2 (0.2)
Glycosylated haemoglobin increased	2 (0.2)
Low density lipoprotein increased	2 (0.2)
White blood cell count decreased	2 (0.2)
White blood cell count increased	2 (0.2)
Aspartate aminotransferase abnormal	1 (0.1)
Blood bilirubin increased	1 (0.1)
Blood chloride decreased	1 (0.1)
Blood creatinine increased	1 (0.1)
Blood lactate dehydrogenase increased	1 (0.1)
Blood prolactin increased	1 (0.1)
Blood sodium decreased	1 (0.1)
Blood triglycerides	1 (0.1)
Drug screen positive	1 (0.1)
Electrocardiogram t wave amplitude decreased	1 (0.1)
Glucose urine present	1 (0.1)
Haemoglobin increased	1 (0.1)

Summary of Clinical Safety, p. 206

7.4.2 Laboratory Findings

Based on mean changes from Double-blind baseline to end point for the majority of the laboratory analytes, the effects of PP3M on the results of chemistry and hematology laboratory tests did not show clinically relevant differences from those of placebo. With the exception of serum prolactin, no treatment-related pattern in the frequency of markedly abnormal values was observed for any clinical laboratory parameter.

Table 58: PSY-3012 Laboratory Values—Mean Change from Baseline (DB) to End Point (DB)

Parameter	Placebo	PP3M
ALT (U/L)	-0.3	-1.7
Albumin (g/L)	-0.6	-0.9
Alk Phos (U/L)	-1.4	0.4
AST (U/L)	0.2	-1.0
Bicarbonate (mmol/L)	0.59	0.26
Bilirubin (µmol/L)	0.586	0.152
BUN (mmol/L)	-0.063	-0.096
Calcium (mmol/L)	0.0085	-0.0002
Chloride (mmol/L)	0.7	0.3
Creatinine (µmol/L)	-1.76	-0.82
GGT (U/L)	-0.9	0.4
HbA1C (fraction)	-0.0007	0
LDH (U/L)	-2.3	-0.3
Phosphate (mmol/L)	-0.0175	0.0005
Potassium (mmol/L)	-0.03	-0.07
Prolactin (µmol/L)	-15.6	4.12
Protein (g/L)	-0.3	-0.2
Sodium (mmol/L)	0.3	0
Hemoglobin (g/L)	1.0	0
Platelets (x10E9/L)	6.4	-1.5
Leukocytes (x10E9/L)	0.181	-0.078
Neutrophils (%)	0.31	0.28

Study report, p. 143-146

Table 59: PSY-3012 Fasting Glucose and Lipids in US Units—Mean Change from Baseline (DB) to End Point (DB)

	Placebo (N=145)	PP3M (N=160)
CHEMISTRY		
<u>Cholesterol (mg/dL)</u>		
Mean baseline (SD)	193.95 (38.741)	183.56 (38.643)
Mean change (SD)	-0.42 (32.997)	0.93 (24.092)
<u>Glucose (mg/dL)</u>		
Mean baseline (SD)	97.37 (14.570)	99.83 (15.887)
Mean change (SD)	-1.63 (14.490)	-1.19 (17.417)
<u>HDL Cholesterol (mg/dL)</u>		
Mean baseline (SD)	51.57 (16.925)	51.30 (17.150)
Mean change (SD)	-0.45 (9.216)	-1.30 (10.615)
<u>LDL Cholesterol (mg/dL)</u>		
Mean baseline (SD)	115.96 (34.708)	108.04 (32.410)
Mean change (SD)	-0.44 (28.419)	1.07 (20.454)
<u>Triglycerides (mg/dL)</u>		
Mean baseline (SD)	136.36 (75.113)	122.92 (77.979)
Mean change (SD)	-2.04 (74.097)	5.13 (61.777)

Study report, p. 1798

Shifts in Glucose Levels

During the Double-blind Phase, there was a low incidence of shifts from normal to high glucose levels (placebo 2%, PP3M 3%), and from impaired to high glucose levels (placebo 3%, PP3M 3%).

Table 60: Psy-3012 Fasting Glucose--Treatment-Emergent Shifts from Baseline (OL) to Maximum Post Baseline (DB) Value

	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Total no. subjects (a)	136 (94)	152 (95)
Normal to high	3 (2)	5 (3)
Impaired glucose tolerance to high	4 (3)	5 (3)
Normal/impaired glucose tolerance to high	7 (5)	10 (6)
<126 mg/dL to ≥140 mg/dL	5 (3)	5 (3)
<126 mg/dL to ≥200 mg/dL	1 (1)	1 (1)
<126 mg/dL to ≥300 mg/dL	1 (1)	0

Study report, p.154

Shifts in Fasting Lipids

During the Double-blind Phase, 13.5% of the PP3M treatment group shifted from normal to low HDL and 8.1% shifted from normal to high triglycerides.

Table 61: PSY-3012 Fasting Lipids: Treatment -Emergent Shifts from Baseline (DB) during the Double-Blind Phase

Parameter	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Cholesterol (mg/dL)	128	148
<200 mg/dL to ≥ 240 mg/dL	5 (3.9)	2 (1.4)
Hdl cholesterol (mg/dL))	127	148
≥ 40 mg/dL to <40 mg/dL	12 (9.4)	20 (13.5)
Ldl cholesterol (mg/dL)	127	148
<100 mg/dL to ≥ 160 mg/dL	1 (0.8)	0
Triglycerides (mg/dL)	128	148
<150 mg/dL to ≥ 200 mg/dL	2 (1.6)	12 (8.1)

Study report, p. 1800

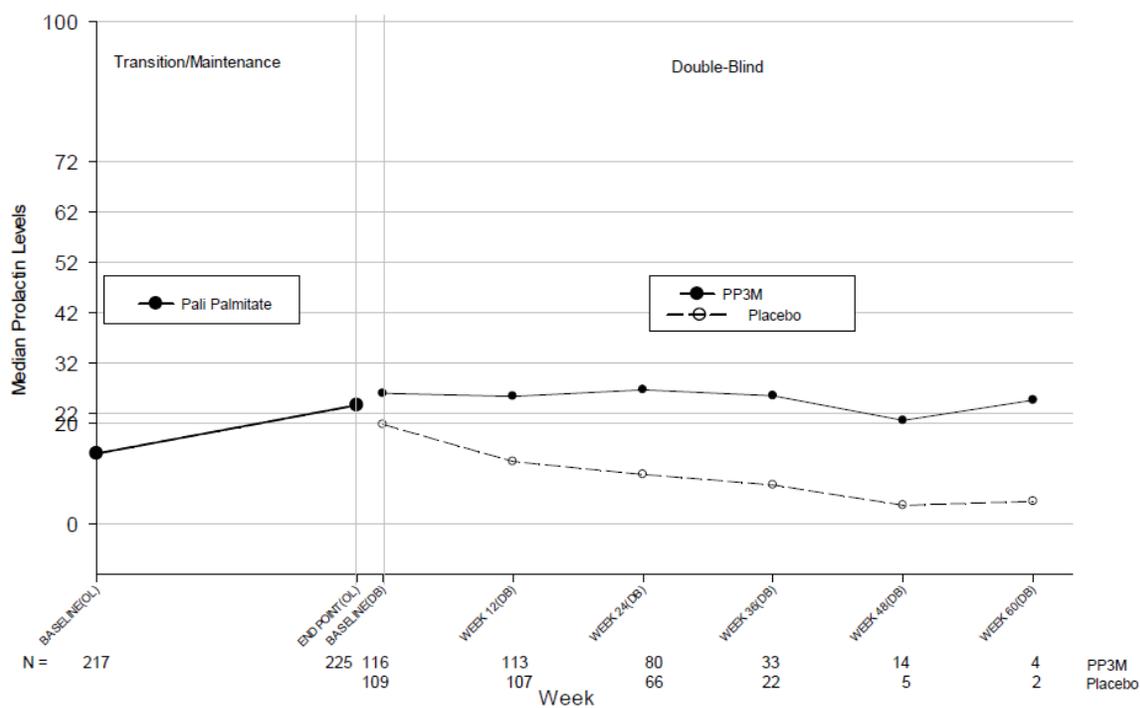
Serum Prolactin

Mean increases in prolactin concentrations from baseline were observed for subjects of both sexes who received PP1M/PP3M in each of the study phases. During the Double-blind Phase in the PP3M group, the mean increase from Double-blind baseline to Double-blind end point was +2.90ug/L for males and +7.48ug/L for females.

Decrease in mean value from Double-blind baseline to Double-blind end point was observed in prolactin levels in the placebo group. This decrease indicated that the effect

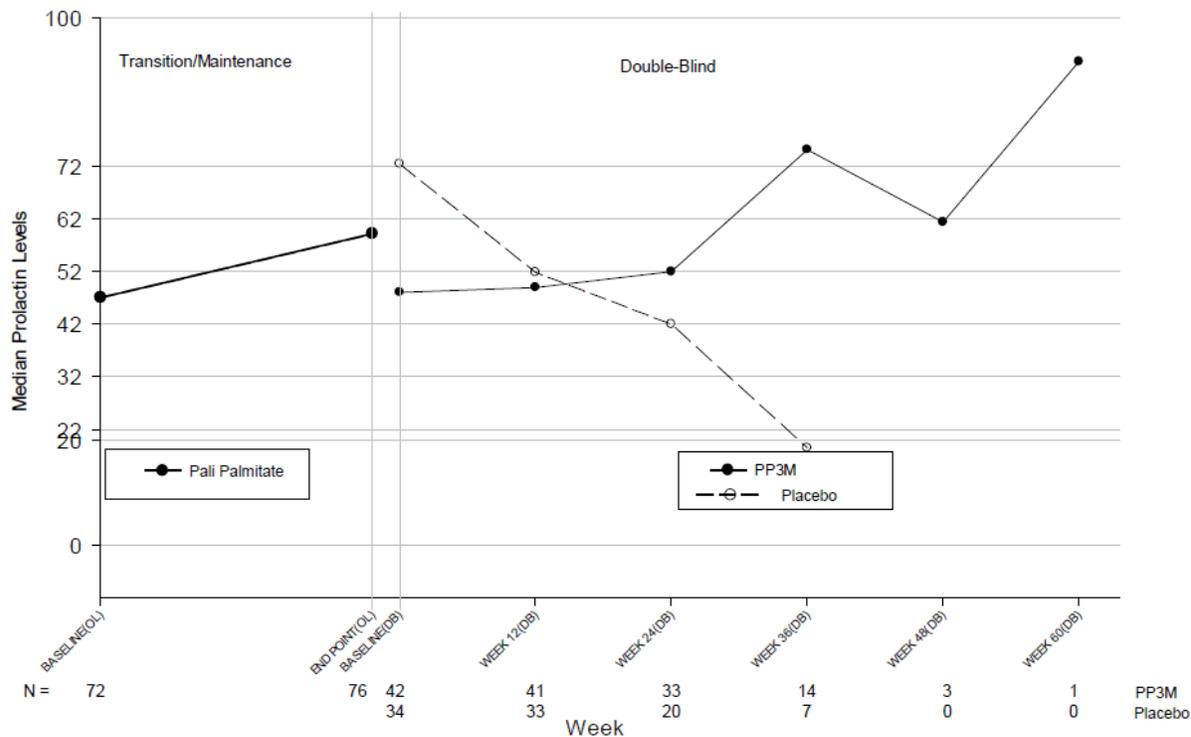
of PP1M/PP3M on prolactin levels was reversible. For male subjects who continued to receive PP3M, median prolactin levels were stable throughout the Double-blind Phase. For female subjects, median prolactin levels remained stable during the first 6 months of the Double-blind Phase, followed by a further median increase observed across a small number of subjects remaining in the Double-blind Phase beyond Week 24. These changes are demonstrated in the figures below:

Figure 9: PSY-3012 Median Prolactin Values for Male Subjects Who Entered the Double-Blind Phase Over Time



Study report, p.148

Figure 10: PSY-3012 Median Prolactin Values for Female Subjects Who Entered the Double-Blind Phase Over Time



Study report, p.149

Individually Clinically Significant Abnormalities

Abnormally low HDL cholesterol levels were reported for 8% and 5% of subjects in the Placebo and PP3M groups, respectively. Abnormally high LDL cholesterol levels were reported for 9% and 11% of subjects in the Placebo and PP3M groups, respectively. Abnormally low LDL cholesterol levels were reported for 11% and 17% of subjects in the Placebo and PP3M groups, respectively. In general, treatment-emergent markedly abnormal values were recorded at a low incidence as demonstrated in the table below:

Table 62: Psy-3012 Number of Subjects with Treatment-Emergent Markedly Abnormal Lab Values Relative to Baseline (OL) at Any Time During the Double-Blind Phase

	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Chloride (mmol/L)	142	155
Abnormally High	0	0
Abnormally Low	0	1 (1)
Cholesterol (mmol/L)	142	155
Abnormally High	2 (1)	1 (1)
Gamma Glutamyl Transferase (U/L)	142	155
Abnormally High	1 (1)	1 (1)
Glucose (mmol/L)	142	155
Abnormally High	1 (1)	0
Abnormally Low	0	0
HDL Cholesterol (mmol/L)	142	155
Abnormally Low	12 (8)	7 (5)
LDL Cholesterol (mmol/L)	142	155
Abnormally High	13 (9)	17 (11)
Abnormally Low	15 (11)	27 (17)
Phosphate (mmol/L)	142	155
Abnormally High	0	0
Abnormally Low	2 (1)	3 (2)
Potassium (mmol/L)	142	155
Abnormally High	2 (1)	1 (1)
Abnormally Low	0	0
Triglycerides (mmol/L)	142	155
Abnormally High	0	1 (1)
Eosinophils (%)	140	155
Abnormally High	2 (1)	3 (2)
Leukocytes (x10E9/L)	140	155
Abnormally High	2 (1)	1 (1)
Abnormally Low	2 (1)	2 (1)
Lymphocytes (%)	140	155
Abnormally High	0	0
Abnormally Low	1 (1)	1 (1)

Study report, p.151-153

7.4.3 Vital Signs

Mean Changes from Baseline in Vital Signs

Throughout the Double-blind Phase, no clinically notable changes were recorded in the mean supine or standing pulse rates, systolic or diastolic blood pressure in either of the treatment groups as demonstrated in the table below:

Table 63: Psy-3012 Vital Signs--Mean Change from Baseline (DB) to End Point (DB)

	Placebo (N=145)	PP3M (N=160)
Supine pulse rate (bpm)		
Mean baseline	73.6	73.2
Mean change	-1.1	-0.5
Supine SBP (mmHg)		
Mean baseline	117.8	118.7
Mean change	1.9	-0.2
Supine DBP (mmHg)		
Mean baseline	74.9	75.0
Mean change	0.3	-0.6
Standing pulse rate (bpm)		
Mean baseline	79.6	79.7
Mean change	-0.6	0.4
Standing SBP (mmHg)		
Mean baseline	118.1	118.4
Mean change	1.6	1.0
Standing DBP (mmHg)		
Mean baseline	76.9	76.5
Mean change	0.4	0.7
Pulse (standing-supine) (bpm)		
Mean baseline	6.0	6.6
Mean change	0.5	0.8
SBP (standing-supine) (mmHg)		
Mean baseline	0.3	-0.4
Mean change	-0.3	1.2
DBP (standing-supine) (mmHg)		
Mean baseline	2.0	1.5
Mean change	0.1	1.3

Study report, p.157-158

Treatment-Emergent Abnormal Increases in Vital Signs

Higher incidence of treatment-emergent abnormal increases was recorded in the PP3M group than in the placebo group for standing pulse rate (bpm) (7.5% vs. 4.1%) and for standing DBP (mmHg) (1.9% vs. 1.4%). The incidence of orthostatic hypotension assessed by orthostatic changes in blood pressure and pulse rate was low in the Double-blind Phase ($\leq 2\%$).

Table 64: PSY-3012 Number of Subjects with Treatment-Emergent Abnormal Vital Signs Relative to Baseline (DB) at Any Time During the Double-Blind Phase

Parameter	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Supine pulse rate (bpm)	145	160
Decrease ≥ 15 and value ≤ 50	0	0
Increase ≥ 15 and value ≥ 100	1 (0.7)	1 (0.6)
Supine SBP (mmHg)	145	160
Decrease ≥ 20 and value ≤ 90	2 (1.4)	1 (0.6)
Increase ≥ 20 and value ≥ 180	0	0
Supine DBP (mmHg)	145	160
Decrease ≥ 15 and value ≤ 50	0	0
Increase ≥ 15 and value ≥ 105	0	0
Standing pulse rate (bpm)	145	160
Decrease ≥ 15 and value ≤ 50	0	1 (0.6)
Increase ≥ 15 and value ≥ 100	6 (4.1)	12 (7.5)
Standing SBP (mmHg)	145	160
Decrease ≥ 20 and value ≤ 90	2 (1.4)	1 (0.6)
Increase ≥ 20 and value ≥ 180	0	0
Standing DBP (mmHg)	145	160
Decrease ≥ 15 and value ≤ 50	2 (1.4)	0
Increase ≥ 15 and value ≥ 105	2 (1.4)	3 (1.9)

Study report, p. 2003

Since at Baseline (DB) all subjects would have been 3 months post-PP3M injection, their data were also analyzed relative to the Predose Baseline (OL). These data are detailed in the table below and are similar to the data above.

Table 65: PSY-3012 Number of Subjects with Treatment-Emergent Abnormal vital Signs Relative to Predose (OL) at Any Time During the Double-Blind Phase

Parameter	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Supine pulse rate (bpm)	145	160
Decrease ≥ 15 and value ≤ 50	0	1 (0.6)
Increase ≥ 15 and value ≥ 100	0	2 (1.3)
Supine SBP (mmHg)	145	160
Decrease ≥ 20 and value ≤ 90	1 (0.7)	1 (0.6)
Increase ≥ 20 and value ≥ 180	0	0
Supine DBP (mmHg)	145	160
Decrease ≥ 15 and value ≤ 50	1 (0.7)	0
Increase ≥ 15 and value ≥ 105	0	0
Standing pulse rate (bpm)	145	160
Decrease ≥ 15 and value ≤ 50	0	1 (0.6)
Increase ≥ 15 and value ≥ 100	4 (2.8)	14 (8.8)
Standing SBP (mmHg)	145	160
Decrease ≥ 20 and value ≤ 90	1 (0.7)	1 (0.6)
Increase ≥ 20 and value ≥ 180	0	0
Standing DBP (mmHg)	145	160
Decrease ≥ 15 and value ≤ 50	2 (1.4)	1 (0.6)
Increase ≥ 15 and value ≥ 105	2 (1.4)	3 (1.9)

Study report, p. 2004

Orthostatic Hypotension

Orthostatic hypotension was defined as a decrease in systolic (>20 mmHg), or diastolic (>10 mmHg) blood pressure after standing for at least 2 minutes relative to supine position with an increase in pulse rate of >15 beats per minute.

Five subjects (1.3%) experienced treatment-emergent orthostatic hypotension during the Maintenance phase. Two subjects in the Placebo group (1.4%) and 2 subjects in the PP3M group (1.3%) experienced treatment-emergent orthostatic hypotension during the

Double-blind Phase. None of the vital sign abnormalities were reported as SAEs or resulted in study discontinuation.

Weight, Waist Circumference, and BMI

From Open-label baseline to Double-blind end point, mean body weight (both in actual values and percent change), mean waist circumference, and mean BMI increased. The mean body weight increases observed in the PP3M group were larger than those for the placebo group (2.38 kg vs. 0.55 kg).

Table 66: PSY-3012 Weight, BMI, and Weight Circumference--Change from Baseline (OL) to End Point (DB)

	Placebo (N=145)	PP3M (N=160)
Weight (kg)		
Mean baseline (SD)	77.12 (15.498)	77.98 (14.982)
Mean change (SD)	0.55 (5.376)	2.38 (6.225)
Body mass index (kg/m²)		
Mean baseline (SD)	26.14 (4.543)	26.21 (4.467)
Mean change (SD)	0.20 (1.834)	0.77 (2.070)
Waist (cm)		
Mean baseline (SD)	89.70 (12.831)	90.55 (14.193)
Mean change (SD)	-0.07 (5.677)	2.05 (6.740)

Study report, p. 159

Abnormal increases of $\geq 7\%$ in body weight from Double-blind baseline to Double-blind end point were reported for 15 subjects (10%) in the PP3M group and 1 subject (1%) in the placebo group. Abnormal increases of $\geq 7\%$ in body weight from Open-label baseline to Double-blind end point were reported for 38 subjects (24%) in the PP3M group and 25 subjects (18%) in the placebo group.

Table 67: PsSY-3012 Number of Subject with Abnormal Weight Percent Change from Baseline (DB and OL) at Endpoint (DB)

Number of Subjects With Abnormal Weight Percent Change From Baseline (DB) at End Point (DB)		
	Placebo (N=145)	PP3M (N=160)
	n (%)	n (%)
Abnormal weight percent change	142	157
Decrease \geq 7%	12 (8)	2 (1)
Increase \geq 7%	1 (1)	15 (10)

Number of Subjects With Abnormal Weight Percent Change From Baseline (OL) at End Point (DB)		
	Placebo (N=145)	PP3M (N=160)
	n (%)	n (%)
Abnormal weight percent change	142	157
Decrease \geq 7%	18 (13)	16 (10)
Increase \geq 7%	25 (18)	38 (24)

Study report, p. 160

7.4.4 Electrocardiograms (ECGs)

According to the Applicant, cardiovascular safety data from Study PSY-3012 were in agreement with the findings from the studies of paliperidone ER (including the thorough QT/QTc study) and the studies of PP1M. No new cardiovascular safety signal was detected.

Double-Blind Phase

Abnormally high heart rate occurred in a higher percentage of subjects in the placebo group than in the PP3M group (7% vs. 2%). Abnormally low heart rate occurred in 3% of subjects in both treatment groups.

Administration of PP3M was not associated with clinically significant mean increases from average predose values in QTc intervals. The mean change in QTcLD from average predose values was similar for both PP3M and placebo groups. No subjects in either treatment group had maximum value over 480 msec at any time during the Double-blind Phase for any of the corrected QT interval values. 3% of subjects in the placebo group and 5% of subjects in the PP3M group had increases in QTcLD between 30 and 60 msec. No subject had QTcLD increase over 60 msec.

Table 68: Psy-3012 Number of Subjects with Treatment-Emergent Abnormal ECG Values Relative to Average Predose at Any Time During the Double-Blind Phase

	Placebo (N=145) n (%)	PP3M (N=160) n (%)
Heart Rate	141	155
Abnormally High	10 (7)	3 (2)
Abnormally Low	4 (3)	4 (3)
PR Duration	141	155
Abnormally High	3 (2)	2 (1)
QRS Duration	141	155
Abnormally High	0	2 (1)
Abnormally Low	0	0
QT Interval	141	155
Abnormally High	0	0
Abnormally Low	0	0

Study report, p. 163

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This long-term trial was not specifically designed to assess dose response, or safety and tolerability of any of the fixed doses of PP3M relative to placebo in the double-blind phase. Subjects who completed the open-label phase on a distinct dose level of PP1M were converted to a corresponding dose of PP3M before being randomized to placebo or continuation of the same dose of PP3M during the double-blind phase.

7.5.2 Time Dependency for Adverse Events

Please see previous discussions of injection site reactions, prolactin levels, and weight gain.

7.5.3 Drug-Demographic Interactions

An examination of population subgroups did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects \geq 65 years of age.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

PSY-3012

One pregnancy was reported during this study:

Subject 60400505 received PP1M/PP3M during the Open-label Phase and then placebo during the Double-blind Phase. She was randomized to the placebo group 1 year prior to the date of her last menstrual period. She had an elective abortion approximately 5 weeks into her pregnancy. The investigator considered the causality as not related.

PSY-1005

Two pregnancies were reported during this study:

Subject 604103 was a 42-year-old woman who discontinued the study due to an ectopic pregnancy, which was recorded as a serious adverse event. The subject received an injection of PP3M 300 mg eq. approximately 10 months before the event in Period 2 (Panel B). The investigator considered the causality as doubtful.

Subject 603014 was a 26-year-old woman who received 300 mg eq. paliperidone palmitate (F015) in Period 2. On Day 153 of Period 2, pregnancy was discovered based on a positive pregnancy test. The subject was discontinued from the study. No further contact with the subject could be established, and the outcome of pregnancy was not known.

Ongoing Study PSY-3011

As of the cutoff date for the NDA submission, one pregnancy has been reported:

Subject 40071701 was a 29-year-old woman who became pregnant in the Double-blind Phase of the study. The date of the last menstrual period and expected delivery date were not reported. The outcome for drug exposure during pregnancy was not reported. The blind has not been broken for this case. The subject refused all follow up after being withdrawn from the study, and no further information is available at this time.

An additional pregnancy was reported with the 4-Month Safety Update:

Subject 40861045 was a 21-year-old woman from China who became pregnant in the DB Phase of the study. The date of the last menstrual period was in April 2014; expected delivery date was not reported. The subject's pregnancy was confirmed on 31

May 2014. Concomitant medications were not reported. Study treatment was withdrawn on 6 June 2014. The outcome for drug exposure during pregnancy was not reported. The blind has not been broken for this case. The subject was lost to follow up after withdrawal from the study, and no information is available on the outcome of her pregnancy.

Reviewer comment: None of the above cases add any information about the safety of PP3M exposure during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

PP1M is not approved for use in the pediatric population. The Applicant has requested and been granted a waiver for the study of PP3M in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

PP3M is an injectable medication. The label states that it should be administered by a health care provider. Thus, according to the Applicant, the potential is considerably less than that of oral medications.

No adverse events of overdose were reported in Study PSY-3012. Overdoses with other substances in the context of a suicide attempt were reported for Study PSY-1005 and Study PSY-3011.

Drug Abuse

According to the Applicant, the pharmacologic profile of paliperidone indicates that the abuse and dependence potential of paliperidone is minimal.

Withdrawal and Rebound

The Applicant states that due to the long-acting nature of the PP3M formulation, a systematic approach to evaluation of withdrawal events via a checklist or other standardized questionnaire was not performed in the clinical development program.

7.7 Additional Submissions / Safety Issues

Because of the difficulties with incomplete dosing during the early panels of the pivotal PK study (PSY-1005), a request for information was sent to the Applicant (1/30/2015 e-mail). The Agency's questions covered topics such as whether a Human Factors Study had been completed, the training of the investigators, risk mitigation strategies, syringeability, and in-use stability. The following is a brief summary of the Agency's questions and the Applicant's responses:

FDA Question #1: It is our understanding that in the course of your development program for paliperidone palmitate extended-release injectable suspension (3-month injection) there were errors involving shaking of the product sufficiently to obtain proper suspension of the active ingredient prior to injection...Please clarify if you have conducted a summative human factors study for your proposed paliperidone palmitate product.

Summary of Applicant Response: JRD has conducted both a formative Human Factors Study and a summative Human Factors Study (HFS) for the paliperidone palmitate 3-month product, including its associated devices and labeling. The studies included observed simulated use of the representative product by its expected users and selected post-use knowledge probes from directed participant interviews. The observed actions of the 15 participants in the summative HFS did not find patterns of use error, or any use errors, associated with product mixing (vigorous shaking for 15 seconds). Simulated injections performed using the available Instructions for Use or IFU (but without any training) resulted in the delivery of the entire syringe contents. Interviews of study participants indicated a high knowledge and understanding of the need to shake the pre-filled syringe (PFS) until the drug is fully suspended. The Applicant concluded that the overall results of the study validated that the product and its IFU meet users' needs and intended uses, and are sufficiently safe and usable.

FDA Question #2: We are also interested in understanding specifically what training and processes were put in place during your clinical development program to mitigate the risk of improper preparation of this product. Please submit a detailed summary of all use errors identified during your clinical development program as well as the training and other risk mitigation strategies.

Summary of Applicant Response: During earlier panels of Phase 1 clinical trial R092670-PSY-1005 (panels A and C) incomplete bioavailability of paliperidone palmitate 3-month formulation was observed which was attributed to insufficient shaking. In order to mitigate this issue, prior to initiation of additional dosing panels (B and D), the study staff were provided with training and instructions on administration of the study drug.

Prior to initiation of phase 3 clinical studies, a comprehensive training plan was developed and documented. This included Investigator Meeting Training, Training at Site Initiation Visit, and Training at Routine Monitoring Visits. This training included a slide presentation on the consequences of inadequate shaking and a video demonstrating proper injection technique. Two key forms as part of the study documents contained bolded and colored reminders on the importance of proper shaking before injection. In addition, a user friendly leaflet (Instructions for Use or IFU) with pictograms was included in each drug kit.

During the pivotal Phase 3 clinical study R092670-PSY- 3012, there were no reports of use errors. During the ongoing Phase 3 clinical study R092670-PSY-3011, there have been 13 use errors reported (out of 2796 injections administered). Included in the 13 reported use errors were 8 use errors relating to partial injection and 1 for which the injection could not be started. The investigation on the returned samples identified insufficient shaking as the root cause for the difficulties observed during injection. To mitigate these use errors, the re-training of site drug administrators was performed and an additional label was implemented providing instruction “VIGOROUSLY shake for 15 seconds” for all kits in the clinical supplies.

The risk mitigation strategy on the clinical consequences of partial injections or blocked needles during the clinical trial program is summarized below:

- Blocked needles prior to injection: if a needle was blocked prior to being injected into a subject and if another medication kit was available, then it was permitted for the SDA to remove the old needle and replace it with a needle from a new kit.
- Partial injection: if a needle became blocked during the injection into a subject, it was recommended that the needle and syringe be withdrawn. If another kit was available at the site, the investigator had the option to replace the needle from a new kit and administer the partially used syringe (after vigorous shaking). Patients with the partial dose were closely monitored.

FDA Question #3: Provide your rationale for why you believe all use-related risks associated with your product have been mitigated to an acceptable level.

Summary of Applicant Response: Based on the HFS and the clinical trial experience, an IFU was designed that provided significant emphasis on product mixing both in written instructions and in figures. The syringe label also states in large font: “SHAKE VIGOROUSLY for at least 15 seconds” and includes an illustration next to this statement depicting the technique.

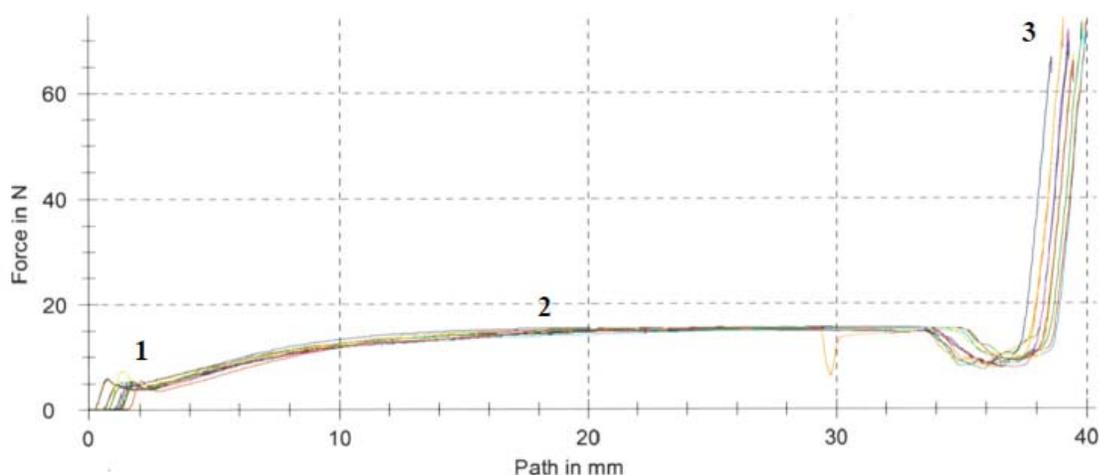
Also, to improve the ability of the syringe to deliver the drug over the kitted product used in panel A and C of Phase 1 clinical trial, “thin wall” needles, of the same gauge and length, were selected and used in the subsequent panels of the phase 1 clinical trial, as well as the phase 3 trials, and for the commercial product. This needle design mitigation is intended to reduce the injection force and risk of needle clogging due to their larger internal diameter. The Applicant has also submitted a document detailing the comparable performance and benefit of these needles in delivery performance (i.e., piston travel forces).

FDA Question #4: Provide all available data on the likelihood of failures (e.g. syringeability, etc.) should the product be shaken for a time period shorter than the labeled 15 seconds (e.g. 0, 5 or 10 seconds) and provide the data that were used to establish the 15 second shaking time.

Summary of Applicant Response: To evaluate the injectability characteristics during development, injection force testing was performed on non-shaken samples and on samples after 5 and 15 seconds shaking time.

A typical injection profile of a syringe following the required 15 seconds of vigorous shaking is shown in the figure below. The profile shows an initial small spike due to the force needed to start moving the rubber piston (Piston Release Force or PRF) and the force needed to move the piston during the injection of the product (Piston Travel Force or PTF).

Figure 11: Injection Profile of Batch, 1.75-mL Syringe after 15 Seconds Shaking Time

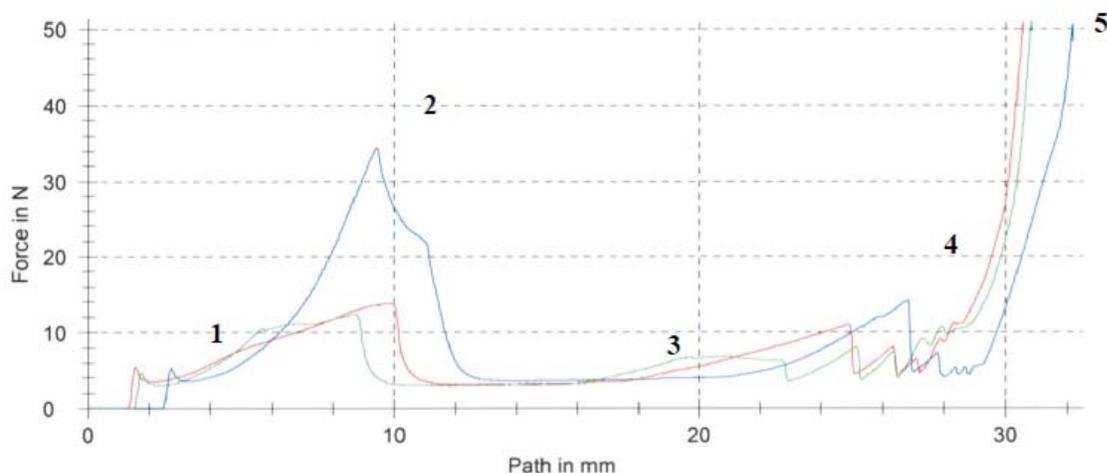


- 1: PRF: piston release force
- 2: PTF: piston travel force
- 3: End of injection (rubber stopper hits the tip of the syringe)

Response to FDA Communication of 30 January 2015, p. 9

When a sample is tested without shaking a difference in the piston force profile can be observed as demonstrated in the figure below:

Figure 12: Injection Profile of a Non-Shaken Batch, 1.75-mL Syringe



- 1: PRF: piston release force
- 2: Forming a channel
- 3: PTF: piston travel force
- 4: Expelling remaining slurry
- 5: End of injection (rubber stopper hits the tip of the syringe)

Response to FDA Communication of 30 January 2015, p. 9

The resuspendability and injectability characteristics of the formulation were evaluated on samples shaken vigorously for 5 and 15 seconds by determining the PTF. The data showed that after 5 seconds of vigorously shaking, an acceptable resuspendability was observed for most of the sample population. In a limited number of samples an increased PTF value was observed in the first part of the injection profile (3-10 mm). After 15 seconds of vigorously shaking, all samples showed acceptable PTF and flat injection profiles. The Applicant concludes that an acceptable resuspendability and injectability is typically achieved even with reduced shaking, but that the 15 seconds shaking instruction recommended in the IFU will allow an additional safety window.

FDA Question #5: Provide data to support the proposed 5 minutes in-use stability period.

Summary of Applicant Response: An in use stability study was performed whereby the appearance and piston travel force was measured after 15 seconds of shaking and compared to samples of the same batch after, 15 seconds of shaking followed by 90 minutes holding time (with no additional shaking immediately prior to testing). The data demonstrated that after a holding period of 90 minutes, the appearance and piston travel force remained acceptable as compared to the initial values.

After shaking, a normal initial PTF value of 13 N was measured. After the 90 minutes holding time, the same PTF values were measured. A flat PTF profile was observed, indicating that the suspension was sufficiently homogeneous. The Applicant concludes that the data support an in use period well beyond the proposed 5 minutes. However, the applicant does not propose to change the labeling “since it is good clinical practice to inject the product as soon as reasonably practical after suspension.”

The Division of Psychiatry Products also requested a CDRH consultation to evaluate the drug kit. The CDRH reviews are still pending. Please see the CDRH review for further details.

7.8 120 Day Safety Update for Study PSY-3011

The Applicant submitted the 4-month Safety Update (4MSU) on 2/13/2015. The safety update presents blinded cumulative safety data up to a clinical cutoff of 11 November 2014 collected in the ongoing Phase 3 Study PSY-3011 in adults with schizophrenia. Study PSY-3011 is a randomized, double-blind, noninferiority study comparing paliperidone palmitate 3-month formulation (PP3M) with paliperidone palmitate 1-month formulation (PP1M). The study design was previously described in Section 7.1.1 of this NDA review.

Overall Extent of Exposure

As of 11 November 2014 cutoff date, 1,429 subjects have been enrolled into the ongoing blinded study PSY-3011 and 1,016 subjects were randomized in a 1:1 ratio to PP3M and PP1M leading to an estimate of 508 subjects having received at least one dose of PP3M in the DB Phase of the study. As of the 11 November 2014 cutoff date, 869 subjects (86%) received at least 24 weeks of treatment, and 452 subjects (44%) received at least 48 weeks of treatment with investigational product (PP1M or PP3M) in the DB Phase. Thus, an additional 211 subjects received at least 48 weeks of treatment with an investigational product (PP1M or PP3M), compared to the data presented for this study in the SCS as of the 31 May 2014 cutoff date. Based on the 1:1 randomization ratio between PP3M and PP1M it is estimated that an additional estimated 106 subjects had received at least 48 weeks of exposure to PP3M.

Thus, based on the 3 studies included in this NDA (PSY-1005, PSY-3011, and PSY-3012), an estimated total of 1,195 subjects received at least one injection of PP3M as of the 11 November 2014 cutoff date, with an estimated 254 subjects having at least 48 weeks of PP3M exposure in Phase 3 studies.

Table 69: Cumulative Frequency Distribution of Total Drug Exposure

Duration of exposure	PSY-3012 ^a	PSY-3011 ^b		Total Estimated PP3M Exposure in Phase 3 Studies	
		11 November 2014 cutoff		31 May 2014 cutoff (SCS)	11 November 2014 cutoff
	n	Blinded Double-Blind Treatment n	Estimated PP3M Exposure n		
≥ 1 day	379	1016	508	887	887
≥ 24 Weeks	137	869	434	501	571
≥ 48 Weeks	28	452	226	148	254

4-Month Safety Update, p. 10

Deaths

As of the clinical cutoff date of 11 November 2014, only 1 new death (secondary to hepatocellular carcinoma) was reported. The following is the narrative for the death:

Subject 40610704, a 56-year-old male from Australia, whose medical history included hepatitis C and alcohol abuse, and a recent diagnosis of prostatic adenocellular carcinoma, was randomized to double-blind treatment in the study. After Visit 21, the subject exhibited signs of biliary obstruction. He was diagnosed with moderate hepatocellular carcinoma and was hospitalized following a CT scan that showed occlusion of the portal vein. The subject's oncology reviews were reported as primary liver cancer with poor prognosis. The subject was receiving supportive treatment. Following an initial discharge from the hospital, he was readmitted 12 days later for pain management and palliation. The subject's state deteriorated and he died the same day. An autopsy was not performed. The investigator considered the causality between hepatocellular carcinoma and study agent as not related. The blind has not been broken for this case.

SAEs

The SAEs/TEAEs in the DB Phase occurred during administration of either PP1M or PP3M. In all cases, regardless of current treatment assignment, subjects had a prior 17-week exposure to PP1M in the OL phase. The Applicant notes that this prior exposure to PP1M could confound the causal attribution of the SAE/TEAE to either formulation (PP1M or PP3M) in the DB phase.

As of the 4-Month Safety Update cutoff (11 November 2014), treatment-emergent SAEs were reported for 72 subjects (7.1%) in the DB Phase. New treatment-emergent SAEs were reported in the DB phase for 11 subjects since the NDA submission safety cutoff (31 May 2014). According to the Applicant, "this increase (from 61 subjects [6.0%] to 72 subjects [7.1%]) was primarily due to new events in the psychiatric disorders SOC, and was likely related to the natural changes in the course of the underlying disease during

the extended period of double-blind treatment with investigational product (PP1M or PP3M).”

The only new treatment-emergent SAEs of clinical interest in the DB phase was a suicide attempt. The following is the narrative:

Subject 40860925, a 19-year-old female from China, was treated in the DB phase of the study. After attempting suicide by drinking pesticide, she received emergency treatment and was recovering in a local hospital. The investigator considered the causality between suicide attempt and study agent as doubtful. The blind has not been broken for this case.

The 11 new SAEs that occurred during the Double-blind Phase after the NDA submission safety cutoff are detailed in the table below:

Table 70: PSY-3011 Additional SAEs from SCS Cutoff to 4MSU Cutoff

Body System or Organ Class Dictionary-Derived Term	Blinded DB Treatment n
Psychiatric Disorders	
Schizophrenia	2
Psychiatric Symptoms	1
Delusion	1
Suicide Attempt	1
Schizophrenia, paranoid type	1
Anxiety Disorder	1
Hallucination, auditory	1
Restlessness	1
Infections and Infestations	
Meningitis bacterial*	1
Neoplasms benign, malignant and unspecified	
Hepatocellular carcinoma	1
Prostate cancer	1

*This was not a new SAE. This SAE was classified as pyrexia (General disorders and administrations site conditions) in the SCS. Source: 4MSU, p. 90-91

Adverse Events Leading to Treatment Discontinuation

The TEAEs leading to discontinuation were reported at low rates (2.9%; 29 out of 1016 subjects) in the DB Phase of this ongoing study. Most events belonged to the psychiatric disorders SOC. No individual events leading to discontinuation were reported at the rates of 1% or above.

The only new treatment-emergent event of clinical interest leading to discontinuation between the SCS cutoff date and the 11 November 2014 cutoff date for this safety update was a suicide attempt in the DB phase (see SAE for Subject 40860925). With the exception of 1 new case of akathisia leading to discontinuation, no new EPS-related adverse events in this category were reported. The table below lists the additional AEs leading to study drug discontinuation during the DB Phase (after SCS cutoff to 4MSU cutoff date):

Table 71: PSY-3011 TEAEs Leading to Study Drug Discontinuation During the DB Phase from SCS Cutoff to 4MSU Cutoff

Body System or Organ Class Dictionary-Derived Term	Blinded DB Treatment n
Psychiatric Disorders	
Anxiety	1
Depression	1
Suicide Attempt	1
Nervous System Disorders	
Akathisia	1
Somnolence	1
Epilepsy	1
Tremor	1
Reproductive System and Breast Disorders	
Galactorrhea	1
Menstrual Irregular	1
Injury, Poisoning, and Procedural Complications	
Bone Contusion	1
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity	1

Common Adverse Events during Double-Blind Phase

Blinded cumulative summary of the most common TEAEs (occurring in at least 2% of subjects) that occurred as of the cutoff date of 11 November 2014 in the safety analysis set during the DB Phase are in the table below. The most common TEAEs were weight increased (21.1%) and nasopharyngitis (7.4%). Other TEAEs occurring in at least 2% of subjects during the DB Phase were mostly in the psychiatric and nervous system disorders SOCs. The same events at very similar rates were previously reported in the Summary of Clinical Safety.

Table 72: Study PSY-3011 Most Common TEAEs (≥ 2%) During Double-Blind Phase as of November 11, 2014

Body System Or Organ Class Dictionary-Derived Term	Double-Blind Treatment (N=1016) n (%)
Total no. subjects with adverse events	684 (67.3)
Investigations	295 (29.0)
Weight increased	214 (21.1)
Weight decreased	27 (2.7)
Psychiatric disorders	177 (17.4)
Anxiety	51 (5.0)
Insomnia	43 (4.2)
Schizophrenia	34 (3.3)
Infections and infestations	171 (16.8)
Nasopharyngitis	75 (7.4)
Nervous system disorders	144 (14.2)
Headache	47 (4.6)
Akathisia	37 (3.6)
General disorders and administration site conditions	89 (8.8)
Injection site pain	26 (2.6)
Injection site induration	21 (2.1)

4MSU, p.12

Injection Site-Related Events

As of 11 November 2014 cutoff date, the most common events related to injection site reaction (reported by at least 2% of subjects) were injection site pain (2.6% in the DB Phase) and injection site induration (2.1% in the DB Phase). None of the events in this category were serious. Between the SCS cutoff date and 11 November 2014, there were no cases of injection site-related events that led to discontinuation of treatment.

Reviewer Comment: Based on all 3 studies included in this NDA (PSY-1005, PSY-3011, and PSY-3012), an estimated total of 1,195 subjects received at least one injection of PP3M as of the 11 November 2014 cutoff date, with an estimated total of 254 subjects having at least 48 weeks of PP3M exposure in Phase 3 studies. Review of the additional blinded safety data available from the ongoing Phase 3 study did not identify any new safety signals.

8 Postmarket Experience

PP3M is not authorized for marketing or commercially available in any country. Since no postmarketing data are available for the 3-month formulation, the Applicant has submitted an assessment based on the data for PP1M.

Based on the (b) (4) syringes of PP1M distributed worldwide from launch to 30 June 2014, the estimated exposure is 7,332,275 person-months or 611,023 person years. To capture all medically confirmed and non-medically confirmed (consumer) cases of adverse events reported with the use of PP1M, the Applicant conducted a search of the Global Medical Safety (GMS) worldwide safety database (SCEPTRE). The search of SCEPTRE was conducted cumulatively to 31 May 2014. The review focused on fatal cases with selected causes of death (cardiovascular, cancer, sudden and unexplained deaths, completed suicide, stroke, neuroleptic malignant syndrome, venous thromboembolism, and rhabdomyolysis), important European Union Risk Management Plan potential risks, specific populations, relevant drug interactions, and medication errors. The SCEPTRE search retrieved 3,519 spontaneous cases involving PP1M either as suspect, co-suspect, or suspect-interacting drug in the treatment of schizophrenia.

According to the Applicant, this review of post-marketing cumulative data for PP1M in the schizophrenic population was generally consistent with the established safety profile of paliperidone ER. No new significant safety issues were identified.

4-Month Safety Update

Based on the (b) (4) syringes of PP1M distributed worldwide from launch to 31 December 2014, the estimated exposure is 9,215,241 person-months or 767,937 person-years. According to the Applicant, review of the safety data from the marketed use of PP1M through 31 December 2014 did not reveal any new significant safety issues.

9 Appendices

9.1 Literature Review/References

The Applicant initially conducted a search of the literature to support submissions for the licensing of paliperidone ER for the treatment of schizophrenia. [REDACTED] (b) (4)

[REDACTED] In addition, subsequent updated searches have been conducted to support the submission of paliperidone palmitate for the treatment of schizophrenia [REDACTED] (b) (4)

Most recently, the Applicant has conducted a search of the literature covering the period from 01 March 2014 to 31 May 2014 to support the use of PP3M for the [REDACTED] (b) (4). This literature review summarizes major safety findings from non-Company sponsored, published reports related to paliperidone. Published safety data associated with administration of paliperidone were identified via a comprehensive search of the biomedical literature in MEDLINE®, EMBASE™, Derwent, Biosis, and Adis Reactions.

Seven articles were identified during the current search including 2 case reports (1 article reported 3 individual cases) and 5 clinical studies. A brief summary of these articles is provided in the Applicant's table below:

Table 73: Applicant's Brief Summary of Publications (3/1/2014 to 5/31/2014)

Reference	Type of Study	N	Patient Characteristics	Dosing	Relevant Safety Findings
Safety Data - Clinical Studies					
Ercoreca 2013 ¹ (Abstract)	Observational study to analyze the concomitant psychiatric pharmacotherapy of outpatients treated with paliperidone palmitate LAI.	301 (182 men and 119 women)	Outpatients treated with paliperidone palmitate LAI and attended in the pharmacy department of a secondary hospital	Not available	In most of the analyzed prescriptions, patients on treatment with paliperidone palmitate LAI were also receiving other oral antipsychotic drugs. The use of higher dose of paliperidone palmitate LAI than the maximum approved dose was common.
Storch 2013 ³ (Full publication [original research])	Randomized, double-blind, placebo-controlled study to investigate the efficacy and tolerability of paliperidone augmentation of SRIs in patients with treatment-resistant OCD.	34	Patients who met DSM-IV criteria and remain symptomatic despite 2 or more adequate SRIs reuptake inhibitor trials	Paliperidone (mean [SD] dose: 4.94 [2.36] mg/day) or matching placebo (mean [SD] dose: 6.2 [2.6] mg/day) for 8 weeks	Paliperidone augmentation was well-tolerated and has potential efficacy in the short-term treatment of some patients with serotonin reuptake inhibitors-resistant OCD. There were no significant group differences observed with regard to the adverse events and premature discontinuation.
Suzuki 2014a ⁴ (Full publication [original article])	A prospective, open-label, flexible-dose, naturalistic, observational study to evaluate the effects of switching from risperidone to paliperidone on clinical symptoms and cognitive functions in elderly patients with schizophrenia.	17 (5 males and 12 females)	Patients with schizophrenia who received risperidone monotherapy	Mean (SD) risperidone dose (baseline): 4.1 (1.5) mg/day and paliperidone dose (12 weeks): 6.2 (3.3) mg/day	The DIEPSS and BAS significantly improved after switching from risperidone to paliperidone. Improvement was also found on AIMS. The mean change from baseline in z-score of the digit sequencing task was significantly increased. The change in all items of the PANSS and the CGI-S were not significant; however, changes in some cognitive function were correlated with changes in EPS.

Reference	Type of Study	N	Patient Characteristics	Dosing	Relevant Safety Findings
Safety Data - Case Reports					
Hsu 2013 ² (full publication [letter to the Editor])	Case report on tardive dyskinesia induced by a switch from haloperidol depot to paliperidone palmitate.	1	39-year-old Han Chinese woman	Haloperidol depot 40 mg/month for 9 months, paliperidone palmitate 100 mg ^a on Day 1 and Day 8, then monthly for 2 months.	Tardive dyskinesia occurred after the fourth dose of paliperidone palmitate (post discontinuation of haloperidol depot)
Yamamuro 2014 ⁶ (Full publication)	Case reports on treatment of Tourette's disorder with paliperidone ER.	3	10-year-old boy who developed facial motor tics at the age of 8 years 11-year-old boy who developed motor tics such as blinking and coughing at the age of 9 years 13-year-old boy who developed motor and vocal tics beginning at the age of 8 years	Haloperidol 1.5 mg/day, paliperidone ER 3 mg/day Paliperidone ER 3 mg/day, which was increased to 6 mg/day after 6 weeks Haloperidol 1.5 mg/day for 2 years, paliperidone ER 3 mg/day, which was increased to 6 mg/day after 3 weeks	In two cases, Tourette's disorder symptoms were remarkably improved by switching from haloperidol to paliperidone ER, and in another case, paliperidone ER showed clinically significant efficacy in treating Tourette's disorder symptoms as the first-line drug. In all cases, no significant adverse side effects were detected.

Clinical Review
 Christina P. Burkhart, M.D.
 NDA 207946
 INVEGA TRINZA (Paliperidone Palmitate Extended-Release Injectable Suspension)

Reference	Type of Study	N	Patient Characteristics	Dosing	Relevant Safety Findings
Pharmacokinetic Data- Clinical Studies					
Suzuki 2014b ³ (Full publication [original paper])	A prospective, open-label, flexible-dose, naturalistic, observational study to investigate the relationship between the plasma concentration of paliperidone and clinical and drug-induced EPS in elderly patients with schizophrenia.	15 (6 males and 9 females)	Patients with schizophrenia who received risperidone monotherapy.	Mean (SD) risperidone dose (baseline): 4.1(1.8) mg/day, paliperidone dose (12 weeks): 6.2 (3.7) mg/day	Increased plasma concentration may not result in worsening of EPS or increase in prolactin level. Also, linear clinical efficacy may not be obtained.
Yang 2014 ⁷ (Full publication [original paper])	An open-label, prospective study to measure the steady-state plasma levels of risperidone and paliperidone and to assess the associated clinical response and safety profiles.	25 patients (15 males and 10 females)	Adult patients with a diagnosis of schizophrenia according to the DSM-IV	Mean [SD] risperidone dose (baseline): 4.0 [1.2] mg/day. Paliperidone ER 6 mg/day for 6 weeks	Plasma levels of the active moiety (risperidone plus 9-OH-risperidone) while taking risperidone (mean dose: 4.0 mg) were significantly higher than plasma levels of 9-OH-risperidone while taking 6 mg of paliperidone ER. Significant reduction in PANSS and CGI-S scores were noted from baseline to Week 6. The safety profile remained similar.

9-OH-risperidone=9-hydroxy-risperidone, AIMS=Abnormal Involuntary Movement Scale, BAS=Barnes Akathisia Scale, CGI-S=Clinical Global Impression- Severity scale, DIEPSS= Drug-induced Extrapyramidal Symptoms Scale, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, ER=extended-release, EPS=extrapyramidal symptoms, LAI=long-acting injection, OCD=obsessive-compulsive disorder, PANSS=Positive and Negative Syndrome Scale, SD= standard deviation, SRI=serotonin reuptake inhibitor

Literature Review, p. 7-9

The data presented in the Applicant's current review of the literature indicate that the benefit-to-risk ratios for the use of paliperidone ER in the treatment of schizophrenia and paliperidone palmitate in the treatment of schizophrenia, remain favorable. No new clinically significant safety findings were identified.

9.2 Labeling Recommendations

Dr. Rekic (Pharmacometrics) concludes that the submitted population PK analysis supports labeling claims in regards to dose administration. Specifically, Dr. Rekic agrees with the following proposals by the Applicant:

- The applicant's proposed dosing regimen is acceptable.
- The applicant's proposed dosing regimens outside of scheduled time points are acceptable.
- The applicant's proposal for switching from PP3M formulation to oral extended release tablets is appropriate.
- The dose should not be adjusted due to patient's CYP2D6 status.
- The dose should not be adjusted due to patient's age, race, gender, or BMI.

Dr. Rekic did not agree with the Applicant's recommendations to (b) (4)

(b) (4) Dr. Rekic states that the applicant's proposal to (b) (4) is not justified by the 16% expected increase in maximum concentrations at steady state. Please see Dr. Rekic's full review for further details.

A Collaborative Review of patient labeling (Patient Package Insert or PPI) was performed by Twanda Scales (Office of Medical Policy) and Susannah O'Donnell

(Division of Medical Policy Programs). They concluded that the PPI was acceptable with the following recommended changes.

- Change the font to Ariel, 10 point
- Add limitation of use indication: to use in people who have been treated with INVEGA SUSTENNA for at least 4 months
- Add Pregnancy Registry information
- Revise the list of side effects to be consistent with the common adverse reactions in the label

The Division of Pediatric and Maternal Health has also been consulted to give DPP input for Sections 8.1 to 8.4 of the label.

We are currently in labeling negotiations with the Applicant.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned. Paliperidone palmitate is not a new molecular entity; there is considerable premarket and postmarketing experience with paliperidone palmitate.

9.4 PSY-1005 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure

Application Number: **NDA 207946**

Submission Date(s): **November 18, 2014**

Applicant: **Janssen Pharmaceuticals, Inc.**

Product: **Paliperidone Palmitate Extended –Release Injectable Suspension for Intramuscular Use (3-month formulation)**

Reviewer: **Christina P. Burkhardt, M.D.**

Date of Review: **February 6, 2015**

Covered Clinical Study (Name and/or Number): **PSY-1005**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>40 PI/ 357 SI</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <u>NA</u> Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/> <u>NA</u>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/> <u>NA</u>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>NA</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/> <u>NA</u>	No <input type="checkbox"/> (Request explanation from applicant)

9.5 PSY-3012 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number: **NDA 207946**

Submission Date(s): **November 18, 2014**

Applicant: **Janssen Pharmaceuticals, Inc.**

Product: **Paliperidone Palmitate Extended –Release Injectable Suspension for Intramuscular Use (3-month formulation)**

Reviewer: **Christina P. Burkhart, M.D.**

Date of Review: **February 6, 2015**

Covered Clinical Study (Name and/or Number): **PSY-3012**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 65 PI/ 334 SI		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: 2</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/> NA	No <input type="checkbox"/> (Request explanation from applicant)

(b) (6) (Site (b) (6))

Details of Disclosable Financial Arrangements/Agreements:

The investigator received compensation in the form of honoraria to speak promotionally about INVEGA® SUSTENNA®.

Steps Taken to Minimize Bias:

Study PSY-3012 was a randomized, multicenter, double-blind, relapse prevention study of paliperidone palmitate 3 month formulation for the treatment of subjects with schizophrenia. To minimize investigator bias, subjects had to meet pre-specified endpoint criteria (e.g. minimum 25% or 10-point increase from double-blind baseline in PANSS total score at two separate visits 3 to 7 days apart) in order to be included in the primary analysis set that was

subject to a planned interim analysis. An Independent Data Monitoring Committee (IDMC) independently reviewed the results of the interim analysis and provided a recommendation to the sponsor whether to continue the study or terminate the study early. In addition, all case report forms were collected and data analyzed by Janssen Research and Development, LLC. Site (b) (6) enrolled 14 out of the total of 305 subjects who were randomized to double-blind treatment in PSY-3012.

(b) (6) (Site (b) (6))

Details of Disclosable Financial Arrangements/Agreements:

The investigator received compensation in the form of grant support and consultancy.

Steps Taken to Minimize Bias:

Study PSY-3012 was a randomized, multicenter, double-blind, relapse prevention study of paliperidone palmitate 3 month formulation for the treatment of subjects with schizophrenia. To minimize investigator bias, subjects had to meet pre-specified endpoint criteria (e.g. minimum 25% or 10-point increase from double-blind baseline in PANSS total score at two separate visits 3 to 7 days apart) in order to be included in the primary analysis set that was subject to a planned interim analysis. An Independent Data Monitoring Committee (IDMC) independently reviewed the results of the interim analysis and provided a recommendation to the sponsor whether to continue the study or terminate the study early. In addition, all case report forms were collected and data analyzed by Janssen Research and Development, LLC. Site (b) (6) enrolled 15 out of the total of 305 subjects who were randomized to double-blind treatment in Study PSY-3012.

Reviewer Comment: The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. OSI has inspected both these sites and no significant regulatory violations were noted at these sites.

9.6 PSY-3011 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure

Application Number: **NDA 207946**

Submission Date(s): **November 18, 2014**

Applicant: **Janssen Pharmaceuticals, Inc.**

Product: **Paliperidone Palmitate Extended –Release Injectable Suspension for Intramuscular Use (3-month formulation)**

Reviewer: **Christina P. Burkhart, M.D.**

Date of Review: **February 6, 2015**

Clinical Review
 Christina P. Burkhart, M.D.
 NDA 207946
 INVEGA TRINZA (Paliperidone Palmitate Extended-Release Injectable Suspension)

Covered Clinical Study (Name and/or Number): **PSY-2011**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/> X	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 202 PI		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NA</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/> NA	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/> NA	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/> NA	No <input type="checkbox"/> (Request explanation from applicant)

9.7 PSY-3012 Time and Events Schedule

TIME AND EVENTS SCHEDULE

Period	Screen-ing	Transition						Maintenance				Double-Blind									
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Visits every 4 weeks ^a	Visits every 8 weeks ^a	Visits every 12 weeks ^a	Week 54 PK	Week 55 PK	EOS/ Early WD Visit	
Week	-3 to -1		1	5	9	13	14	17	21	25	29	33	37	41							
Day	-21 to -1	1	8	36	64	92	99	120	148	176	204	232	260	288							
Window (days)		NA	±3	±7	±7	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	NA	
Screening/Administrative Procedures																					
Informed consent	X																				
Psychiatric evaluation	X																				
History ^b	X																				
Inclusion/exclusion criteria	X	X																			
Physical examination		X									X									X	
Randomization											X										
Tolerability test ^c	X																				
Study drug administration																					
Administer study medication		X ^{d,e}	X	X	X	X		X			X			X				X			
Pharmacokinetic Procedures																					
PK Sample collection ^f		X			X	X	X	X	X	X	X	X	X	X	X				X ^g	X ^g	X
Pharmacogenomic Procedures																					
Pharmacogenomic consent ^h	X																				
Blood sample collection		X																			
Biomarker Procedures																					
Blood sample for biomarkers								X	X	X	X	X	X	X						X	
Efficacy Procedures																					
PANSS ⁱ	X	X		X	X	X		X	X	X	X	X	X	X	X					X	
Mini PANSS ^j							X											X	X		

Period	Screen-ing	Transition						Maintenance				Double-Blind									
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Visits every 4 weeks ^a	Visits every 8 weeks ^a	Visits every 12 weeks ^a	Week 54 PK	Week 55 PK	EOS/ Early WD Visit	
Week	-3 to -1		1	5	9	13	14	17	21	25	29	33	37	41							
Day	-21 to -1	1	8	36	64	92	99	120	148	176	204	232	260	288							
Window (days)		NA	±3	±7	±7	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	NA	
CGI-S ¹		X		X	X	X		X	X	X	X	X	X	X	X					X	
PSP		X			X			X			X			X			X			X	
Other Assessments																					
Medication Preference Questionnaire	X																			X	
Involvement Evaluation Questionnaire ^k		X						X			X			X			X			X	
SF12		X																		X	
Healthcare Resource Utilization Questionnaire		X						X			X			X			X			X	
Patient Stated-choice Preference Survey ^l						X ^m	X ^m	X ^m													
Safety Assessments																					
Vital signs ⁿ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X
Height	X																				
Temperature		X									X									X	
Body weight	X	X				X				X	X			X			X			X	
Waist circumference	X	X				X				X	X			X			X			X	
Electrocardiogram (ECG) ^o	X	X				X				X				X			X			X	
Subject Injection Site Ratings VAS ^p		X	X	X	X	X		X			X			X			X				
Investigator Injection Site Ratings ^q		X	X	X	X	X		X			X			X			X			X	
AMS/BARS/SAS	X	X						X	X	X	X		X				X			X	
C-SSRS Baseline Version	X																				

Clinical Review
 Christina P. Burkhart, M.D.
 NDA 207946
 INVEGA TRINZA (Paliperidone Palmitate Extended-Release Injectable Suspension)

Period	Screening	Transition						Maintenance				Double-Blind								
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Visits every 4 weeks ^a	Visits every 8 weeks ^a	Visits every 12 weeks ^a	Week 54 PK	Week 55 PK	EOS/ Early WD Visit
Week	-3 to -1		1	5	9	13	14	17	21	25	29	33	37	41						
Day	-21 to -1	1	8	36	64	92	99	120	148	176	204	232	260	288						
Window (days)		NA	±3	±7	±7	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	NA
C-SSRS Since Last Visit Version		X	X	X	X	X		X	X	X	X	X	X	X	X					X
Clinical Laboratory Tests ^d	X	X									X						X			
Adverse Events ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Concomitant Medication	X ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Telephone Contact ^f																				Every two weeks between Visits (14 days +/- 4 days) or as needed.

Footnotes to the Time and Events Schedule:

NOTE: Study medication injection **must not** be given before PK sample collection, and should occur only after all efficacy and safety assessments are completed. It is also recommended that vital sign and ECG assessments be completed before any blood samples are collected.

Abbreviations: ADMS= Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CGI-S=Clinical Global Impression-Severity scale; C-SSRS=Columbia Suicide Severity Scale; ECG=electrocardiogram; EOS=End-of-Study; NA=not applicable; PANSS=Positive and Negative Syndrome Scale; PK=pharmacokinetic; PSP=Personal and Social Performance Scale; SAS=Simpson Angus Scale; SF12=Short Form Health Survey; VAS=Visual Analog Scale; WD=withdrawal

- ^a After Visit 14 (Week 41), visits will take place every 4 weeks. Assessments listed for every 12 weeks will be performed at Week 41, Week 53, Week 65, etc. Assessments listed for every 8 weeks will be performed at Week 37, Week 45, Week 53, Week 61, etc. The assessments in these columns will be performed mutually inclusive of each other.
- ^b Medical, psychiatric, and medication histories. Smoking history will also be recorded.
- ^c Paliperidone ER 6 mg tablets will be given for 4 to 6 consecutive days (last dose must be given by Day -1) to test for paliperidone tolerability in subjects without a written, documented history of previous use or exposure to oral risperidone, oral paliperidone, paliperidone palmitate, or 1 dose of i.m. Risperdal CONSTA.
- ^d Before the first injection of study medication on Day 1, the results of all screening assessments must be available to the Investigator and washout of prohibited concomitant medication as well as oral tolerability testing must be completed. Before use, shake syringe vigorously for 15 seconds. Please refer to Table 2 and Table 3 in the protocol for details of study drug administration.
- ^e Day 1 injection of PP1M does not apply to subjects who are being switched from another depot antipsychotic (including Risperdal CONSTA), or stable subjects who are continuing on current treatment with PP1M at enrollment.
- ^f Venous samples of 4 mL should be obtained prior to dose administration on each PK day. Unscheduled PK samples may be obtained at the Investigator's discretion for cases of severe or serious adverse events that may be potentially related to unexpected increases in plasma concentrations of study drug.
- ^g PK samples should be obtained 10 days (Week 54) and 20 days (Week 55) after study drug injection at Week 53.
- ^h To participate in the optional pharmacogenomic component of the study, subjects must sign the pharmacogenomic informed consent form indicating willingness to participate. A 10 mL blood sample will be collected from those subjects who have signed this form. A sample collected at a different time point (although should be avoided) does not constitute a protocol violation.
- ⁱ In addition to indicated visits, the PANSS and CGI-S should be administered whenever the investigator thinks a subject may be experiencing a relapse event. Note: If any of the PANSS criteria for relapse are exceeded on a given day, the PANSS assessments must be repeated 3-7 days later to confirm a relapse event.
- ^j A mini-PANSS consists of items P1, P2, P3, P6, P7, G8, and will be used as screening for potential relapse at the prespecified time points. In instances when the mini-PANSS meets one or more of the item scores criteria for relapse, the relapse must be confirmed with a full PANSS assessment 3-7 days later. In instances when the mini-PANSS does not meet criteria for relapse, but a relapse is suspected, an unscheduled full PANSS assessment should be completed on the same day.
- ^k The Involvement Evaluation Questionnaire will be accompanied by supplemental questions, as described in the protocol.
- ^l Patient Stated-choice Preference Survey to be completed only by English-speaking patients at United States sites. The survey will not be conducted in any other countries, regardless of whether the subjects in those other countries speak English.
- ^m Patient stated-choice preference survey will be conducted only once during Visit 6 or at any time later during the study, but preferably during Visits 6, 7, or 8 (Weeks 13, 14, or 17, respectively). See Section 9.5 in the protocol.
- ⁿ Blood pressure and heart rate will be measured after the subject is supine for 5 minutes and again after the subject is standing for 2 minutes.
- ^o A total of 3 ECG tracings will be obtained before the first dose of the study drug. Two of these ECGs should be obtained during the Screening Phase, at least 24 hours apart. The second ECG during the Screening Phase should be scheduled timely to ensure the cardiologist-read report is available before Visit 2. The third ECG should be obtained at the baseline visit (Visit 2). The ECGs should be recorded at approximately the same time each day (preferably in a fasted state in the morning).
- ^p To be obtained within 30 minutes of injection. At the EOS, the investigator will rate the site of the final injection.
- ^q Please refer to following table for details on clinical chemistry, hematology, urinalysis, and pregnancy testing.
- ^r Adverse events will be collected from the time informed consent is signed until the subject's last study related procedure.
- ^s Oral antipsychotics and other disallowed medications should be tapered during the screening period.
- ^t During the Double-blind Phase of the study, regular telephone contact with the patient and/or identified support person is recommended in between regularly scheduled visits. The optimal timing of the telephone contacts is up to the discretion of the investigator, but is recommended at least once every two weeks.

TIME AND EVENTS SCHEDULE FOR CLINICAL LABORATORY TESTS

Period	Screening	Transition	Double-Blind		EOS/Early WD Visit
			11	14 (and every 12 weeks thereafter)	
Visit	1	2	11	14 (and every 12 weeks thereafter)	
Week	-3 to -1		29	41	
Day	-21 to -1	1	204	288	
Hematology					
Hemoglobin	X	X ^a	X	X	X
RBC count	X	X ^a	X	X	X
Platelets	X	X ^a	X	X	X
WBC count with differential	X	X ^a	X	X	X
Hemoglobin A1c	X		X	X	X
Serum chemistry					
Sodium/Potassium/ Chloride/Bicarbonate	X	X ^a	X	X	X
BUN/Creatinine	X	X ^a	X	X	X
AST/ALT/GGT	X	X ^a	X	X	X
Alkaline phosphatase	X	X ^a	X	X	X
Total bilirubin	X	X ^a	X	X	X
Prolactin ^b		X ^a	X	X	X
LDH	X	X ^a	X	X	X
Calcium/Phosphorus	X	X ^a	X	X	X
Albumin/Total protein	X	X ^a	X	X	X
Thyroid stimulating hormone ^c	X				
Metabolic Chemistry (all fasting)					
Insulin		X	X	X	X
C-Peptide		X	X	X	X
Glucose	X	X ^a	X	X	X
Total cholesterol	X	X ^a	X	X	X
Triglycerides	X	X ^a	X	X	X
HDL and LDL	X	X ^a	X	X	X
Urine testing					
Urinalysis ^d	X	X ^a	X	X	X
Urine drug screen	X	X ^a	X	X	X
Pregnancy testing^e					
Serum B-HCG	X				X
Urine B-HCG		X	X	X	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamylaminotransferase; B-HCG=human beta choriogonadotropin; HDL and LDL=high- and low-density lipoproteins; LDH=lactate dehydrogenase; RBC=red blood cells; WBC=white blood cells.

^a Visit 2 Baseline (Day 1) samples do not need to be repeated if the Visit 1 (Screening) labs have been collected within 7 days of Visit 2. With the exception of the urine B-HCG sample, the remainder of the clinical laboratory results collected on Visit 2 does not need to be received back from the central lab prior to first injection of study medication.

^b Results of prolactin will be blinded to the investigator and sponsor

^c If values are outside the laboratory's normal range, free T4 will also be analyzed.

^d Urine macro panel includes dipstick (pH, color, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase). Sediment will be performed only if clinically relevant and includes: red blood cells, white blood cells, epithelial cells, crystals, casts, bacteria

^e Pregnancy testing applies to females of childbearing potential only

PSY-3012 Protocol, p. 19-23

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA P BURKHART
05/01/2015

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05/11/2015