CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022264Orig1s015

Trade Name:	INVEGA SUSTENNA
Generic or Proper Name:	Paliperidone palmitate
Sponsor:	Janssen Pharmaceuticals Inc.
Approval Date:	December 20, 2017
Indication:	INVEGA SUSTENNA® is an atypical antipsychotic indicated for □ Treatment of schizophrenia in adults. □ Treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressant.

CENTER FOR DRUG EVALUATION AND RESEARCH

022264Orig1s015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022264/S-015

SUPPLEMENT APPROVAL

Janssen Research & Development, L.L.C.
Attention: Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
E11710
Titusville, NJ 08560

Dear Dr. Geter-Douglass:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 11, 2014, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invega Sustenna (paliperidone palmitate) extended-release injectable suspension 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg.

We acknowledge receipt of your amendment dated June 20, 2017, which constituted a complete response to our May 11, 2015, action letter.

This Prior Approval supplemental new drug application proposes revisions to the product label based on findings from protocol R092670-SCH-3006 titled "A Fifteen-Month, Prospective, Randomized, Active- Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated".

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, and text for patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-3971, or email shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MITCHELL V Mathis
12/20/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22264/S-015

COMPLETE RESPONSE

Janssen Pharmaceuticals, Inc.
Attention: Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. Geter-Douglass:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invega Sustenna (paliperidone palmitate) extended-release injectable suspension 39, 78, 117, 156, 234 mg.

We acknowledge receipt of your amendments dated August 21, 2014, September 24, 2014, December 19, 2014, and February 25, 2015.

This "Prior Approval" efficacy supplemental new drug application proposes revisions to the product label based on findings from study R092670-SCH-3006 titled "A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated."

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. In our view, study R092670-SCH-3006 does not provide substantial evidence that paliperidone palmitate delays time to treatment failure in adults with schizophrenia who have been incarcerated, even though the results, on face, seem to demonstrate superiority of paliperidone palmitate based on the pre-specified primary endpoint and analysis.

   Treatment failure was defined as: 1) arrest/incarceration; 2) psychiatric hospitalization; 3) suicide; 4) discontinuation of antipsychotic treatment due to inadequate efficacy or poor tolerability; 6) treatment supplementation with another antipsychotic due to inadequate efficacy; and/or 7) increase in psychiatric services to prevent imminent psychiatric hospitalization.

Overall, 39.8% of subjects in the paliperidone palmitate group and 53.7% of subjects in the comparator group met the definition for treatment failure ($p<0.05$). In our view, however, these results are not interpretable.

A total of 139 patients (31.3%) discontinued the study early without meeting the definition of a treatment failure, and, importantly, there were more discontinuations in the paliperidone palmitate group (n=81, 35.8%) than in the oral antipsychotic group (n=58, 26.6%). Furthermore, in 60 patients (26.5%) in the paliperidone palmitate group and 42 patients (19.3%) in the oral antipsychotic group, the reasons for discontinuation reported in the case report forms were either "lost to follow-up" or "withdrawal by subject" in the case report forms. Thus, there is no way to know whether or not these patients experienced treatment failure, and the relatively large differences between treatment groups undermine the interpretability of the results. To place this problem into perspective, in the paliperidone palmitate group, 39.8% of subjects were categorized as treatment failures and, as such, had endpoint events, whereas the disposition of a relatively large proportion of subjects, 26.5%, was unknown.

To assess the potential impact of the discontinuations, we performed two exploratory analyses on the explanatory Intent-to-Treat (eITT) set: 1) categorizing all 139 dropouts without an event as treatment failures; and 2) categorizing the 102 dropouts assessed as "lost to follow-up" or "withdrawal by subject" as treatment failures. Neither analysis yielded a statistically significant difference in delaying time to treatment failure (the *p*-values were 0.28 and 0.19, respectively). These analyses underscore the considerable uncertainty of the study's conclusions, given the high numbers of discontinuations and the disparity between treatment groups. Thus, we reached the conclusion that study R092670-SCH-3006 failed to provide substantial evidence in support of the intended labeling revisions.

2. We recognize the potential importance of improved compliance with antipsychotic treatment, but substantial evidence of effectiveness would be needed to support this sNDA approval. We would reconsider the requested labeling revisions if you could provide another similar, but more clearly positive, study to address the dropout concern, and we strongly encourage you to seek our guidance during the planning stage.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the (b) (4) using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For (b) (4), provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

If you have any questions, please email Ann Sohn, Regulatory Project Manager, at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

MITCHELL V Mathis
05/11/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA SUSTENNA® safely and effectively. See full prescribing information for INVEGA SUSTENNA®.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2006

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. (5.1)**
- **INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis. (5.1)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.5)	06/2017
Warnings and Precautions (5.5)	12/2017
Warnings and Precautions (5.8)	02/2017
Warnings and Precautions (5.10)	06/2017

----------INDICATIONS AND USAGE----------

INVEGA SUSTENNA® is an atypical antipsychotic indicated for

- Treatment of schizophrenia in adults. (1)
- Treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants. (1)

----------DOSAGE AND ADMINISTRATION----------

- For intramuscular injection only. (2.1)
- Each injection must be administered only by a health care professional. (2.1)
- For deltoid injection, use 1-inch 23G needle for patients weighing less than 90 kg or 1½-inch 22G needle for patients weighing 90 kg or more. For gluteal injection, use 1½-inch 22G needle regardless of patient weight. (2.1)

Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose[a] (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia (2.2)	234 mg	156 mg	39-234 mg[b]	234 mg
Schizoaffective disorder (2.2)	234 mg	156 mg	78-234 mg[c]	234 mg

[a] Administered 5 weeks after the first injection.
[b] The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).
[c] Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

- For patients naïve to oral paliperidone or oral or injectable risperidone, establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®. (2.2)
- Missed Doses: To manage either a missed second initiation dose or a missed monthly maintenance dose, refer to the Full Prescribing Information. (2.3)
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min): INVEGA SUSTENNA® is not recommended. (2.5)
- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Administer 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Follow with monthly injections of 78 mg in either the deltoid or gluteal muscle. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release injectable suspension: 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to paliperidone, risperidone, or to any excipients in INVEGA SUSTENNA®. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack). (5.2)
- *Neuroleptic Malignant Syndrome* Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *QT Prolongation* Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. (5.4)
- *Tardive Dyskinesia* Discontinue drug if clinically appropriate. (5.5)
- *Metabolic Changes* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain. (5.6)
- *Orthostatic Hypotension and Syncope* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis* Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing INVEGA SUSTENNA® if clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Hyperprolactinemia* Prolactin elevations occur and persist during chronic administration. (5.10)
- *Potential for Cognitive and Motor Impairment* Use caution when operating machinery. (5.11)
- *Seizures* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.12)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

- *Drugs that may cause orthostatic hypotension* An additive effect may occur when co-administered with INVEGA SUSTENNA®. (7.1)
- *Strong CYP3A4/P-glycoprotein (P-gp) inducers*: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during a dosing interval for INVEGA SUSTENNA®. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (2.5, 7.1, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8 1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.*

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death *[see Warnings and Precautions (5.1)]*.**
- **INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:

- Schizophrenia in adults *[see Clinical Studies (14.1)]*.
- Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

Each injection must be administered only by a healthcare professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration, whenever product and container permit.

INVEGA SUSTENNA® is intended for intramuscular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle.

INVEGA SUSTENNA® must be administered using only the needles that are provided in the INVEGA SUSTENNA® kit.

The recommended needle size for administration of INVEGA SUSTENNA® into the deltoid muscle is determined by the patient's weight:

- For patients weighing less than 90 kg, the 1-inch, 23 gauge needle is recommended.
- For patients weighing 90 kg or more, the 1½-inch, 22 gauge needle is recommended.

Deltoid injections should be alternated between the two deltoid muscles.

The recommended needle size for administration of INVEGA SUSTENNA® into the gluteal muscle is the 1½-inch, 22 gauge needle regardless of patient weight.

Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be

alternated between the two gluteal muscles.

2.2 Schizophrenia and Schizoaffective Disorder

For patients who have never taken oral paliperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®.

The recommended dosing of INVEGA SUSTENNA® for each approved indication is displayed in Table 1. The recommended initiation of INVEGA SUSTENNA® is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Table 1: Recommended Dosing of INVEGA SUSTENNA® for Adults with Schizophrenia or Schizoaffective Disorder

Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose[a] (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia	234 mg	156 mg	39-234 mg[b]	234 mg
Schizoaffective disorder	234 mg	156 mg	78-234 mg[c]	234 mg

[a] Administered 5 weeks after the first injection.
[b] The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).
[c] Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of INVEGA SUSTENNA® should be considered *[see Clinical Pharmacology (12.3)]*, as the full effect of the dose adjustment may not be evident for several months.

2.3 Missed Doses

Avoiding Missed Doses

It is recommended that the second initiation dose of INVEGA SUSTENNA® be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 4 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

Management of a Missed Second Initiation Dose

If the target date for the second INVEGA SUSTENNA® injection (one week ± 4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection. In case of a missed second initiation dose follow the dosing instructions provided in Table 2.

Table 2: Management of a Missed Second Initiation Dose

TIMING OF MISSED SECOND INITIATION DOSE	DOSING
Less than 4 weeks since first injection	**Administer the second initiation dose of 156 mg in the deltoid muscle as soon as possible.** 1. It is recommended to administer a third injection of 117 mg in either the deltoid or gluteal muscle 5 weeks after the first injection (regardless of the timing of the second injection). 2. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
4 to 7 weeks since first injection	**Resume dosing with two injections of 156 mg in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
More than 7 weeks since first injection	**Restart dosing with recommended initiation** *(see Section 2.2, Table 1)*: 1. Administer a 234 mg deltoid injection on Day 1. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.

Management of a Missed Maintenance Dose

In case of a missed maintenance dose follow the dosing instructions provided in Table 3.

Table 3: Management of a Missed Maintenance Dose

TIMING OF MISSED MAINTENANCE DOSE	DOSING
4 to 6 weeks since last injection	**Resume regular monthly dosing as soon as possible at the patient's previously stabilized dose, followed by injections at monthly intervals.**

More than 6 weeks to 6 months since last injection	**Resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 234 mg, then the first 2 injections should each be 156 mg) in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later at the same dose. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.
More than 6 months since last injection	**Restart dosing with recommended initiation** (*see Section 2.2, Table 1*)*:* 1. Administer a 234 mg deltoid injection on Day 1. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.

2.4 Use with Risperidone or with Oral Paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA SUSTENNA® is coadministered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA SUSTENNA® with other antipsychotics is limited.

2.5 Dosage Adjustments

Renal Impairment

INVEGA SUSTENNA® has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), initiate INVEGA SUSTENNA® with a dose of 156 mg on treatment day 1 and 117 mg one week later. Administer both doses in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

INVEGA SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Coadministration with Strong CYP3A4/P-glycoprotein (P-gp) Inducers

Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during the 1-month dosing interval for INVEGA SUSTENNA®, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release

tablets *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

2.6 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia or schizoaffective disorder from other antipsychotics to INVEGA SUSTENNA®, or concerning concomitant administration with other antipsychotics.

Switching from Oral Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®.

Previous oral antipsychotics can be gradually discontinued at the time of initiation of treatment with INVEGA SUSTENNA®. Recommended initiation of INVEGA SUSTENNA® is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle *[see Dosage and Administration (2.2)]*. Patients previously stabilized on different doses of INVEGA® Extended-Release tablets can attain similar paliperidone steady-state exposure during maintenance treatment with INVEGA SUSTENNA® monthly doses as depicted in Table 4.

Table 4: Doses of INVEGA® and INVEGA SUSTENNA® Needed to Attain Similar Steady-State Paliperidone Exposure During Maintenance Treatment

Formulation	**INVEGA® Extended-Release Tablet**	**INVEGA SUSTENNA® Injection**
Dosing Frequency	**Once Daily**	**Once every 4 weeks**
Dose (mg)	12 9 6 3	234 156 117 39-78

Switching from Long-Acting Injectable Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®.

When switching patients currently at steady-state on a long-acting injectable antipsychotic, initiate INVEGA SUSTENNA® therapy in place of the next scheduled injection. INVEGA SUSTENNA® should then be continued at monthly intervals. The one-week initiation dosing regimen as described in Section 2.2 is not required. See Table 1 above for recommended monthly maintenance dosing. Based on previous clinical history of tolerability and/or efficacy, some patients may benefit from lower or higher maintenance doses within the available strengths (39 mg, 78 mg, 117 mg, 156 mg, and 234 mg). The 39 mg strength was not studied in the long-term schizoaffective disorder

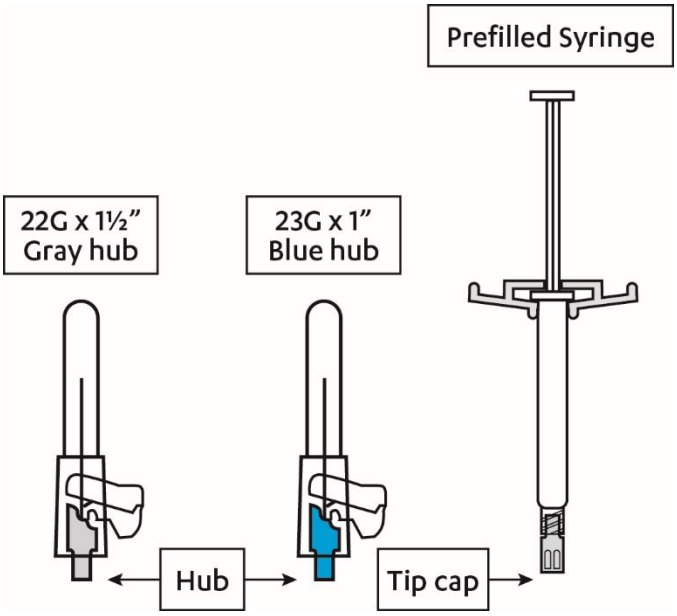
study. Monthly maintenance doses can be administered in either the deltoid or gluteal muscle *[see Dosage and Administration (2.2)]*.

If INVEGA SUSTENNA® is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

2.7 Instructions for Use

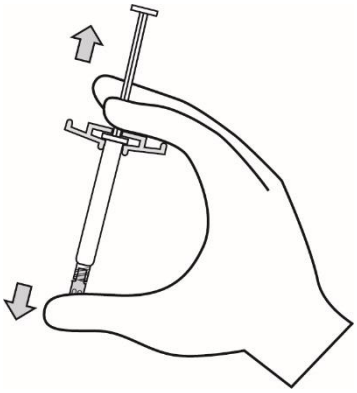
Each injection must be administered only by a healthcare professional.

The kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge needle and a 1-inch 23 gauge needle) for intramuscular injection.



INVEGA SUSTENNA® is for single use only.

a. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.



b. Select the appropriate needle.

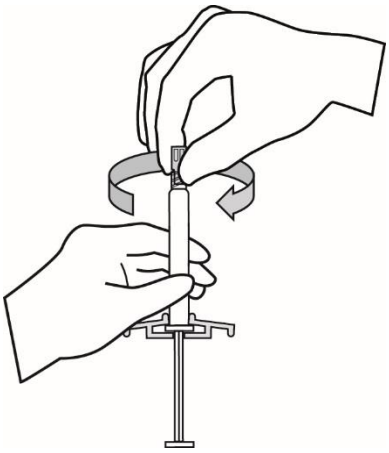
   For DELTOID injection:

   - If the patient weighs less than 90 kg, use the 1-inch **23** gauge needle (needle with **blue** colored hub).
   - If the patient weighs 90 kg or more, use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).

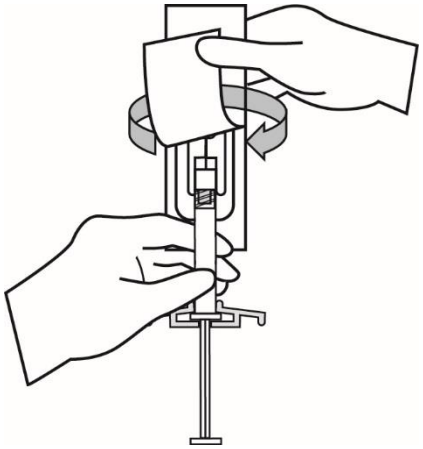
   For GLUTEAL injection:

   Use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub) regardless of patient's weight.

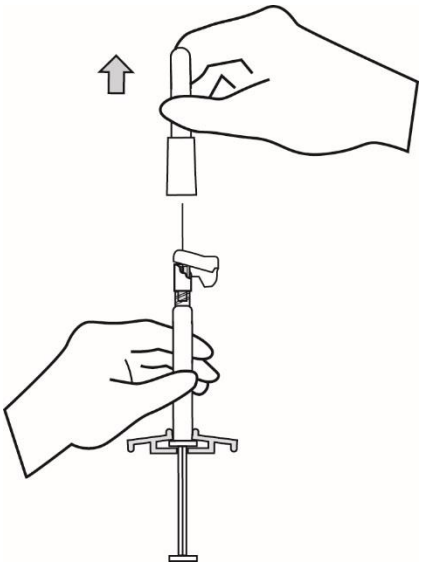
c. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



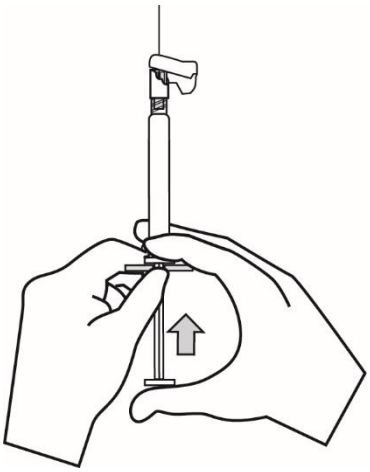
d. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



e. Pull the needle sheath away from the needle with a straight pull. Do not twist the sheath as the needle may be loosened from the syringe.



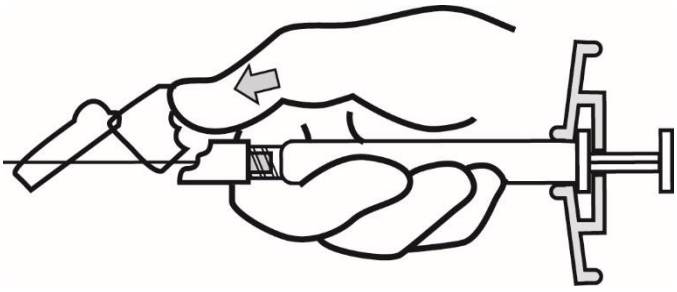
f. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.



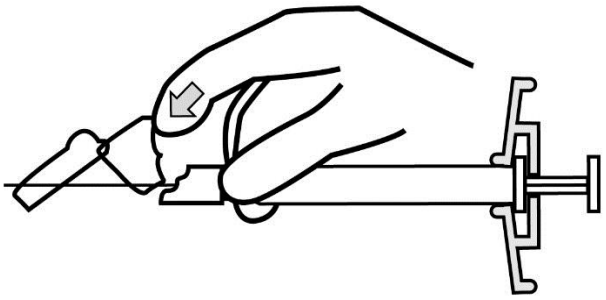
g. Inject the entire contents intramuscularly slowly, deep into the selected deltoid or gluteal muscle of the patient. Do not administer by any other route.

h. After the injection is complete, use either thumb or finger of one hand (h1, h2) or a flat surface (h3) to activate the needle protection system. The needle protection system is fully activated when a ‘click’ is heard. Discard the syringe with needle appropriately.

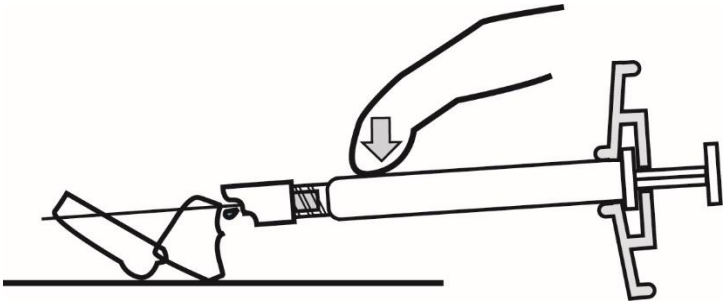
h1



h2



h3



3 DOSAGE FORMS AND STRENGTHS

INVEGA SUSTENNA® is available as a white to off-white aqueous extended-release injectable suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate.

4 CONTRAINDICATIONS

INVEGA SUSTENNA® is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA SUSTENNA® formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course

of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA SUSTENNA® is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA®, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and

medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

5.4 QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA SUSTENNA® administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only

one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA SUSTENNA® in subjects with schizophrenia and in the long-term study in subjects with schizoaffective disorder, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study in subjects with schizophrenia, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA SUSTENNA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA SUSTENNA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA SUSTENNA® despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase

cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials. Hyperglycemia and diabetes have been reported in trial subjects treated with INVEGA SUSTENNA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Pooled data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 5.

Table 5: Change in Fasting Glucose from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

		INVEGA SUSTENNA®					
	Placebo	39 mg	78 mg	156 mg	234/39 mg[a]	234/156 mg[a]	234/234 mg[a]
		Mean change from baseline (mg/dL)					
	n=367	n=86	n=244	n=238	n=110	n=126	n=115
Serum Glucose Change from baseline	-1.3	1.3	3.5	0.1	3.4	1.8	-0.2
		Proportion of Patients with Shifts					
Serum Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	4.6% (11/241)	6.3% (4/64)	6.4% (11/173)	3.9% (6/154)	2.5% (2/79)	7.0% (6/86)	6.6% (5/76)

[a] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*.

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA® was associated with a mean change in glucose of -0.4 mg/dL at Week 29 (n=109) and +6.8 mg/dL at Week 53 (n=100).

During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA® was associated with mean change in glucose of +5.3 mg/dL (n=518). At the endpoint of the subsequent 15-month double-blind period of the study, INVEGA SUSTENNA® was associated with a mean change in glucose of +0.3 mg/dL (n=131) compared with a mean change of +4.0 mg/dL in the placebo group (n=120).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Pooled data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 6.

Table 6: Change in Fasting Lipids from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

		INVEGA SUSTENNA®					
	Placebo	**39 mg**	**78 mg**	**156 mg**	**234/39 mg[a]**	**234/156 mg[a]**	**234/234 mg[a]**
				Mean change from baseline (mg/dL)			
Cholesterol	**n=366**	**n=89**	**n=244**	**n=232**	**n=105**	**n=119**	**n=120**
Change from baseline	-6.6	-6.4	-5.8	-7.1	-0.9	-4.2	9.4
LDL	**n=275**	**n=80**	**n=164**	**n=141**	**n=104**	**n=117**	**n=108**
Change from baseline	-6.0	-4.8	-5.6	-4.8	0.9	-2.4	5.2
HDL	**n=286**	**n=89**	**n=165**	**n=150**	**n=105**	**n=118**	**n=115**
Change from baseline	0.7	2.1	0.6	0.3	1.5	1.1	0.0
Triglycerides	**n=366**	**n=89**	**n=244**	**n=232**	**n=105**	**n=119**	**n=120**
Change from baseline	-16.7	7.6	-9.0	-11.5	-14.1	-20.0	11.9
				Proportion of Patients with Shifts			
Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	3.2% (7/222)	2.0% (1/51)	2.0% (3/147)	2.1% (3/141)	0% (0/69)	3.1% (2/65)	7.1% (6/84)
LDL Normal to High (<100 mg/dL to ≥160 mg/dL)	1.1% (1/95)	0% (0/29)	0% (0/67)	0% (0/46)	0% (0/41)	0% (0/37)	0% (0/44)
HDL Normal to Low (≥40 mg/dL to <40 mg/dL)	13.8% (28/203)	14.8% (9/61)	9.6% (11/115)	14.2% (15/106)	12.7% (9/71)	10.5% (8/76)	16.0% (13/81)
Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	3.6% (8/221)	6.1% (3/49)	9.2% (14/153)	7.2% (10/139)	1.3% (1/79)	3.7% (3/82)	10.7% (9/84)

[a] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*.

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, the mean changes from baseline in lipid values are presented in Table 7.

Table 7: Change in Fasting Lipids from Long-term Open-label Pharmacokinetic and Safety Study in Subjects with Schizophrenia

	INVEGA SUSTENNA® 234 mg	
	Week 29	**Week 53**
	Mean change from baseline (mg/dL)	
Cholesterol	**n=112**	**n=100**
Change from baseline	-1.2	0.1
LDL	**n=107**	**n=89**
Change from baseline	-2.7	-2.3
HDL	**n=112**	**n=98**
Change from baseline	-0.8	-2.6
Triglycerides	**n=112**	**n=100**
Change from baseline	16.2	37.4

The mean changes from baseline in lipid values during the initial 25-week open-label period and at the endpoint of the subsequent 15-month double-blind period in a long-term study in subjects with schizoaffective disorder are presented in Table 8.

Table 8: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizoaffective Disorder

	Open-Label Period	Double-Blind Period	
	INVEGA SUSTENNA®	Placebo	INVEGA SUSTENNA®
	Mean change from baseline (mg/dL)		
Cholesterol	**n=198**	**n=119**	**n=132**
Change from baseline	-3.9	-4.2	2.3
LDL	**n=198**	**n=117**	**n=130**
Change from baseline	-2.7	-2.8	5.9
HDL	**n=198**	**n=119**	**n=131**
Change from baseline	-2.7	-0.9	-0.7
Triglycerides	**n=198**	**n=119**	**n=132**
Change from baseline	7.0	2.5	-12.3

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥ 7% of body weight from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 9.

Table 9: Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥ 7% Gain in Body Weight from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

		INVEGA SUSTENNA®					
	Placebo	39 mg	78 mg	156 mg	234/39 mg[a]	234/156 mg[a]	234/234 mg[a]
	n=451	n=116	n=280	n=267	n=137	n=144	n=145
Weight (kg) Change from baseline	-0.4	0.4	0.8	1.4	0.4	0.7	1.4
Weight Gain ≥ 7% increase from baseline	3.3%	6.0%	8.9%	9.0%	5.8%	8.3%	13.1%

[a] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*.

In a long-term open-label pharmacokinetic and safety study in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA® was associated with a mean change in weight of +2.4 kg at Week 29 (n=134) and +4.3 kg at Week 53 (n=113).

During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA® was associated with a mean change in weight of +2.2 kg and 18.4% of subjects had an increase in body weight of ≥ 7% (n=653). At the endpoint of the subsequent 15-month double-blind period of the study, INVEGA SUSTENNA® was associated with a mean change in weight of -0.2 kg and 13.0% of subjects had an increase in body weight of ≥ 7% (n=161); the placebo group had a mean change in weight of -0.8 kg and 6.0% of subjects had an increase in body weight of ≥ 7% (n=168).

5.7 Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA SUSTENNA®-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope

in the long-term studies in subjects with schizophrenia and schizoaffective disorder were similar to those observed in the short-term studies.

INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.8 Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA SUSTENNA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including INVEGA SUSTENNA®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count < $1000/mm^3$) and follow their WBC until recovery.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in

reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Prolactin data from two long-term, double-blind, placebo-controlled studies with INVEGA SUSTENNA® are presented below; one study was in a population of patients with schizophrenia; the second study was in patients with schizoaffective disorder.

Schizophrenia

In a long-term maintenance trial of INVEGA SUSTENNA® in schizophrenia patients (Study PSY-3001), see *Clinical Studies (14.1)*, elevations of prolactin to above the reference range (> 18 ng/mL in males and > 30 ng/mL in females) relative to open-label baseline at any time during the double-blind phase were noted in a higher percentage of the patients in the INVEGA SUSTENNA® group than those in the placebo group in males (51.9% vs. 29.0%) and in females (50.5% vs. 42.9%). During the double-blind phase, 4 females (4.2%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=1; menstruation irregular N=1), while 2 females (2.2%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.9%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 33-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.9 (22.3) ng/mL in males (N=490) and 35.2 (39.6) ng/mL in females (N=358). At the end of the open-label phase, mean (SD) prolactin values were 24.7 (22.5) ng/mL in males (N=470) and 59.5 (38.1) ng/mL in females (N=333). During the open-label phases 49.2% of females and 47.7% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of

females experienced potentially prolactin-related adverse reactions compared to males (5.3% vs. 1.8%). Amenorrhea (2.5%) in females and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Schizoaffective Disorder

In a long-term maintenance trial of INVEGA SUSTENNA® in patients with schizoaffective disorder (Study SCA-3004) see *Clinical Studies (14.2)*, elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.72 ng/mL in females) relative to open-label baseline at any time during the 15-month double-blind phase were noted in a higher percentage of patients in the INVEGA SUSTENNA® group than those in the placebo group in males (55.6% vs. 23.2%) and in females (44.3% vs. 25.0%). During the 15-month double-blind phase, 11 females (13.9%) in the INVEGA SUSTENNA® group had 14 potentially prolactin-related adverse reactions (hyperprolactinemia N=3; blood prolactin increased N=4; libido decreased N=1; amenorrhea N=3; galactorrhea N=3), while 5 females (5.8%) in the placebo group had 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=2; blood prolactin increased N=1; amenorrhea N=2; galactorrhea N=1). Six males (7.1%) in the INVEGA SUSTENNA® group experienced 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=4; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.2%) in the placebo group experienced adverse reaction of blood prolactin increased.

Prior to the 15-month double-blind phase (during the 25-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.6 (14.0) ng/mL in males (N=352) and 39.1 (44.6) ng/mL in females (N=302). At the end of the open-label phase, mean (SD) prolactin values were 32.8 (17.2) ng/mL in males (N=275) and 72.4 (46.5) ng/mL in females (N=239). During the open-label phase, 48.9% of females and 53.3% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (10.0% vs. 9.0%). Amenorrhea (5.8%) and galactorrhea (2.9%) in females and libido decrease (2.8%) and erectile dysfunction (2.5%) in males were observed with a rate greater than 2%.

5.11 Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA® *[see Adverse Reactions (6.1)]*. Antipsychotics, including INVEGA SUSTENNA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

5.12 Seizures

In the four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. INVEGA SUSTENNA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.14 Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA SUSTENNA®, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

5.15 Disruption of Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA SUSTENNA® to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- QT prolongation *[see Warnings and Precautions (5.4)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.5)]*

- Metabolic changes *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions (5.9)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.10)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Priapism *[see Warnings and Precautions (5.14)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure

The data described in this section are derived from a clinical trial database consisting of a total of 3817 subjects (approximately 1705 patient-years exposure) with schizophrenia who received at least one dose of INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA SUSTENNA®-treated subjects, 1293 received INVEGA SUSTENNA® in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA SUSTENNA® in the maintenance trial (median exposure 229 days during the initial 33-week open-label phase of this study, of whom 205 continued to receive INVEGA SUSTENNA® during the double-blind placebo-controlled phase of this study [median exposure 171 days]), and 1675 received INVEGA SUSTENNA® in five non-placebo controlled trials (three noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study, and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA SUSTENNA® initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

The safety of INVEGA SUSTENNA® was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA® to selected oral antipsychotic therapies in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study; 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind, placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® was also evaluated in a long-term study in adult subjects with schizoaffective disorder. A total of 667 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 147 days); 164 subjects continued to receive INVEGA SUSTENNA® during the 15-month double-blind placebo-controlled period of this study (median exposure 446 days). Adverse reactions that occurred more frequently in the INVEGA SUSTENNA® than the placebo group (a 2% difference or more between groups) were weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials

Commonly Observed Adverse Reactions: The most common (at least 5% in any INVEGA SUSTENNA® group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials in subjects with schizophrenia were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder**.** No occurrences of adverse events reached this threshold in the long-term double-blind, placebo-controlled study in subjects with schizoaffective disorder.

Discontinuation of Treatment Due to Adverse Events: The percentage of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled schizophrenia trials were similar for INVEGA SUSTENNA®- and placebo-treated subjects.

The percentage of subjects who discontinued due to adverse events in the open-label period of the long-term study in subjects with schizoaffective disorder was 7.5%. During the double-blind, placebo-controlled period of that study, the percentages of subjects who discontinued due to adverse events were 5.5% and 1.8% in INVEGA SUSTENNA®- and placebo-treated subjects, respectively.

Dose-Related Adverse Reactions: Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, among the adverse reactions that occurred with ≥ 2% incidence in the subjects treated with INVEGA SUSTENNA®, only akathisia increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 2% incidence in INVEGA SUSTENNA®-treated subjects from the four fixed-dose studies.

Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA SUSTENNA®-Treated Patients: Table 10 lists the adverse reactions reported in 2% or more of INVEGA SUSTENNA®-treated subjects and at a greater proportion than in the placebo group with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

Table 10: Incidences of Adverse Reactions 2% or More of INVEGA SUSTENNA®-Treated Patients (and Greater than Placebo) with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

		INVEGA SUSTENNA®					
System Organ Class Adverse Reactions	**Placebo[a] (N=510)**	**39 mg (N=130)**	**78 mg (N=302)**	**156 mg (N=312)**	**234/39 mg[b] (N=160)**	**234/156 mg[b] (N=165)**	**234/234 mg[b] (N=163)**
Total percentage of subjects with adverse reactions	70	75	68	69	63	60	63
Gastrointestinal disorders							
Abdominal discomfort/abdominal pain upper	2	2	4	4	1	2	4
Diarrhea	2	0	3	2	1	2	2
Dry mouth	1	3	1	0	1	1	1
Nausea	3	4	4	3	2	2	2
Toothache	1	1	1	3	1	2	3
Vomiting	4	5	4	2	3	2	2
General disorders and administration site conditions							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site reactions	2	0	4	6	9	7	10
Infections and infestations							
Nasopharyngitis	2	0	2	2	4	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4
Urinary tract infection	1	0	1	<1	1	1	2
Investigations							
Weight increased	1	4	4	1	1	1	2
Musculoskeletal and connective tissue disorders							
Back pain	2	2	1	3	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2
Myalgia	1	2	1	<1	1	0	2
Pain in extremity	1	0	2	2	2	3	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Anxiety	7	8	5	3	5	6	6
Nightmare	<1	2	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders							
Cough	1	2	3	1	0	1	1
Vascular disorders							
Hypertension	1	2	1	1	1	1	0

Percentages are rounded to whole numbers. Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA SUSTENNA® dose groups and which occurred at greater incidence than in the placebo group.

[a] Placebo group is pooled from all studies and included either deltoid or gluteal injection depending on study design.

[b] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*

Adverse reactions for which the INVEGA SUSTENNA® incidence was equal to or less than placebo are not listed in the table, but included the following: dyspepsia, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain upper/stomach discomfort, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse reactions were collapsed and are grouped under "Injection site reactions".

Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA®

The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.

Cardiac disorders: atrioventricular block first degree, bradycardia, bundle branch block, palpitations, postural orthostatic tachycardia syndrome, tachycardia

Ear and labyrinth disorders: vertigo

Eye disorders: eye movement disorder, eye rolling, oculogyric crisis, vision blurred

Gastrointestinal disorders: constipation, dyspepsia, flatulence, salivary hypersecretion

Immune system disorders: hypersensitivity

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, hyperinsulinemia, increased appetite

Musculoskeletal and connective tissue disorders: arthralgia, joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, nuchal rigidity

Nervous system disorders: bradykinesia, cerebrovascular accident, cogwheel rigidity, convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope

Psychiatric disorders: insomnia, libido decreased, restlessness

Reproductive system and breast disorders: amenorrhea, breast discharge, breast enlargement/breast swelling, breast tenderness/breast pain, ejaculation disorder, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: nasal congestion

Skin and subcutaneous tissue disorders: drug eruption, pruritus, pruritus generalized, rash, urticaria

Demographic Differences

An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects 65 years of age and older.

Extrapyramidal Symptoms (EPS)

Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials in adult subjects with schizophrenia provided information regarding EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale scores which evaluates dyskinesia, and (4) use of anticholinergic medications to treat EPS (Table 11), and (5) incidence of spontaneous reports of EPS (Table 12).

Table 11: Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults

	Percentage of Subjects			
		INVEGA SUSTENNA®		
Scale	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Parkinsonism[a]	9	12	10	6
Akathisia[b]	5	5	6	5
Dyskinesia[c]	3	4	6	4
Use of Anticholinergic Medications[d]	12	10	12	11

[a] For parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items)

[b] For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint

[c] For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint

[d] Percent of subjects who received anticholinergic medications to treat EPS

Table 12: Extrapyramidal Symptoms (EPS)-Related Events by MedDRA Preferred Term – Schizophrenia Studies in Adults

	Percentage of Subjects			
		INVEGA SUSTENNA®		
EPS Group	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Overall percentage of subjects with EPS-related adverse events	10	12	11	11
Parkinsonism	5	6	6	4
Hyperkinesia	2	2	2	4
Tremor	3	2	2	3
Dyskinesia	1	2	3	1
Dystonia	0	1	1	2

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia
Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness
Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia
Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the maintenance trial in subjects with schizophrenia exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA SUSTENNA® 156 mg group (18% and 11%, respectively) than in the INVEGA SUSTENNA® 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study in subjects with schizophrenia involving 234 mg initiation dosing, the incidence of any EPS was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA SUSTENNA® 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA SUSTENNA® 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

In the long-term study in subjects with schizoaffective disorder, EPS reported during the 25-week open-label INVEGA SUSTENNA® treatment included hyperkinesia (12.3%), parkinsonism (8.7%), tremor (3.4%), dyskinesia (2.5%), and dystonia (2.1%). During the 15-month double-blind treatment, the incidence of any EPS was similar to that of the placebo group (8.5% and 7.1% respectively). The most commonly reported treatment-emergent EPS-related adverse events (> 2%) in any treatment group in the double-blind phase of the study (INVEGA SUSTENNA® versus placebo) were hyperkinesia (3.7% vs. 2.9%), parkinsonism (3.0% vs. 1.8%), and tremor (1.2% vs. 2.4%).

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Pain Assessment and Local Injection Site Reactions

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 9.8; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

In the 13-week study involving 234 mg initiation dosing in subjects with schizophrenia, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA SUSTENNA® and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA SUSTENNA® groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA SUSTENNA® and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA SUSTENNA® and placebo groups.

Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

The following is a list of additional adverse reactions that have been reported in clinical trials with oral paliperidone:

Cardiac disorders: bundle branch block left, sinus arrhythmia

Gastrointestinal disorders: abdominal pain, small intestinal obstruction

General disorders and administration site conditions: edema, edema peripheral

Immune system disorders: anaphylactic reaction

Infections and infestations: rhinitis

Musculoskeletal and connective tissue disorders: musculoskeletal pain, torticollis, trismus

Nervous system disorders: grand mal convulsion, parkinsonian gait, transient ischemic attack

Psychiatric disorders: sleep disorder

Reproductive system and breast disorders: breast engorgement

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, pneumonia aspiration

Skin and subcutaneous tissue disorders: rash papular

Vascular disorders: hypotension, ischemia

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of paliperidone; because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: angioedema, ileus, swollen tongue, thrombotic thrombocytopenic purpura, urinary incontinence, and urinary retention.

Cases of anaphylactic reaction after injection with INVEGA SUSTENNA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the *Adverse Reactions (6)* sections of the package inserts for those products.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with INVEGA SUSTENNA®

Because paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Table 13: Clinically Important Drug Interactions with INVEGA SUSTENNA®

Drugs with Potential for Inducing Orthostatic Hypotension	
Clinical Impact	Because INVEGA SUSTENNA® has the potential for inducing orthostatic hypotension, an additive effect may occur when INVEGA SUSTENNA® is administered with other therapeutic agents that have this potential *[see Warning and Precautions (5.7)]*
Intervention	Monitor orthostatic vital signs in patients who are vulnerable to hypotension *[see Warnings and Precautions (5.7)]*
Examples	Nitrates Antihypertensive medicines: thiazide diuretics (e.g. hydrochlorothiazide); beta blockers (e.g. acebutolol); angiotensin-converting enzyme (ACE) inhibitors (e.g. lisinopril); angiotensin II receptor blockers (ARBs) (e.g. candesartan); calcium channel blockers (e.g. amlodipine); alpha-blockers (e.g. prazosin), alpha-agonists (e.g. clonidine), other diuretics (e.g. loop, K-sparing), vasodilators (e.g. hydralazine)
Strong Inducers of CYP3A4 and P-gp	
Clinical Impact	The concomitant use of paliperidone and strong inducers of CYP3A4 and P-gp may decrease the exposure of paliperidone *[see Clinical Pharmacology (12.3)]*
Intervention	Avoid using CYP3A4 and/or P-gp inducers with INVEGA SUSTENNA® during the 1-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets *[see Dosage and Administration (2.5)]*
Examples	Carbamazepine, rifampin, St John's Wort
Dopamine Agonist	
Clinical Impact	Paliperidone may antagonize the effect of levodopa and other dopamine agonist
Intervention	Monitor and manage patient as clinically appropriate
Examples	Levodopa, bromocriptine, ropinirole and pramipexole

7.2 Drugs Having No Clinically Important Interactions with INVEGA SUSTENNA®

Clinically meaningful pharmacokinetic interaction between INVEGA SUSTENNA® and valproate (including valproic acid and divalproex sodium) is not expected. Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of INVEGA SUSTENNA® is required when administered with valproate *[see Clinical Pharmacology (12.3)]*. Additionally, no dosage adjustment is necessary for valproate when co-administered with INVEGA SUSTENNA® *[See Clinical Pharmacology (12.3)]*.

Pharmacokinetic interaction between lithium and INVEGA SUSTENNA® is also unlikely.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19; an interaction with inhibitors or inducers of these isozymes is unlikely. *[see Clinical Pharmacology (12.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

Adequate and well controlled studies with INVEGA SUSTENNA® have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. INVEGA SUSTENNA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Data

Human Data

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in neonates following *in utero* exposure to antipsychotics in the third trimester. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Animal Data

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 250 mg/kg, which is 10 times the maximum recommended human 234 mg dose of INVEGA SUSTENNA® on a mg/m^2 body surface area basis.

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human dose of 12 mg/day of orally administered paliperidone [INVEGA®] on a mg/m^2 body surface area basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 body surface area basis (see RISPERDAL® package insert).

8.2 Labor and Delivery

The effect of INVEGA SUSTENNA® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of INVEGA SUSTENNA® in patients < 18 years of age have not been established.

In a study in which juvenile rats were treated with oral paliperidone from days 24 to 73 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2-3 times those in adolescents.

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the maximum recommended human dose of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of paliperidone on growth and sexual maturation have not been fully evaluated in children and adolescents.

8.5 Geriatric Use

Clinical studies of INVEGA SUSTENNA® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment *[see Clinical Pharmacology (12.3)]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, adjust dose based on

renal function *[see Dosage and Administration (2.5)]*.

8.6 Renal Impairment

Use of INVEGA SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Dose reduction is recommended for patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

INVEGA SUSTENNA® has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment *[Clinical Pharmacology (12.3)]*.

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to INVEGA SUSTENNA®. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA SUSTENNA® (paliperidone) is not a controlled substance.

9.2 Abuse

Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

9.3 Dependence

Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA®. Because INVEGA SUSTENNA® is to be administered by healthcare professionals, the potential for overdosage by patients is low.

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other

potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation. Torsades de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the *OVERDOSAGE* section of the risperidone package insert.

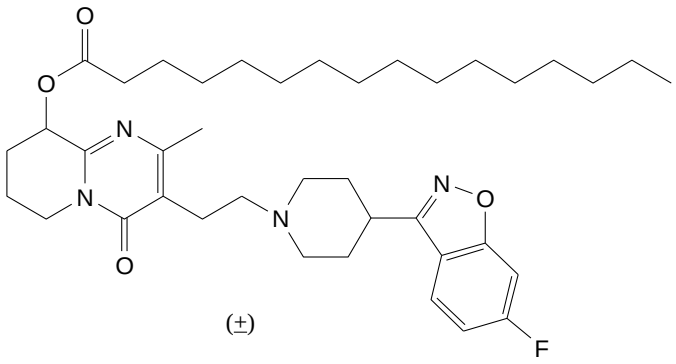
10.2 Management of Overdosage

Contact a Certified Poison Control Center for the most up to date information on the management of INVEGA SUSTENNA® overdosage (1-800-222-1222 or www.poison.org). Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. There is no specific antidote to paliperidone.

Consider the prolonged-release characteristics of INVEGA SUSTENNA® and the long apparent half-life of paliperidone when assessing treatment needs and recovery.

11 DESCRIPTION

INVEGA SUSTENNA® is an atypical antipsychotic. INVEGA SUSTENNA® contains paliperidone palmitate. The active ingredient, paliperidone palmitate, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. INVEGA SUSTENNA® contains a racemic mixture of (+)- and (-)- paliperidone palmitate. The chemical name is (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate. Its molecular formula is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. The structural formula is:



(±)

Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate.

INVEGA SUSTENNA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in the following dose strengths of paliperidone palmitate (and deliverable volumes of the prefilled syringes): 39 mg (0.25 mL), 78 mg (0.5 mL), 117 mg (0.75 mL), 156 mg (1.0 mL), and 234 mg (1.5 mL). The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively. The inactive ingredients are polysorbate 20 (12 mg/mL), polyethylene glycol 4000 (30 mg/mL), citric acid monohydrate (5 mg/mL), disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection.

INVEGA SUSTENNA® is provided in a prefilled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber). The kit also contains 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone is unknown. The efficacy of paliperidone in schizophrenia could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

Paliperidone is a centrally active dopamine Type 2 (D_2) 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 H_1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro.*

12.3 Pharmacokinetics

Absorption and Distribution

Due to its extremely low water solubility, the 1-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma

concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T_{max} of 13 days. The release of the drug starts as early as day 1 and lasts for as long as 126 days.

Following intramuscular injection of single doses (39 mg - 234 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 234 mg on day 1 and 156 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA SUSTENNA® results in sustained therapeutic concentrations. The AUC of paliperidone following INVEGA SUSTENNA® administration was dose-proportional over a 39 mg-234 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 78 mg. The mean steady-state peak:trough ratio for an INVEGA SUSTENNA® dose of 156 mg was 1.8 following gluteal administration and 2.2 following deltoid administration.

Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6–1.8.

Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74%.

Metabolism and Elimination

In a study with oral immediate-release ^{14}C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ^{14}C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

The median apparent half-life of paliperidone following INVEGA SUSTENNA® single-dose administration over the dose range of 39 mg - 234 mg ranged from 25 days - 49 days.

Long-Acting Paliperidone Palmitate Injection versus Oral Extended-Release Paliperidone

INVEGA SUSTENNA® is designed to deliver paliperidone over a monthly period while extended-release oral paliperidone is administered on a daily basis. The initiation regimen for INVEGA

SUSTENNA® (234 mg/156 mg in the deltoid muscle on Day 1/Day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

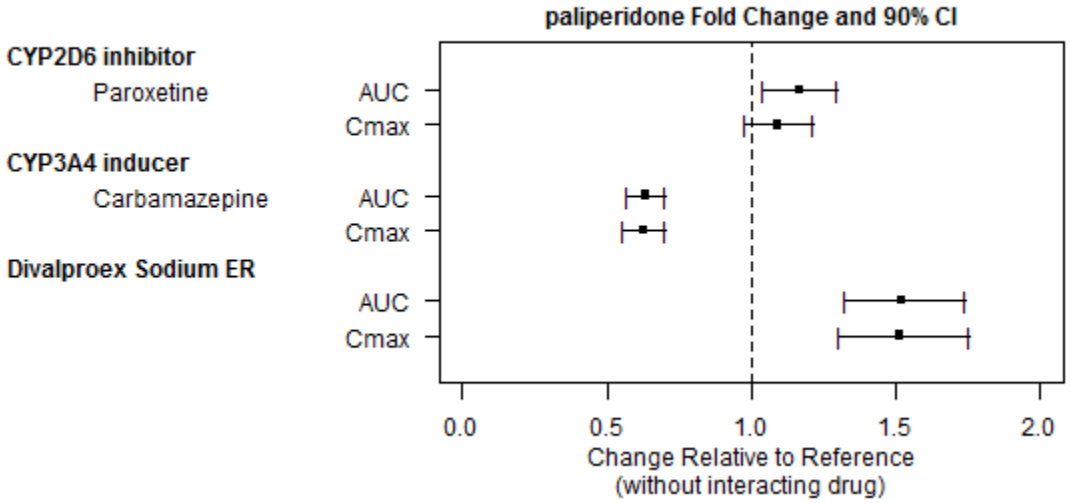
In general, overall initiation plasma levels with INVEGA SUSTENNA® were within the exposure range observed with 6-12 mg extended-release oral paliperidone. The use of the INVEGA SUSTENNA® initiation regimen allowed patients to stay in this exposure window of 6-12 mg extended-release oral paliperidone even on trough pre-dose days (Day 8 and Day 36). The intersubject variability for paliperidone pharmacokinetics following delivery from INVEGA SUSTENNA® was lower relative to the variability determined from extended-release oral paliperidone tablets. Because of the difference in median pharmacokinetic profiles between the two products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Drug Interaction Studies

No specific drug interaction studies have been performed with INVEGA SUSTENNA®. The information below is obtained from studies with oral paliperidone.

Effects of other drugs on the exposures of paliperidone are summarized in Figure 1. After oral administration of 20 mg/day of paroxetine (a potent CYP2D6 inhibitor), an increase in mean C_{max} and AUC values at steady-state was observed (see Figure 1). Higher doses of paroxetine have not been studied. The clinical relevance is unknown. After oral administration, a decrease in mean C_{max} and AUC values at steady state is expected when patients are treated with carbamazepine, a strong inducer of both CYP3A4 and P-gp *[see Drug Interactions (7.1)]*. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone.

Figure 1: The effects of other drugs on paliperidone pharmacokinetics.



Clinically meaningful pharmacokinetic interaction between INVEGA SUSTENNA® and valproate (including valproic acid and divalproex sodium) is not expected. Oral administration of divalproex sodium extended-release tablets (two 500 mg tablets once daily at steady-state) with oral paliperidone extended-release tablets resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone.

After oral administration of paliperidone, the steady-state C_{max} and AUC of divalproex sodium extended-release tablets were not affected in 13 patients stabilized on divalproex sodium extended-release tablets. In a clinical study, subjects on stable doses of divalproex sodium extended-release tablets had comparable valproate average plasma concentrations when oral paliperidone extended-release tablets 3-15 mg/day was added to their existing divalproex sodium extended-release tablets treatment *[see Drug Interactions (7.2)]*.

In vitro studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism, however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone; they contribute to only a small fraction of total body clearance. *In vitro* studies demonstrated that paliperidone is a substrate of P-glycoprotein (P-gp) *[see Drug Interactions (7.2)]*.

In vitro studies in human liver microsomes demonstrated that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is

not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available, and the clinical relevance is unknown.

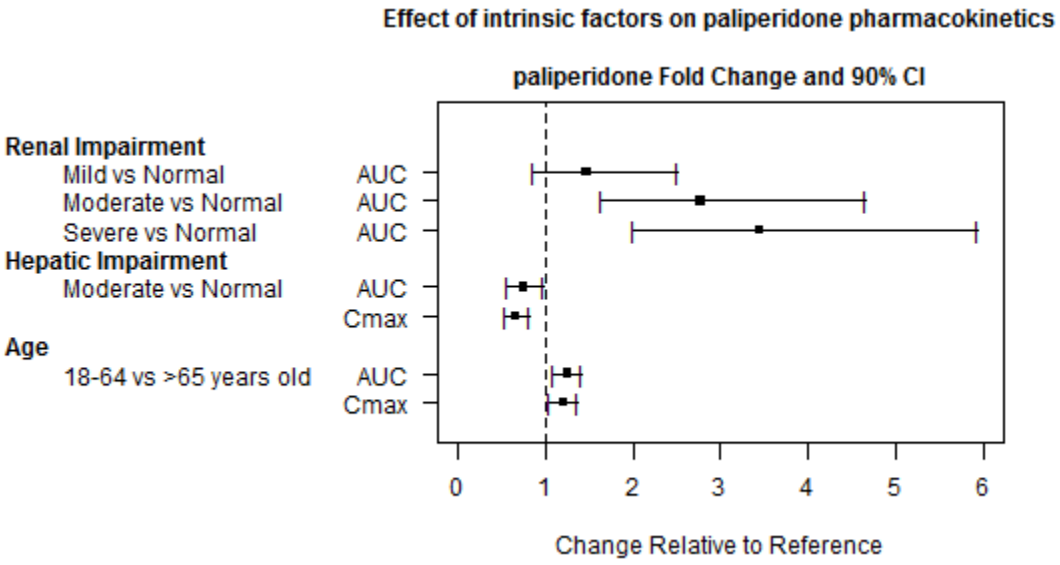
Studies in Specific Populations

No specific pharmacokinetic studies have been performed with INVEGA SUSTENNA® in specific populations. All the information is obtained from studies with oral paliperidone or is based on the population pharmacokinetic modelling of oral paliperidone and INVEGA SUSTENNA®. Exposures of paliperidone in specific populations (renal impairment, hepatic impairment and elderly) are summarized in Figure 2 *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)]*.

After oral administration of paliperidone in patients with moderate hepatic impairment, the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Paliperidone has not been studied in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

After oral administration of paliperidone in elderly subjects, the C_{max} and AUC increased 1.2-fold compared to young subjects. However, there may be age-related decreases in creatinine clearance *[see Dosage and Administration (2.5) and Use in Specific Populations (8.5)]*.

Figure 2: Effects of intrinsic factors on paliperidone pharmacokinetics.



Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone.

Slower absorption was observed in females in a population pharmacokinetic analysis. At apparent steady-state with INVEGA SUSTENNA®, the trough concentrations were similar between males and females.

Lower C_{max} was observed in overweight and obese subjects. At apparent steady-state with INVEGA SUSTENNA®, the trough concentrations were similar among normal, overweight, and obese subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 16, 47, and 94 mg/kg/month, which is 0.6, 2, and 4 times, respectively, the maximum recommended human dose (MRHD) of 234 mg of INVEGA SUSTENNA® on a mg/m^2 body surface area basis. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 47 mg and 94 mg/kg/month. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet for 18 months to mice and for 25 months to rats at daily doses of 0.63, 2.5, and 10 mg/kg, which are 0.2 to 3 times in mice and 0.4 to 6 times in rats the MRHD of 16 mg/day of risperidone on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the MRHD of risperidone on a mg/m^2 body surface area basis (see RISPERDAL® package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2-receptor antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown *[see Warnings and Precautions (5.10)]*.

Mutagenesis

Paliperidone palmitate showed no genotoxic potential in the Ames reverse mutation test or the mouse lymphoma assay. No evidence of genotoxic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the *in vivo* rat micronucleus test.

Impairment of Fertility

No fertility studies were conducted with paliperidone palmitate.

In a rat fertility study orally administered paliperidone increased pre- and post-implantation losses and slightly decreased the number of live embryos at doses up to 2.5 mg/kg/day, a dose which is 2 times the MRHD of 12 mg on mg/m^2 basis. This dose also caused slight maternal toxicity but there was no effect on the percentage of treated female rats that became pregnant. Pre- and post-implantation losses, the number of live embryos and maternal toxicity were not affected at 0.63 mg/kg/day, a dose, which is half of the MRHD of 12 mg/day of orally administered paliperidone on mg/m^2 basis. The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, which are up to 2 times the MRHD of 12 mg on mg/m^2 basis, although sperm count and sperm viability studies were not conducted with paliperidone.

In a sub-chronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested 0.31 to 5.0 mg/kg/day, which are 0.6 to 10 times the MRHD of 16 mg on mg/m^2 basis, resulted in decreases in serum testosterone and decreases in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased at the last observation two months after treatment was discontinued.

14 CLINICAL STUDIES

14.1 Schizophrenia

Short-Term Monotherapy (Studies 1, 2, 3, 4)

The efficacy of INVEGA SUSTENNA® in the acute treatment of schizophrenia was evaluated in four short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia. The fixed doses of INVEGA SUSTENNA® in these studies were given on days 1, 8, and 36 in the 9-week study, and additionally on day 64 of the 13-week studies, i.e., at a weekly interval for the initial two doses and then every 4 weeks for maintenance.

Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30 item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210.

In Study 1 (PSY-3007), a 13-week study (n=636) comparing three fixed doses of INVEGA SUSTENNA® (initial deltoid injection of 234 mg followed by 3 gluteal or deltoid doses of either 39 mg/4 weeks, 156 mg/4 weeks or 234 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA® were superior to placebo in improving the PANSS total score.

In Study 2 (PSY-3003), another 13-week study (n=349) comparing three fixed doses of INVEGA SUSTENNA® (78 mg/4 weeks, 156 mg/4 weeks, and 234 mg/4 weeks) to placebo, only 156 mg/4 weeks of INVEGA SUSTENNA® was superior to placebo in improving the PANSS total score.

In Study 3 (PSY-3004), a third 13-week study (n=513) comparing three fixed doses of INVEGA SUSTENNA® (39 mg/4 weeks, 78 mg/4 weeks, and 156 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA® were superior to placebo in improving the PANSS total score.

In Study 4 (SCH-201), the 9-week study (n=197) comparing two fixed doses of INVEGA SUSTENNA® (78 mg/4 weeks and 156 mg/4 weeks) to placebo, both doses of INVEGA SUSTENNA® were superior to placebo in improving PANSS total score.

A summary of the mean baseline PANSS scores along with the mean changes from baseline in the four short-term acute schizophrenia studies are provided in Table 14.

Table 14: Schizophrenia Short-term Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	INVEGA SUSTENNA® (39 mg/4 weeks)*	86.9 (11.99)	-11.2 (1.69)	-5.1 (-9.01, -1.10)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	86.2 (10.77)	-14.8 (1.68)	-8.7 (-12.62, -4.78)
	INVEGA SUSTENNA® (234 mg/4 weeks)*	88.4 (11.70)	-15.9 (1.70)	-9.8 (-13.71, -5.85)
	Placebo	86.8 (10.31)	-6.1 (1.69)	--
Study 2[b]	INVEGA SUSTENNA® (78 mg/4 weeks)	89.9 (10.78)	-6.9 (2.50)	-3.5 (-8.73, 1.77)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	90.1 (11.66)	-10.4 (2.47)	-6.9 (-12.12, -1.68)
	Placebo	92.4 (12.55)	-3.5 (2.15)	--
Study 3	INVEGA SUSTENNA® (39 mg/4 weeks)*	90.7 (12.25)	-19.8 (2.19)	-6.6 (-11.40, -1.73)
	INVEGA SUSTENNA® (78 mg/4 weeks)*	91.2 (12.02)	-19.2 (2.19)	-5.9 (-10.76, -1.07)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	90.8 (11.70)	-22.5 (2.18)	-9.2 (-14.07, -4.43)
	Placebo	90.7 (12.22)	-13.3 (2.21)	--
Study 4	INVEGA SUSTENNA® (78 mg/4 weeks)*	88.0 (12.39)	-4.6 (2.43)	-11.2 (-16.85, -5.57)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	85.2 (11.09)	-7.4 (2.45)	-14.0 (-19.51, -8.58)
	Placebo	87.8 (13.90)	6.6 (2.45)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

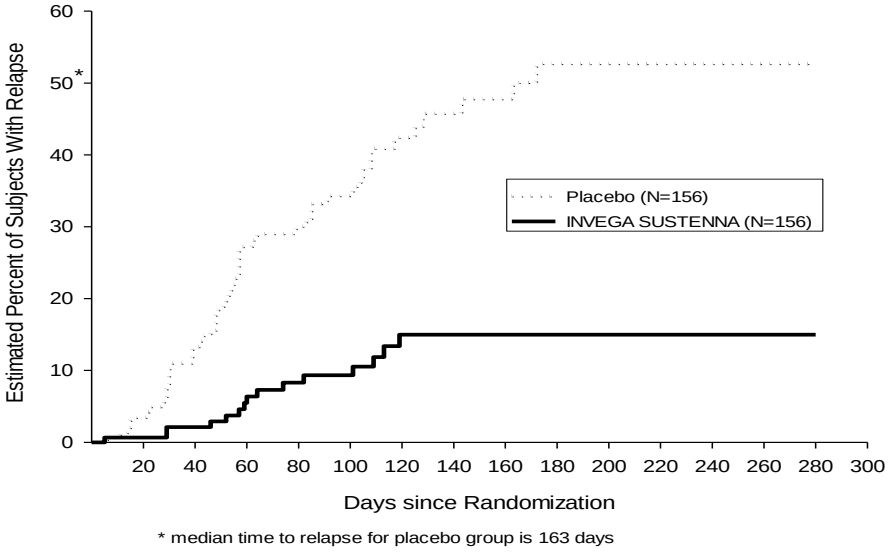
[b] Because an insufficient number of subjects received the 234 mg/4 weeks dose, results from this group are not included.

* $p<0.05$ (Doses statistically significantly superior to placebo).

Maintenance Monotherapy Treatment (Study 5: PSY-3001)

The efficacy of INVEGA SUSTENNA® in maintaining symptomatic control in schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving adult subjects who met DSM-IV criteria for schizophrenia. This study included a minimum 12-week, fixed-dose stabilization phase, and a randomized, placebo-controlled phase to observe for relapse. During the double-blind phase, patients were randomized to either the same dose of INVEGA SUSTENNA® they received during the stabilization phase, i.e., 39 mg, 78 mg, or 156 mg administered every 4 weeks, or to placebo. A total of 410 stabilized patients were randomized to either INVEGA SUSTENNA® or to placebo until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as time to first emergence of one or more of the following: psychiatric hospitalization, ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items. The primary efficacy variable was time to relapse. A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with INVEGA SUSTENNA® compared to placebo, and the study was stopped early because maintenance of efficacy was demonstrated. Thirty-four percent (34%) of subjects in the placebo group and 10% of subjects in the INVEGA SUSTENNA® group experienced a relapse event. There was a statistically significant difference between the treatment groups in favor of INVEGA SUSTENNA®. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 3. The time to relapse for subjects in the placebo group was statistically significantly shorter than for the INVEGA SUSTENNA® group. An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

Figure 3: Kaplan-Meier Plot of Cumulative Proportion of Subjects with Relapse Over Time (Schizophrenia Study 5)



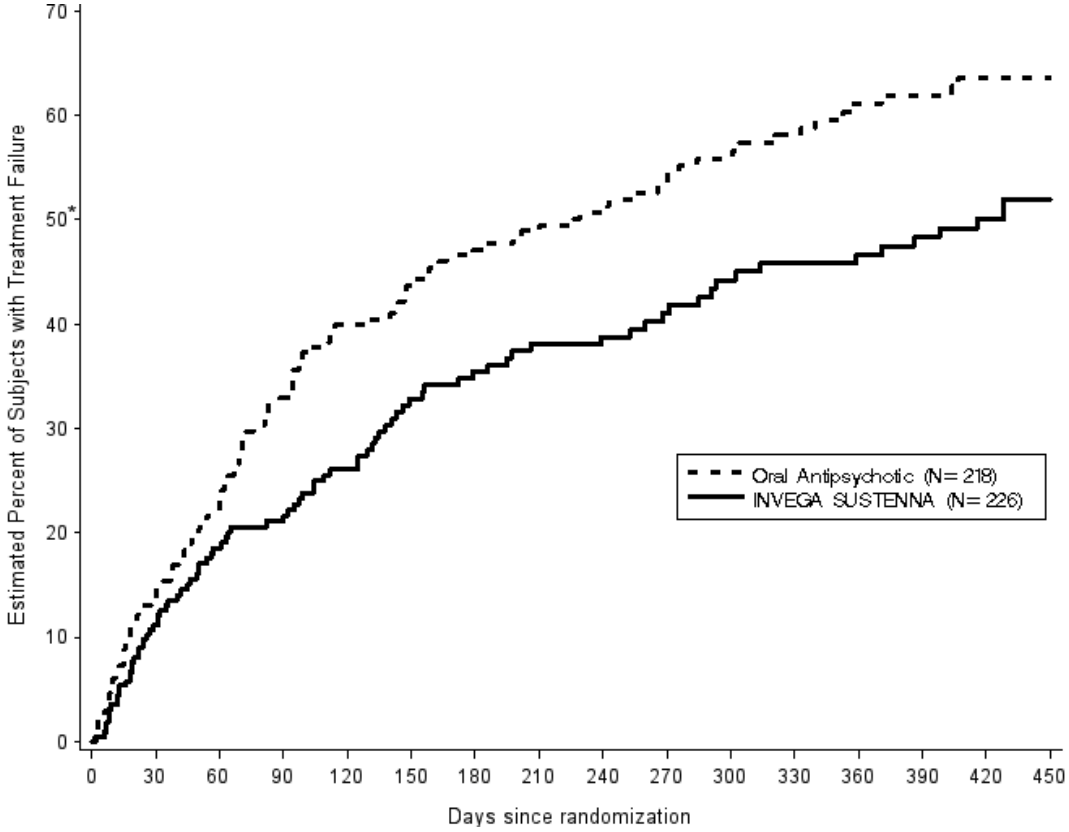
Long-Term Comparative Monotherapy Treatment versus Oral Antipsychotic Therapy (Study 6: SCH-3006)

The efficacy of INVEGA SUSTENNA® in delaying time to treatment failure compared with selected oral antipsychotic medications was established in a long-term, randomized, flexible-dose study in subjects with schizophrenia and a history of incarceration. Subjects were screened for up to 14 days followed by a 15-month treatment phase during which they were observed for treatment failure.

The primary endpoint was time to first treatment failure. Treatment failure was defined as one of the following: arrest and/or incarceration; psychiatric hospitalization; discontinuation of antipsychotic treatment because of safety or tolerability; treatment supplementation with another antipsychotic because of inadequate efficacy; need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization; discontinuation of antipsychotic treatment because of inadequate efficacy; or suicide. Treatment failure was determined by an Event Monitoring Board (EMB) that was blinded to treatment assignment. A total of 444 subjects were randomly assigned to either INVEGA SUSTENNA® (N = 226; median dose 156 mg) or one of up to seven pre-specified, flexibly-dosed, commonly prescribed oral antipsychotic medications (N = 218; aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone). The selection of the oral antipsychotic medication was determined to be appropriate for the patient by the investigator. A statistically significantly longer time to first treatment failure was seen for INVEGA SUSTENNA® compared with oral antipsychotic medications. The median time to treatment failure was 416 days and 226 days for INVEGA SUSTENNA® and antipsychotic medications, respectively. A Kaplan-Meier plot of time to first treatment failure is shown in Figure

4. The frequencies of first treatment failure events by type are shown in Table 15. The time to first psychiatric hospitalization or arrest and/or incarceration was also statistically significantly longer for the INVEGA SUSTENNA® group compared to the oral antipsychotic group.

Figure 4: Kaplan-Meier Plot of Time to First Treatment Failure in a Long-Term, Randomized, Flexible-Dose Study in Subjects with Schizophrenia and a History of Incarceration* (Schizophrenia Study 6)



* Median time to first treatment failure: 416 days with INVEGA SUSTENNA®; 226 days with oral antipsychotics

Table 15: Components of Composite Endpoint in a Long-Term, Randomized, Flexible-Dose Study in Subjects with Schizophrenia and a History of Incarceration (Schizophrenia Study 6)

Event Type	INVEGA SUSTENNA® N=226 frequency (%)	Oral Antipsychotics N=218 frequency (%)	Hazard Ratio[a] [95% CI]
First Treatment Failures	90 (39.8%)	117 (53.7%)	0.70 [0.53, 0.92]
First Treatment Failure Component Events			
▪ Arrest and/or incarceration	48 (21.2%)	64 (29.4%)	
▪ Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	
▪ Discontinuation of antipsychotic treatment because of safety or tolerability	15 (6.6%)	8 (3.7%)	
▪ Treatment supplementation with another antipsychotic because of inadequate efficacy	5 (2.2%)	6 (2.8%)	
▪ Need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	
▪ Discontinuation of antipsychotic treatment because of inadequate efficacy	1 (0.4%)	9 (4.1%)	
▪ Suicide	0	0	
Arrest and/or Incarceration or Psychiatric Hospitalization Events, regardless of whether they were first events[b]	76 (33.6%)	98 (45.0%)	0.70 [0.52, 0.94]

[a] Hazard ratio of INVEGA SUSTENNA® to Oral Antipsychotics based on Cox regression model for time-to-event analysis. Note that the hazard ratio did not appear constant throughout the trial.

[b] Analysis results, which incorporated relevant events collected after discontinuation for those who discontinued, were consistent with the results from the pre-specified analysis of this secondary endpoint.

14.2 Schizoaffective Disorder

Maintenance Treatment – Monotherapy and as Adjunct to Mood Stabilizer or Antidepressant (SAff Study 1: SCA-3004)

The efficacy of INVEGA SUSTENNA® in maintaining symptom control in schizoaffective disorder was established in a long-term double-blind, placebo-controlled, flexible-dose randomized-withdrawal study designed to delay relapse in adult subjects who met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders. The population included subjects with schizoaffective bipolar and depressive types. Subjects received INVEGA SUSTENNA® either as monotherapy or as an adjunct to stable doses of antidepressant or mood stabilizers.

This study included a 13-week, open-label, flexible-dose (INVEGA SUSTENNA® 78 mg, 117 mg, 156 mg, or 234 mg) lead-in period which enrolled a total of 667 subjects who had 1) acute exacerbation of psychotic symptoms; 2) score ≥4 on ≥3 PANSS items of delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, tension, and poor impulse control; and 3) prominent mood symptoms ≥16 on the Young Mania Rating Scale (YMRS) and/or the Hamilton Rating Scale for Depression, 21-item version (HAM-D-21). Subjects were 19 to 66 years old (mean 39.5 years) and 53.5% were male. The mean scores at open-label enrollment of PANSS total was 85.8 (range 42 to 128), HAM-D-21 was 20.4 (range 3 to 43), YMRS was 18.6 (range 0 to 50), and CGI-S-SCA was 4.4 (range 2 to 6).

After the 13-week open-label flexible-dose INVEGA SUSTENNA® treatment, 432 subjects met stabilization criteria (PANSS total score ≤70, YMRS ≤12, and HAM-D-21 ≤12) and continued into the 12-week open-label fixed-dose stabilization period.

A total of 334 subjects who met stabilization criteria for 12 consecutive weeks were randomized (1:1) to continue the same dose of INVEGA SUSTENNA® or to placebo in the 15-month, double-blind, maintenance period. For the 164 subjects who were randomized to INVEGA SUSTENNA®, dose distribution was 78 mg (4.9%), 117 mg (9.8%), 156 mg (47.0%), and 234 mg (38.4%). The primary efficacy variable was time to relapse. Relapse was defined as the first occurrence of one or more of the following: 1) psychiatric hospitalization; 2) intervention employed to avert hospitalization; 3) clinically significant self-injury, suicidal or homicidal ideation or violent behavior; 4) a score of ≥6 (if the score was ≤4 at randomization) of any of the individual PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, or poor impulse control; 5) on two consecutive assessments within 7 days: ≥25% increase (if the score at randomization was >45) or ≥10-point increase (if the score at randomization was ≤45) in total PANSS score; a score of ≥5 (if

the score was ≤3 at randomization) of any of the individual PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, or poor impulse control; an increase of ≥2 points (if the score was 1 [not ill] to 3 [mildly ill] at randomization) or increase of ≥1 point (if the score was ≥4 [moderately ill or worse] at randomization) in CGI-S-SCA overall score.

There was a statistically significant difference in time to relapse between the treatment groups in favor of INVEGA SUSTENNA®. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 5.

Figure 5: Kaplan-Meier Plot of Cumulative Proportion of Subjects with Relapse Over Time (SAff Study 1)

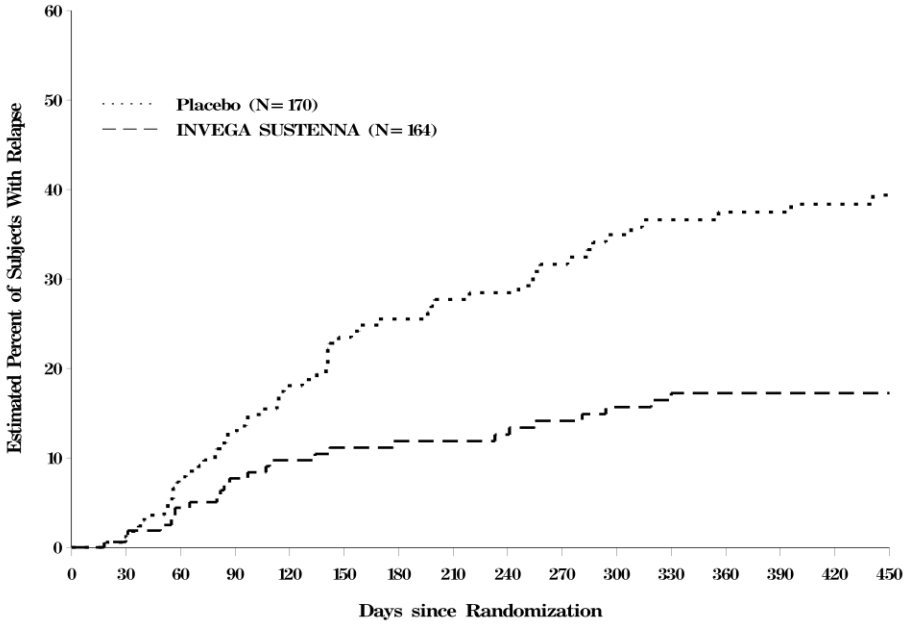


Table 16 summarizes the number of subjects with relapse in the overall population, by subgroup (monotherapy vs. adjunctive therapy), and by symptom type at the first occurrence of relapse.

Table 16: Summary of Relapse Rates (SAff Study 1).

	Number (Percent) of Subjects Who Relapsed	
	Placebo N=170	**INVEGA SUSTENNA® N=164**
All Subjects	57 (33.5%)	25 (15.2%)
Monotherapy subset	N=73	N=78
	24 (32.9%)	9 (11.5%)
Adjunct to Antidepressants or	N=97	N=86
Mood Stabilizer subset	33 (34.0%)	16 (18.6%)
Psychotic Symptoms[a]	53 (31.2%)	21 (12.8%)
Mood Symptoms[b]		
Any Mood Symptoms	48 (28.2%)	18 (11.0%)
Manic	16 (9.4%)	5 (3.0%)
Depressive	23 (13.5%)	8 (4.9%)
Mixed	9 (5.3%)	5 (3.0%)

[a] 8 subjects experienced a relapse without psychotic symptoms.
[b] 16 subjects experienced a relapse without any mood symptoms.

16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA SUSTENNA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

39 mg paliperidone palmitate kit (NDC 50458-560-01)

78 mg paliperidone palmitate kit (NDC 50458-561-01)

117 mg paliperidone palmitate kit (NDC 50458-562-01)

156 mg paliperidone palmitate kit (NDC 50458-563-01)

234 mg paliperidone palmitate kit (NDC 50458-564-01)

Storage and Handling

Store at room temperature (25°C, 77°F); excursions between 15°C and 30°C (between 59°F and 86°F) are permitted. Do not mix with any other product or diluent.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal side effect referred to as Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs.

Patients should contact their healthcare provider or report to the emergency room if they experience the following signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness), and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.7)]*.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia they should have their CBC monitored while taking INVEGA SUSTENNA® *[see Warnings and Precautions (5.9)]*.

Hyperprolactinemia

Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of INVEGA SUSTENNA®. Advise them to seek medical attention if they experience any of the following: amenorrhea or galactorrhea in females, erectile dysfunction or gynecomastia in males *[see Warnings and Precautions (5.10)]*.

Interference with Cognitive and Motor Performance

As INVEGA SUSTENNA® has the potential to impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA SUSTENNA® therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.14)]*.

Heat Exposure and Dehydration

Counsel patients on the importance of avoiding overheating and dehydration *[see Warnings and Precautions (5.15)]*.

Concomitant Medication

Advise patients to inform their healthcare providers if they are taking, or plan to take any prescription or over-the-counter drugs as there is a potential for interactions *[see Drug Interactions (7)]*.

Pregnancy

Advise patients that INVEGA SUSTENNA® may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with INVEGA SUSTENNA® *[see Use in Specific Populations (8.1)]*.

INVEGA SUSTENNA® (paliperidone palmitate) Extended-Release Injectable Suspension

Product of Ireland

Manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

PATIENT INFORMATION
INVEGA SUSTENNA® (in-VAY-guh suss-TEN-uh)
(paliperidone palmitate)
Extended-Release Injectable Suspension

What is the most important information I should know about INVEGA SUSTENNA®?

INVEGA SUSTENNA® can cause serious side effects, including:

- **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** INVEGA SUSTENNA® is not for treating dementia-related psychosis.

What is INVEGA SUSTENNA®?

INVEGA SUSTENNA® is a prescription medicine given by injection by a healthcare professional and used to treat:

- schizophrenia in adults
- schizoaffective disorder in adults either alone or with other medicines such as mood stabilizers or antidepressants

It is not known if INVEGA SUSTENNA® is safe and effective in children under 18 years of age.

Who should not receive INVEGA SUSTENNA®?
Do not receive INVEGA SUSTENNA® if you:

- are allergic to paliperidone, paliperidone palmitate, risperidone, or any of the ingredients in INVEGA SUSTENNA®. See the end of this Patient Information leaflet for a complete list of ingredients in INVEGA SUSTENNA®.

What should I tell my healthcare provider before receiving INVEGA SUSTENNA®?

Before you receive INVEGA SUSTENNA®, tell your healthcare provider about all your medical conditions, including if you:

- have had Neuroleptic Malignant Syndrome (NMS)
- have or have had heart problems, including a heart attack, heart failure, abnormal heart rhythm, or long QT syndrome
- have or have had low levels of potassium or magnesium in your blood
- have or have had uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)
- have or have had kidney or liver problems
- have diabetes or have a family history of diabetes
- have had a low white blood cell count
- have had problems with dizziness or fainting or are being treated for high blood pressure
- have or have had seizures or epilepsy
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if INVEGA SUSTENNA® will harm your unborn baby.
    - Infants born to women who are treated with INVEGA SUSTENNA® may have withdrawal symptoms or other symptoms such as tremors, muscle spasms, abnormal movement of arms and legs, and twitching of eyes.
- are breastfeeding or plan to breastfeed. INVEGA SUSTENNA® can pass into your breast milk and may harm your baby. You and your healthcare provider should decide if you will receive INVEGA SUSTENNA® or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show to your healthcare provider or pharmacist when you get a new medicine.

How will I receive INVEGA SUSTENNA®?

- Follow your INVEGA SUSTENNA® treatment schedule exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much INVEGA SUSTENNA® you will receive and when you will receive it.
- INVEGA SUSTENNA® is given as an injection by your healthcare provider into the muscle (intramuscularly) of your arm or your buttocks.
- When you receive your first dose of INVEGA SUSTENNA® you will need to get a second dose 1 week later. After that you will only need to get a dose 1 time a month.

What should I avoid while receiving INVEGA SUSTENNA®?

- INVEGA SUSTENNA® may affect your ability to make decisions, think clearly, or react quickly. **Do not** drive, operate heavy machinery, or do other dangerous activities until you know how INVEGA SUSTENNA® affects you.
- Avoid getting overheated or dehydrated.

What are the possible side effects of INVEGA SUSTENNA®?

INVEGA SUSTENNA® may cause serious side effects, including:

- See **"What is the most important information I should know about INVEGA SUSTENNA®"**
- **stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious problem that can happen in people who receive INVEGA SUSTENNA®. NMS can cause death and must be treated in a hospital. Call your healthcare provider right away if you become severely ill and have any of these symptoms:
  - high fever
  - severe muscle stiffness
  - confusion
  - loss of consciousness
  - changes in your breathing, heartbeat and blood pressure
- **problems with your heartbeat.** These heart problems can cause death. Call your healthcare provider right away if you have any of these symptoms:
  - passing out or feeling like you will pass out
  - dizziness
  - feeling as if your heart is pounding or missing beats
- **uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)**
- **metabolic changes.** Metabolic changes may include high blood sugar (hyperglycemia), diabetes mellitus and changes in the fat levels in your blood (dyslipidemia), and weight gain.
- **low blood pressure and fainting**
- **changes in your blood cell counts**

- **high level of prolactin in your blood (hyperprolactinemia).** INVEGA SUSTENNA® may cause a rise in the blood levels of a hormone called prolactin (hyperprolactinemia) that may cause side effects including missed menstrual periods, leakage of milk from the breasts, development of breasts in men, or problems with erection.
- **problems thinking clearly and moving your body**
- **seizures**
- **difficulty swallowing that can cause food or liquid to get into your lungs**
- **prolonged or painful erection lasting more than 4 hours.** Call your healthcare provider or go to your nearest emergency room right away if you have an erection that lasts more than 4 hours.
- **problems with control of your body temperature especially when you exercise a lot or spend time doing things that make you warm. It is important for you to drink water to avoid dehydration.**

The most common side effects of INVEGA SUSTENNA® include: injection site reactions, sleepiness or drowsiness, dizziness, feeling restlessness or needing to be constantly moving, abnormal muscle movements including tremor (shaking), shuffling, uncontrolled involuntary movements, and abnormal movements of your eyes.

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of INVEGA SUSTENNA®. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of INVEGA SUSTENNA®.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use INVEGA SUSTENNA® for a condition for which it was not prescribed. Do not give INVEGA SUSTENNA® to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about INVEGA SUSTENNA® that is written for healthcare professionals.

This Patient Information leaflet summarizes the most important information about INVEGA SUSTENNA®. If you would like more information, talk with your healthcare provider.

You can ask your healthcare provider or pharmacist for more information that is written for healthcare professionals. For more information, go to www.invegasustenna.com or call 1-800-526-7736.

What are the ingredients in INVEGA SUSTENNA®?

Active ingredient: paliperidone palmitate

Inactive ingredients: polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection

Revised: 12/2017

Manufactured by: Janssen Pharmaceutica NV, Beerse, Belgium
Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11 May 2015

FROM: Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products, HFD-130

TO: File NDA 22264 S-15

SUBJECT: Summary memo and CR recommendation for paliperidone palmitate ER IM injection for delaying time to treatment failure in adults with schizophrenia who have been recently incarcerated

Background and Summary

Paliperidone palmitate ER is an injectable extended-release atypical antipsychotic approved in July 2009 for the once-monthly treatment of schizophrenia. The ER injectable formulation of this drug is useful in clinical practice because it is believed that injectable formulations increase adherence in a population with compliance problems secondary to their illness (e.g., schizophrenia).

In this application the sponsor has attempted to demonstrate what has long been presumed in the treatment of schizophrenia: that a long-acting injectable formulation of an antipsychotic is superior to daily administration of oral antipsychotics on measures important to patients and clinicians—primarily (in this development program) incarceration and hospitalization.

The sponsor designed this program for this approved drug to be a pragmatic assessment of the difference between injectable long-acting antipsychotic and oral antipsychotics in preventing treatment failure (defined below). While they were able to demonstrate a statistical difference in time to treatment failure per the primary endpoint, my statisticians and clinicians are concerned that they have failed to adequately assess efficacy because many patients were lost to follow up or withdrew consent (more in the paliperidone ER injectable group than the oral antipsychotics group), and when these patients are considered treatment failures, statistical significance is lost. I agree with this criticism of the trial and agree with my team that these data, as presented, do not show substantial evidence of a treatment effect on delaying time to treatment failure for paliperidone ER injectable.

Having said this, the idea of pragmatic trial design, particularly for a drug already approved by the usual efficacy standard, is potentially of great use to clinicians and patients, and we should work with the sponsor to increase the next trial's ability to discern a substantial improvement in delaying time to treatment failure.

Clinical Summary and Statistics
Dr. Glenn Manheim has reviewed the clinical development program data and has recommended a complete response secondary to an unclear outcome in patients lost to follow up or who withdrew consent. Dr. Ququan Liu conducted the biometrics review and concluded that the efficacy endpoint has been met as designed, but notes that if early discontinuations were counted as events, then the results are no longer statistically significant.

Efficacy
Study R092670-SCH-3006, "A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated."

Study Design
After an up 14-day screening/washout period, schizophrenic patients with a recent history of incarceration were randomized to paliperidone palmitate ER IM or to one of seven oral antipsychotics. Choice of oral antipsychotic was randomly assigned by the primary investigator.

Four hundred and fifty patients with schizophrenia were randomized to paliperidone palmitate ER IM injection (n=230) or to one of seven oral antipsychotics (n=220). The ITT analysis set included data from 444 patients (226 paliperidone palmitate ER, 218 oral antipsychotics). A total of 181 patients completed the 15-month visit, 41% of the patients in the paliperidone palmitate ER group and 40% of the patients in the oral antipsychotics group. The most frequently reported reasons for early discontinuation without an event in the paliperidone palmitate ER IM and oral antipsychotics groups, respectively, were lost to follow up (15%, 12%), withdrawal by subject (12%, 7%), and other (6%, 6%).

A blinded Treatment Failure Event Monitoring Board (EMB) determined treatment failure based upon a composite primary endpoint consisting of any of the following:

- Arrest /incarceration
- Psychiatric hospitalization
- Suicide
- Discontinuation of antipsychotic treatment due to inadequate efficacy
- Treatment supplementation with another antipsychotic due to inadequate efficacy
- Discontinuation of antipsychotic treatment due to safety or tolerability
- Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization

Major secondary endpoints included:

- Time to first psychiatric hospitalization or first arrest/incarceration. For this analysis, patients who had a psychiatric hospitalization or arrest/incarceration were considered to have an event whether it was the first treatment failure or not.
- Mean change from baseline in PSP total score
- Time to first psychiatric hospitalization. For this analysis, patients who had a psychiatric hospitalization were considered to have an event whether it was the first treatment failure or not.

• Mean change from baseline in the CGI-S score

The Statistical analysis methodology was defined as follows (from the statistical review):

• Analysis sets: The sponsor defined the ITT analysis set as all randomized subjects who received at least 1 dose of their randomly assigned medication. The sponsor further refined the ITT set into eITT (explanatory ITT) and pITT (pragmatic ITT) in terms of analysis time cutoff. For the eITT analysis set, the analysis cutoff time was generally the last injection date +28 days for patients in the paliperidone palmitate group and the last prescription date of the randomized oral medication + the number of medication-supplied days + 1 day for patients in the oral antipsychotic group. For the pITT analysis set, the analysis cutoff time was the date of last contact regardless of medication switches/discontinuation. The eITT analysis set was used for the analyses of the primary and the major secondary efficacy endpoints. The pITT analysis set was used by the sponsor for all effectiveness analyses.
• Analyses of primary efficacy endpoint: The distribution of time to the first treatment failure was estimated by the Kaplan-Meier method for each treatment group. The primary analysis was the log-rank test performed on the eITT analysis set. The hazard ratio and its 95% confidence interval were explored using a Cox proportional hazards model with treatment as a fixed factor. For the eITT analysis set, subjects who did not have an event by the designated analysis time cutoff (as defined in the preceding bullet) were censored on the cutoff date. Early discontinuation due to inadequate efficacy or tolerability was considered as an event per the pre-specified definition.
• Analyses of secondary efficacy endpoints:
-Time to event efficacy endpoints: Similar methods were applied as described for the primary efficacy endpoint.
-Change from baseline in PSP total score at the 15-month: The primary analysis was performed on the eITT analysis set using a mixed model repeated measures (MMRM) ANCOVA with terms for treatment, time, treatment-by-time interaction, and baseline PSP total score. An unstructured covariance matrix was used to model the within-subject correlations.
-Change from baseline in CGI-S at the 15-month: Analysis analogous to that for the PSP analysis was used.
• Multiplicity: To preserve the overall type I error rate at the 2-sided 0.05 significance level, a fixed sequence approach was used to test these hypotheses starting with the primary endpoint, followed by the major secondary endpoints in the order as listed above.

Because the primary endpoint in this open-label trial was a composite endpoint, it was communicated in the IND phase of this development program that the sponsor should follow up patients as completely as possible so that impact from heavily dependent competing risks were interpretable later.

Demographics
Demographic and baseline characteristics were similar in both treatment arms. Mean age was 38 years, the majority of patients were male, and mean time from last incarceration was 42 days (see below).

Patient Demographic and Baseline Characteristics, eITT Population

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects	226	218	444
Age (years)			
N	226	218	444
Mean (SD)	37.7 (10.57)	38.6 (10.36)	38.1 (10.47)
Median	39.0	40.0	40.0
Range	(18; 61)	(19; 61)	(18; 61)
18-25	39 (17.3%)	32 (14.7%)	71 (16.0%)
26-50	161 (71.2%)	161 (73.9%)	322 (72.5%)
51-60	25 (11.1%)	24 (11.0%)	49 (11.0%)
>60	1 (0.4%)	1 (0.5%)	2 (0.5%)
Gender			
N	226	218	444
Male	193 (85.4%)	190 (87.2%)	383 (86.3%)
Female	33 (14.6%)	28 (12.8%)	61 (13.7%)
Race			
N	226	217	443
White	73 (32.3%)	74 (34.1%)	147 (33.2%)
American Indian or Alaska Native	2 (0.9%)	3 (1.4%)	5 (1.1%)
Black or African American	145 (64.2%)	130 (59.9%)	275 (62.1%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	1 (0.5%)	2 (0.5%)
Asian	2 (0.9%)	1 (0.5%)	3 (0.7%)
Other	1 (0.4%)	6 (2.8%)	7 (1.6%)
Multiple	2 (0.9%)	2 (0.9%)	4 (0.9%)
Ethnicity			
N	226	218	444
Hispanic or Latino	31 (13.7%)	36 (16.5%)	67 (15.1%)
Not Hispanic or Latino	185 (81.9%)	176 (80.7%)	361 (81.3%)
Unknown	2 (0.9%)	1 (0.5%)	3 (0.7%)
Not Reported	8 (3.5%)	5 (2.3%)	13 (2.9%)
Time Since Release from the Last Incarceration (days)			
N	226	217	443
Mean (SD)	38.9 (50.29)	45.7 (53.04)	42.2 (51.71)
Median	28.0	35.0	31.0
Range	(1; 575)	(1; 446)	(1; 575)

Source: Statistics Review, results confirmed by Dr. Liu

Results

Time to first treatment failure was statistically significantly longer in the group receiving paliperidone palmitate ER IM compared to those patients receiving oral antipsychotics (p=0.011). The exploratory Cox Regression Analysis produced a hazard ratio of 0.7 (0.532, 0.922) for the eITT analysis set. The analysis performed on the pITT analysis set was also statistically significant (p= 0.010 and a hazard ratio of 0.717 (0.555, 0.925)).

All composite endpoint events occurred more frequently in patients treated with oral antipsychotics compared to subjects treated with paliperidone palmitate, except for discontinuation due to safety/tolerability.

Frequency of Distribution of Component Events of First Treatment Failure—EMB Determination; eITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Total
First treatment failure			
Number of Subjects	226	218	444
Any Event	90 (39.8%)	117 (53.7%)	207 (46.6%)
Arrest/incarceration	48 (21.2%)	64 (29.4%)	112 (25.2%)
Discontinuation of antipsychotic treatment due to inadequate efficacy	1 (0.4%)	9 (4.1%)	10 (2.3%)
Suicide	0	0	0
Discontinuation of antipsychotic treatment due to safety or tolerability	15 (6.6%)	8 (3.7%)	23 (5.2%)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	7 (1.6%)
Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	44 (9.9%)
Treatment supplementation with another antipsychotic due to inadequate efficacy	5 (2.2%)	6 (2.8%)	11 (2.5%)

Source: Dr. Liu's review

Frequency of Distribution of Component Events of First Treatment Failure—EMB Determination; pITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Total
First treatment failure			
Number of Subjects	226	218	444
Any Event	108 (47.8%)	131 (60.1%)	239 (53.8%)
Arrest/incarceration	58 (25.7%)	70 (32.1%)	128 (28.8%)
Discontinuation of antipsychotic treatment due to inadequate efficacy	1 (0.4%)	11 (5.0%)	12 (2.7%)
Suicide	0	0	0
Discontinuation of antipsychotic treatment due to safety or tolerability	21 (9.3%)	9 (4.1%)	30 (6.8%)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	7 (1.6%)
Psychiatric hospitalization	20 (8.8%)	30 (13.8%)	50 (11.3%)
Treatment supplementation with another antipsychotic due to inadequate efficacy	5 (2.2%)	7 (3.2%)	12 (2.7%)

Source: Dr. Lie's review

Exploratory analyses of time to individual components were performed and suggested that the primary efficacy endpoint was driven mostly by arrest/incarceration (see below).

Time to Component Events of Treatment Failure, eITT

Time to Event	Paliperidone Palmitate (N=226)	Oral Antipsychotics (N=218)	HR (95% CI)
Time to Arrest/Incarceration	64 (28.3%)	87 (39.9%)	0.67 (0.49, 0.93)
Time to Psychiatric Hospitalization	22 (9.7%)	25 (11.5%)	0.84 (0.47, 1.49)
Time to Increased Psychiatric Services	4 (1.8%)	7 (3.2%)	0.55 (0.16, 1.88)
Time to Treatment Discontinuation Due to Inadequate Efficacy	2 (0.9%)	15 (6.9%)	0.129 (0.03, 0.57)
Time to Treatment Supplementation	7 (7.1%)	6 (6.0%)	1.104 (0.37, 3.28)
Time to Discontinuation Due to Safety or tolerability	16 (6.6%)	13 (3.8%)	1.183 (0.57, 2.46)
Time to 1st Suicide	0	0	--

Source: Dr. Liu's review.

Sensitivity Analyses

Biometrics performed several sensitivity analyses secondary to the concern that excluded patients may have had an unmonitored event that was part of the composite primary endpoint. One hundred and thirty-nine patients discontinued early without being identified as treatment failures, and there were more patients who discontinued in the paliperidone palmitate ER IM group (36%) than the oral antipsychotics group (27%). The statistical reviewers addressed the concern of patients excluded from the primary analysis without positive evidence of event by making two assumptions in their sensitivity analyses: 1. Treat all patients (n=139) as having had an event; 2. Treat patients who discontinued secondary to "lost to follow-up" or "patient withdrawal" as having had events (n=102). The results of these two approaches are presented below.

Sensitivity Analysis: Time to First Treatment Failure (including all 139 early discontinuations as an event).

Time to Event	Paliperidone Palmitate	Oral Antipsychotics
Number assessed	226	218
Event	171	175
Censored	55	43
Kaplan-Meier Median, Days (95% CI)	143 (124, 190)	134 (94, 164)
Log-Rank Test P-value	0.2805	
HR (95% CI)	0.891 (0.721, 1.100)	

Source: Dr. Liu's review.

Sensitivity Analysis: Time to First Treatment Failure (treating 102 early discontinuations for lost to follow-up or patient withdrawal as an event).

Time to Event	Paliperidone Palmitate	Oral Antipsychotics
Number assessed	226	218
Event	150	159
Censored	76	59
Kaplan-Meier Median, Days (95% CI)	268 (185, 386)	179 (129, 243)
Log-Rank Test P-value	0.1885	
HR (95% CI)	0.861 (0.689, 1.077)	

From the above sensitivity analyses, the utility of paliperidone palmitate compared to oral antipsychotics is inconclusive.

Comments on Sensitivity Analyses: While it is true that the study met its primary endpoint as designed, it seems prudent to me and to my team members, in a trial comparing pragmatic outcomes which are measurable, that every attempt be made to measure those outcomes. This trial had over a hundred patients for whom there are no data about meeting (or not meeting) one of the composites of the primary endpoint, and when those data are included in the analysis as treatment failures, there is no significant difference between the paliperidone palmitate ER IM and oral antipsychotics on Time to First Treatment Failure. This has implications for future trials: the patients must be followed after early discontinuation or withdrawal to positively determine if leaving early is related to the event(s) of interest.

Safety
Secondary to this single study's open-label design and the fact that it was intended to be a "pragmatic trial" in the sense that drug was flexibly-dosed and patient exclusions (including concomitant medications) were limited, evaluation of safety signals was difficult by design. Dr. Mannheim identified no new safety issues of concern from the data.

Summary of Conclusions and Recommendations from Other Review Teams

CMC
There were no changes proposed to the drug product, manufacturing process, or drug specifications, and there are no CMC-related labeling changes. A claim for categorical exclusion was accepted.

Nonclinical Pharmacology/Toxicology
No new nonclinical data were submitted for review for this approved drug product.

Clinical Pharmacology/Biopharmaceutics
No new data were generated as part of this application for this approved drug.

OSI Inspection
Three clinical study sites were inspected and no deficiencies were observed.

Labeling
No labeling changes were made secondary to the recommendations of Complete Response.

Pediatric Plan
No pediatric studies are required.

Post-marketing Commitments/Requirements
No post-marketing commitments or requirements were identified by the team.

Risk Evaluation/Minimization Plan
A REMS is not necessary for this application.

Conclusion
Substantial evidence has not been presented to demonstrate that paliperidone palmitate is superior to oral antipsychotics in delaying time to treatment failure in adults with schizophrenia who have been recently incarcerated.

This question of using long-acting injectables to alter pragmatic outcomes in patients with schizophrenia could be answered with a trial of this design, provided lost-to-follow-up and withdrawal of consent patients are followed to positively determine if they meet the criteria for an event. Our letter to the sponsor should encourage them to conduct another trial of this design with more attention paid to patients who are lost from the trial.

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/s/

MITCHELL V Mathis
05/11/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

OFFICER/EMPLOYEE LIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

TO: Administrative file for NDA 22264 S-015

FROM: Shin-Ye Sandy Chang, Regulatory Health Project Manager
Division of Psychiatry Products, Office of New Drugs

SUBJECT: Officer/Employee List for NDA 22264 S-015

APPLICATION/DRUG: NDA22264 S-015, INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use.

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Atrakchi, Aisar H
Farchione, Tiffany
Lee, Daniel
Muniz, Javier
Sohn, Ann J
Temple, Robert
Williams, LaKisha
Yang, Peiling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	{See Appended Electronic Signature Page}
From	CDR Javier A. Muniz, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22264 S-015
Applicant	Janssen Research & Development, LLC
Date of Submission	June 20, 2017
PDUFA Goal Date	December 20, 2017
Proprietary Name / **Established (USAN) names**	Invega Sustenna paliperidone palmitate
Dosage forms / Strength	Extended-release injectable suspension 39 mg, 78 mg, 117 mg, 156 mg, 234 mg IM injections
Proposed Indication(s)	Maintenance treatment of schizophrenia
Recommended:	Approval

1. Introduction and Background

Paliperidone palmitate (Invega Sustenna) is an injectable extended-release atypical antipsychotic approved in 2009. It is currently indicated for the treatment of schizophrenia and schizoaffective disorder (as monotherapy and as an adjunct to mood stabilizers or antidepressants) in adults. Once injected, paliperidone palmitate is slowly hydrolyzed to paliperidone (NDA 021999), the major active metabolite of risperidone. The mechanism of action of paliperidone palmitate is unknown but has been proposed to be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. It is available in 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg strengths for intramuscular injection (IM).

It has long been assumed by clinicians who treat patients with schizophrenia that long-acting injectable antipsychotic formulations enhance treatment adherence and are therefore potentially advantageous to oral antipsychotics administered daily. In this development program, the Applicant (Janssen) aimed to demonstrate this assumption on outcomes important to patients and clinicians: incarceration and hospitalization. The only clinical trial supporting Supplement 015 (Study SCH-3006) was designed to be a pragmatic assessment of the difference between injectable long-acting antipsychotic and oral antipsychotics in preventing treatment failure (defined in Section 6 below).

The Applicant's original submission for Supplement 015 was received on July 11, 2014. During the first review cycle, the Applicant demonstrated a statistical difference in time to treatment failure on the primary endpoint. However, the review team was concerned that the Applicant failed to assess efficacy adequately, because many patients were lost to follow-up or withdrew consent; this occurred more frequently in the paliperidone palmitate arm than the active control arm consisting of one of seven oral antipsychotics. Importantly, when these

patients lost to follow-up were treated as treatment failures, the statistical significance of the primary outcome was no longer met. Because of these concerns, the Division issued a Complete Response (CR) letter in May, 2015. The CR letter encouraged the Applicant to conduct another trial of the same design, with increased attention to patients lost from the study. In January, 2016, an agreement was reached that the Applicant would once again attempt to contact participants, or their responsible friends or families, from Study SCH-3006. Individuals who could not be reached would be cross-referenced with publicly available police and death records. The Applicant submitted its data collection plan for addressing missing data to the Division on May 26, 2016 and received concurrence from the Division regarding the plan on July 17, 2016.

This Class 2 resubmission includes a Clinical Study Report (CSR) Addendum for Study SCH-3006 that contains the complete results of all additional analyses for the subgroup of dropout subjects, intending to address the Division's concerns regarding the robustness of the study results. With this resubmission, the Applicant seeks to add the results from Study SCH-3006 to the Clinical Trials section of the label.

2. CMC/Device

No new CMC information was submitted with this application.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted with this application.

4. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this supplement.

5. Clinical Microbiology

No new microbiology data were submitted with this resubmission.

6. Clinical/Statistical- Efficacy

Daniel Lee, MD, was the clinical reviewer for this resubmission; he recommends approval. Yang Wang, PhD, was the biostatistics reviewer for this resubmission, and she also recommends approval. Glenn Manheim, MD, reviewed Study SCH-3006 during the first review cycle; thus, only a high level-summary of its design will be discussed here to provide context to the resubmitted data.

Study SCH-3006 was a 15-month, prospective, randomized, active-controlled, open-label, flexible-dose study, comparing paliperidone palmitate with oral antipsychotic treatment in delaying the time to treatment failure in adults with schizophrenia and a history of recent

incarceration. To increase the generalizability of the results, the Applicant made efforts to limit exclusionary criteria and to study subjects in a "naturalistic" setting. After a 14-day screening/washout period, patients in the target population were randomized to receive paliperidone palmitate or one of seven oral antipsychotics (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone), as determined appropriate by the primary investigator. All subjects were to continue in the treatment phase for up to 15 months after the randomization visit, regardless of whether they reached the primary event, unless consent was withdrawn.

A blinded Treatment Failure Event Monitoring Board (EMB) adjudicated that the primary endpoint of treatment failure was met if any of the following events occurred:

- Arrest /incarceration.
- Psychiatric hospitalization.
- Suicide.
- Discontinuation of antipsychotic treatment due to inadequate efficacy.
- Treatment supplementation with another antipsychotic due to inadequate efficacy.
- Discontinuation of antipsychotic treatment due to safety or tolerability.
- Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization.

Major secondary endpoints for this trial were:

- Time to first psychiatric hospitalization or first arrest/incarceration.
- Mean change from baseline in Personal and Social Performance (PSP) scale total score.
- Time to first psychiatric hospitalization.
- Mean change from baseline in the Clinical Global Impression (CGI-S) score.

A total of 450 subjects were randomized. Of these subjects, 444 received at least one dose of paliperidone palmitate (N=226) or an oral antipsychotic (N=218) and were included in the intent-to-treat (ITT) analysis set. Of the subjects included in the ITT analysis set, 181 completed the study and 263 discontinued the study early. One-hundred-thirty-nine of the subjects discontinued participation in Study SCH-3006 without having an explanatory intent-to-treat (eITT) treatment failure event (TFE) during the period from randomization through the end of the period of interest (28 days after the last injection of paliperidone palmitate or one day after the last dose of oral antipsychotic). These subjects were included in the dropout analysis set.

The purpose of the additional data collection conducted by the Applicant was to determine whether any of the 139 subjects who discontinued the study prematurely without an EMB-adjudicated event experienced a TFE from the time of discontinuation to the end of the follow-up period (Month 15-post randomization or Day 450). Of these 139 subjects, the Division agreed that no further data collection was necessary for 43 subjects, for the following reasons:

- Twenty-nine subjects had an EMB-adjudicated TFE that occurred after discontinuation of randomized treatment but was outside the protocol-defined primary period of interest. Their information could be used as reported in the original submission.
- Two subjects moved due to social circumstances, and one subject died of a non-suicide death.

- Eleven (11) subjects had a TFE (arrest and/or incarceration) reported by the principal investigator. However, the EMB had not adjudicated these as a treatment failure. All 11 subjects are included in the supplemental analyses as treatment failures (i.e., in the dropout analysis set).

Thus, the Applicant's additional data collection efforts focused on the remaining 96 subjects. To minimize the potential for recall bias, this additional data collection plan focused on identification of three types of TFEs (i.e., psychiatric hospitalization, arrest and/or incarceration, and suicide). Follow-up information was available for 79 of the 96 subjects (82.3%), and a determination could be made as to whether a treatment failure had occurred.

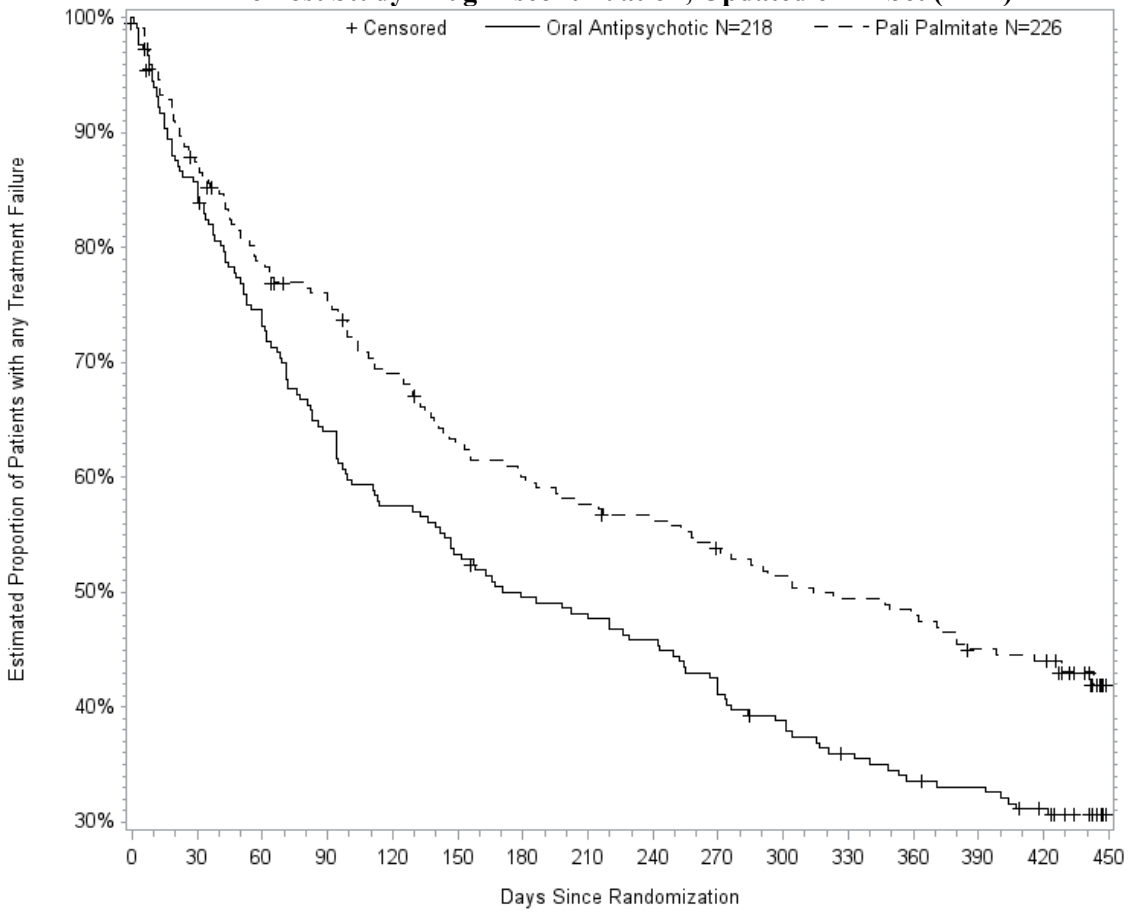
The primary analysis set for the supplemental analysis of Study SCH-3006 were the 139 subjects in the dropout analysis set. The primary objective of supplemental data analysis was to estimate the TFE rate post-study drug discontinuation for each treatment group. The difference in the proportion of subjects with a TFE between the paliperidone palmitate and oral antipsychotic treatment groups within each specific period of interest was tested using Chi-Square test. The distribution of time to the first event was estimated by the Kaplan-Meier method for each treatment group. The difference between the paliperidone palmitate and oral antipsychotic treatment groups, with respect to the distribution of the time to first events, was tested using a log-rank test. The hazard ratio and its 95% CI were estimated using a Cox proportional hazards model, with treatment group as a fixed factor. It should be noted that these supplemental analyses in this resubmission were not powered for testing treatment group differences.

In general, the demographics, disease characteristics, and medical comorbidities were similar between the 81 subjects in the paliperidone palmitate arm and the 58 subjects in the oral antipsychotic arm, among the 139 dropout subjects. In his review, Dr. Lee found no significant baseline characteristics or demographic differences between the 139 dropout subjects and the full trial population.

In the dropout analysis set, 34 (42.0%) of 81 subjects in the paliperidone palmitate arm and 32 (55.2%) of 58 subjects in the oral antipsychotics arm had a TFE at any time after study drug discontinuation. A total of 31 (38.3%) of 81 subjects in the paliperidone palmitate group and 26 (44.8%) of 58 subjects in the oral antipsychotics group had an arrest/incarceration at any time post study discontinuation. Similarly, two (2.5%) of 81 subjects in the paliperidone palmitate arm and four (6.9%) of 58 subjects in the oral antipsychotics arm had a psychiatric hospitalization at any time post study discontinuation. In general, the proportion of subjects with a first TFE, first psychiatric hospitalization, or first arrest/incarceration was higher in the oral antipsychotic group than in the paliperidone palmitate injection group in all four studied time windows (i.e., 30 days, 60 days, 90 days, and at any time post study drug discontinuation). This is consistent with findings for the eITT analysis set in the original submission. Furthermore, the findings are supported by the Applicant's Kaplan-Meier estimates of time to first TFE, psychiatric hospitalization, and arrest/incarceration at any time post study drug discontinuation.

In her review, Dr. Wang replicated the Applicant's findings. Additionally, with the newly available data for the 139 dropout subjects, Dr. Wang updated the datasets and reran Study SCH-3006's primary analysis for time to first treatment failure at any time. The observed proportion of subjects with an event of any treatment failure at any time was higher in the oral antipsychotic group (149 out of 218; 68.4%) than in the paliperidone palmitate injection group (124 out of 226; 54.9%). Statistical significance was achieved, with the p-value of the log-rank test calculated to be 0.0073. This exploratory analysis supports the robustness of the original primary analysis result. The following Kaplan-Meier (Figure 1) curve displays time to the first treatment failure at any time post study drug discontinuation, indicating a statistically significantly higher proportion of subjects had any treatment failure at any time in the oral antipsychotic group compared to the paliperidone palmitate injection group.

Figure 1: Kaplan-Meier Estimates of Time from Randomization to 1st Treatment Failure at Any Time Post Study Drug Discontinuation; Updated eITT Set (FDA)



[Source: Biostatistics review, Figure 7, page 24]

Table 1 summarizes the frequencies of first treatment failure events, by type, as submitted by the Applicant.

Table 1: Components of Composite Endpoint, Study SCH-3006

Event Type	Paliperidone palmitate N=226 frequency (%)	Oral Antipsychotics N=218 frequency (%)	Hazard Ratio[a] [95% CI]
First Treatment Failures[b]	90 (39.8%)	117 (53.7%)	0.70 [0.53, 0.92]
First Treatment Failure Component Events			
• Arrest and/or incarceration	48 (21.2%)	64 (29.4%)	
• Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	
• Discontinuation of antipsychotic treatment because of safety or tolerability	15 (6.6%)	8 (3.7%)	
• Treatment supplementation with another antipsychotic because of inadequate efficacy	5 (2.2%)	6 (2.8%)	
• Need for increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	
• Discontinuation of antipsychotic treatment because of inadequate efficacy	1 (0.4%)	9 (4.1%)	
• Suicide	0	0	
Arrest and/or Incarceration or Psychiatric Hospitalization Events, regardless of whether they were first events [c]	93 (41.2%)	118 (54.1%)	0.69 [0.53, 0.91]

[a] Hazard ratio of INVEGA SUSTENNA to Oral Antipsychotics based on Cox regression model for time-to-event analysis. Note that the hazard ratio did not appear constant throughout the trial.
[b] Events after patient discontinuation were not incorporated.
[c] Events after patient discontinuation were incorporated.
[Source: Table 15; (b) (4)

Dr. Wang concludes in her review that, based on these post-hoc exploratory analyses, there was no evidence that the higher rate of discontinuation in the paliperidone palmitate group than the oral antipsychotic group in the ITT analysis set was related to impending TF due to loss of efficacy or emerging intolerability. Furthermore, the exploratory supplemental analyses of the dropout analysis set support the positive findings from the original submission in showing that treatment with paliperidone palmitate was statistically superior to oral antipsychotics in delaying the time to first TF in adults with schizophrenia and a history of incarceration.

7. Safety

In general, the safety data submitted with this sNDA are consistent with the known safety profile of paliperidone palmitate. Dr. Manheim and Dr. Lee's reviews revealed no safety findings that would require a labeling revision, preclude approval of this supplement, or necessitate other regulatory action.

8. Advisory Committee Meeting

No advisory committee meeting was held for this supplemental application. The evaluation of the safety data did not reveal safety issues that were unexpected for this class, and the design and results of the efficacy trial did not pose particular concerns.

9. Pediatrics

This supplement did not include pediatric data. No new indications were proposed by the Applicant; therefore, this supplement does not trigger new PREA requirements.

10. Other Relevant Regulatory Issues

Because Study SCH-3006 was conducted in patients with schizophrenia who had been incarcerated, the review team during this cycle debated whether ethical principles had been overlooked when studying this vulnerable population. I discussed this application with CAPT Ken Prohaska, DO, an ethicist who frequently works with the Division. Because the patients who participated in this study were not incarcerated at the time of the trial and because an informed consent to participate was given by these individuals, Dr. Prohaska did not think that ethical principles had been violated.

11. Labeling

Labeling was updated to include a description of Study SCH-3006 in the Clinical Studies section. Labeling recommendations by the Office of Prescription Drug Promotion (OPDP) were considered by the review team and incorporated as necessary. In addition, modifications were made throughout the label for consistency with recent class labeling changes. The final label is being negotiated with the Division as of the time of this writing.

12. Recommendations/Risk Benefit Assessment

The current paliperidone palmitate label states that paliperidone palmitate is safe and effective for the maintenance treatment of schizophrenia in adult patients (established during a previous supplement). Traditional maintenance trials for schizophrenia are usually done by comparing an approved drug against a placebo. These traditional trial designs cannot easily address questions that relate to treatment adherence in typical clinical practice, as they tend to exclude individuals who may have an unpredictable or unreliable participation in said studies (e.g., patients with active substance abuse, risk of recidivism, etc.). However, individuals with a

recent history of incarceration represent a substantial subgroup of the schizophrenia population with unique public and mental health needs.

In Study SCH-3006, paliperidone palmitate was shown to be superior to monotherapy from a choice of seven oral standard-of-care treatments in preventing hospitalization or arrest/incarceration. Furthermore, paliperidone palmitate is the first drug to demonstrate effectiveness on these "real-world" endpoints that are relevant to the care of these patients. The results of this study seem to validate the aforementioned clinical assumptions that long-acting injectable antipsychotics are advantageous to oral antipsychotics, likely because of increase treatment adherence. This information provides a significant public health benefit.

Because this product's label already has language describing maintenance treatment of schizophrenia, I do not see any additional risk incurred by describing the results of Study SCH-3006 in the Clinical Trials section of the label. Additionally, no new safety signals were identified that would alter the overall benefit-risk assessment for paliperidone palmitate.

I agree with the recommendations of the review team and recommend for this application to be approved by the PDUFA date.

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/s/

JAVIER A MUNIZ
12/20/2017

MITCHELL V Mathis
12/20/2017

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 27, 2015

FROM: Jing Zhang, MD. PhD.
Medical Team Leader, Division of Psychiatry Products
HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 22264/S-15

Proprietary/ Established name: INVEGA SUSTENNA/paliperidone palmitate

Dosage forms/ Strength: Extended-release injectable suspension: 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg

Indication: Maintenance treatment for patients with schizophrenia having a history of incarceration

Recommendation: Non-approval

I. Introduction and Background

INVEGA, Paliperidone (9-hydroxy-risperidone, R076477), is an active metabolite of risperidone that is an approved atypical antipsychotic. Paliperidone oral formulation, has been approved by the United States (US) Food and Drug Administration (FDA) for the acute treatment of schizophrenia (December 2006, NDA 21-999), maintenance treatment of schizophrenia (April 2007), and acute treatment in adolescents aged 12 to 17 years (April 2011).

INVEGA SUSTENNA (paliperidone palmitate), a long-acting injectable formulation, was approved for the acute and maintenance treatment of schizophrenia in adults in July 2009, and for treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants in November 2014.

The rational of the sponsor interested in study incarcerated population with INVEGA SUSTENNA is that adherence to antipsychotic drugs is a major contributor for

preventing relapse among patients with schizophrenia, and persons with schizophrenia have a higher risk of arrest and incarceration than the general public. Previously-incarcerated individuals with psychotic disorders including schizophrenia also have a higher risk of repeat offending.

To adequately address comparative effectiveness questions regarding the use of paliperidone palmitate in more naturalistic settings. The sponsor conducted a prospective, randomized study R092670-SCH-3006 intended to exam the comparative effectiveness of paliperidone palmitate and oral antipsychotics in a more naturalistic clinical setting. Subjects enrolled in this study were adults with schizophrenia having a recent history of incarceration. The sponsor hypothesized that improved symptom control with paliperidone palmitate treatment lead to lower rates of hospitalization and possibly fewer interactions with law enforcement and resultant arrests/incarcerations.

In this supplemental New Drug Application (sNDA), data collected from study R092670-SCH-3006 are presented to support revisions to (b) (4) CLINICAL STUDIES sections of the INVEGA SUSTENNA USPI.

II. Summary of Conclusions and Recommendations from Review Teams

1. CMC

The supplement does not provide for any changes to the drug product, manufacturing process, or specifications and there are no CMC-related labeling changes. A claim for categorical exclusion under 21 CFR Part 25.31(b) is included in the submission. Approval of the supplement may result in expanded use of the active moiety. However, the concentration of the active moiety at the point of entry into the aquatic environment will be significantly below 1 ppb (calculated to be (b) (4) ppb). Therefore, the claim of categorical exclusion is accepted.

2. Nonclinical Pharmacology/Toxicology

Paliperidone palmitate is an approved drug. No new non-clinical data were generated to support the NDA 22264 supplement S-015.

3. Clinical Pharmacology/Biopharmaceutics

Paliperidone palmitate is an approved drug. No new Clinical pharmacology or bio-pharmaceutic issues were generated to support the NDA 22264 supplement S-015.

4. Clinical Review

The clinical data from this application was reviewed by Glenn Mannheim MD, a medical reviewer and Ququan Liu, PhD., a statistical reviewer. Dr. Liu's review only focused on efficacy review. Please refer to their reviews for more detailed information.

Study R092670-SCH-3006

Study Design

Study R092670-SCH-3006 is a "Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated". The original protocol was submitted to IND 67,356 on 20 April 2010.

The study was conducted from May 5th, 2010 to December 9th, 2013 at 56 sites in US (55 centers) and Puerto Rico (1 center).

The study consisted of an up-to-14-day screening/washout period and a 15-month open-label treatment period. An equipoise-stratified randomization scheme was used in this study. Eligible subjects were randomly assigned in a 1:1 ratio to receive either paliperidone palmitate injection or 1 of 7 pre-specified oral antipsychotics—aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone.

The first dose of paliperidone palmitate was 234 mg, given on Day 1 of the treatment period. The second dose was 156 mg, given on Day 8. Starting on Day 38, flexible monthly maintenance dosing of paliperidone palmitate within the range of 78 to 234 mg was allowed. For oral antipsychotic treatment, subjects generally were treated within the approved dosage ranges for all antipsychotics. Any exception was first discussed with the Medical Monitor and was not considered a treatment failure.

After Day 15, subjects who were determined by the investigator to require a higher dose of paliperidone palmitate could receive supplemental oral paliperidone (3 or 6 mg) daily until the dose of paliperidone palmitate could be increased at the next injection day. Supplemental oral paliperidone was discontinued when the subject received an injection with the new, higher dose of paliperidone palmitate.

If the subject was randomly assigned to receive oral antipsychotic treatment, the specific oral antipsychotic was randomly chosen by a computer program from the set of pre-specified suitable oral antipsychotics. Oral antipsychotic medications were not provided directly by the sponsor. At each visit the investigator provided a voucher and prescription for an oral antipsychotic medication to each subject to bring to a local pharmacy to receive his or her medication. The sponsor provided remuneration for only 1 antipsychotic medication at any one time (ie, the subject's primary study antipsychotic).

Visits were to occur on Days 8, 15, 38, and then monthly thereafter, and at each visit, subjects were to be assessed for the occurrence of treatment failures by the principal investigator. All subjects were to continue in the treatment phase for up to 15 months regardless of whether they reached the primary event. Subjects who discontinued study treatment or experienced a treatment failure event and did not withdraw consent were expected to continue in the study and be followed through Month 15.

The primary efficacy endpoint was the time from subject randomization to the first treatment failure, which was a composite endpoint of

- arrest or incarceration,
- suicide,
- psychiatric hospitalization,
- discontinuation of antipsychotic treatment due to inadequate efficacy,
- treatment supplementation with another antipsychotic due to inadequate efficacy,
- discontinuation of antipsychotic treatment due to safety or toxicity, or
- increase in psychiatric services to prevent imminent psychiatric hospitalization.

Key secondary efficacy endpoints were

- time to first psychiatric hospitalization or arrest/incarceration,
- mean change from baseline in post-randomization to Month 15 in Personal and Social Performance Scale (PSP) total score,
- time to first psychiatric hospitalization, and
- mean change from baseline in post-randomization to Month 15 in CGI-S score.

Efficacy data were analyzed using an intent-to-treat (ITT) approach. Two ITT analysis sets were used—the explanatory ITT (eITT) analysis set and the pragmatic ITT (pITT) analysis set. The eITT analysis set was the primary efficacy analysis set, and included all data from randomization until the end of randomized treatment (28 days after the last injection or 1 day after the last oral dose). The pITT analysis set included all data from randomization until Month 15.

Testing the primary and key secondary hypotheses used a fixed sequence gatekeeper approach.

The primary analysis of the distribution of time to the first treatment failure was estimated by the Kaplan-Meier method for each treatment group. The primary analysis was the log-rank test performed on the eITT analysis set. The hazard ratio and its 95% confidence interval (CI) were estimated using a Cox proportional hazards model with treatment as a fixed factor.

The secondary and exploratory time to event efficacy endpoints were analyzed using methods similar to that described for the primary endpoint. A mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) with terms for treatment, time, treatment-by-time interaction, and baseline PSP total score, was used to test the secondary hypothesis on PSP total score. A similar MMRM analysis was used to test CGI-S score.

Efficacy Results

To be eligible for randomization, subjects were required to be between 18 and 65 years of age with schizophrenia, and to have been taken into custody at least twice in the previous 2 years (at least 1 custody episode must have led to an incarceration), with the latest

release occurring within 90 days of the screening visit. There were few exclusion criteria, and these were mostly related to a history of poor response to paliperidone, evidence or recent history of drug abuse, or high risk for significant safety issues. To ensure that information regarding subject status was available, each subject had a designated individual who was able to provide such information if the subject became unable to.

A total of 450 subjects were randomized, including 230 to the paliperidone palmitate group and 220 to the oral antipsychotic group. A total of 444 subjects were included in ITT population (226 in injection, 218 in oral group).

A total of 181 patients completed the 15-month visit, 41.2% in paliperidone palmitate group and 40.4% of oral antipsychotic group. There were 263 subjects who discontinued from the study early, nearly half (47.1%) reached the primary endpoint. The most frequently reported reasons for early discontinuation without an event in the paliperidone palmitate and the oral antipsychotics groups were lost to follow-up (15.0%, 11.9%), withdrawal by subject (11.5%, 7.3%), and other (6.2%, 5.5%), respectively.

Demographic and disease characteristics were generally similar for the 2 treatment groups. The population was predominately male (86.3%), and the majority were of minority race (62.1% Black/African American). Sixteen percent (16.0%) of subjects were aged 18 to 25 years and 11.5% were aged ≥51 years.

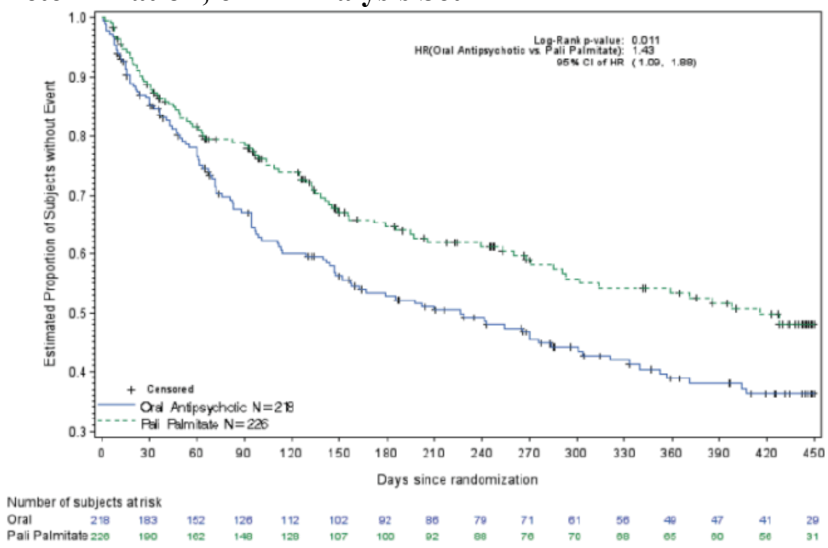
Most (82.6%) had been diagnosed with schizophrenia for 5 years or more, and subjects had an average of 1.1 psychiatric hospitalizations within the last 12 months and 6.5 psychiatric hospitalizations in their lifetime. The mean time since release from the last incarceration was 42.2 days.

Concomitant use of most prescription and over-the-counter medications was permitted during the study, and the only prohibited concomitant drugs were monoamine oxidase inhibitors, carbamazepine or oxcarbazepine. Most subjects (74.3% in injection and 80% in oral) took at least 1 psychotropic medication during the study. There were no notable differences in concomitant use of these drugs between treatment groups, and the most frequently used classes of psychotropic medications during the study were atypical antipsychotics (47.5%) and antidepressants (39.2%).

Primary Endpoint

Based on the sponsor's analysis of the primary efficacy endpoint (eITT), treatment with paliperidone palmitate was superior to treatment with an oral antipsychotic in delaying the time to first treatment failure (p=0.011), with a hazard ratio (95% CI) of 1.43 (1.09, 1.88). A total of 90 (39.8%) subjects in the paliperidone palmitate group and 117 (53.7%) subjects in the oral antipsychotics group had a treatment failure event. Kaplan-Meier estimates of event-free probabilities are presented in Figure 1. The estimated median time (95% CI) to first treatment failure was 416 days for subjects treated with paliperidone palmitate, compared with 226 days for subjects treated with oral antipsychotics.

Figure 1. Kaplan-Meier Estimates of Time to First Treatment Failure per EMB Determination; eITT Analysis Set



Source: the sponor's figure 4

The frequency distribution of type of first treatment failure component events is shown in Table 1. The most common treatment failure outcomes in this trial were arrests and incarcerations and psychiatric hospitalizations. All component events occurred more frequently in subjects treated with oral antipsychotics than in subjects treated with paliperidone palmitate, except for discontinuation due to safety or tolerability (6.6% in paliperidone palmitate, 3.7% in oral antipsychotics).

Table 1. Frequency Distribution of Component Events of First Treatment Failure per EMB Determination; eITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Total
First treatment failure			
Number of Subjects	226	218	444
Any Event	90 (39.8%)	117 (53.7%)	207 (46.6%)
Arrest/incarceration	48 (21.2%)	64 (29.4%)	112 (25.2%)
Discontinuation of antipsychotic treatment due to inadequate efficacy	1 (0.4%)	9 (4.1%)	10 (2.3%)
Suicide	0	0	0
Discontinuation of antipsychotic treatment due to safety or tolerability	15 (6.6%)	8 (3.7%)	23 (5.2%)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	7 (1.6%)
Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	44 (9.9%)
Treatment supplementation with another antipsychotic due to inadequate efficacy	5 (2.2%)	6 (2.8%)	11 (2.5%)

Source: the sponsor's Table TEFTFKM01P

Results of sensitivity analyses that extended the endpoint for treatment failure by 15, 30, 45, or 60 days were conducted by the sponsor and were consistent with the primary analysis. Analysis of time to first treatment failure per investigator determination also led to the conclusion that treatment with paliperidone palmitate was superior to treatment

with oral antipsychotics in delaying time to first treatment failure (p=0.019), with a hazard ratio (95% CI) of 1.39 (1.06, 1.82).

Key Secondary Endpoints

1. Time to First Psychiatric Hospitalization or Arrest/Incarceration

Treatment with paliperidone palmitate was statistically superior to treatment with an oral antipsychotic in delaying the time to first psychiatric hospitalization or arrest/incarceration (p=0.019, eITT), with a hazard ratio (95% CI) of 1.43 (1.06, 1.93) based on the sponsor's analysis. The median time to first psychiatric hospitalization or arrest/incarceration was not estimable (> 450 days) in the paliperidone palmitate group and 274 days in the oral antipsychotics group.

In pITT analysis set, the result nearly reached a statistical significance (p-value =0.056) with a hazard ratio (95% CI) of 0.768 (0.585, 1.009).

2. Mean Change from Baseline in PSP Total Score to Month 15

The overall treatment comparison was not significant (p=0.689, eITT) between treatment groups. There was also no trend favoring paliperidone palmitate during the entire course of the trial. Since this hypothesis was not rejected, the fixed sequence gatekeeper procedure was stopped at this stage. Subsequent analyses of other secondary efficacy variables were considered exploratory.

3. Time to Psychiatric Hospitalization

There was no statistically significant finding in favor of paliperidone palmitate (p-value =0.551) in terms of time to psychiatric hospitalization.

4. Mean Change from Baseline in CGI-S to Month 15

There was no statistically significant difference between treatment groups in CGI-S score at Month 15.

Discussion of Primary Reviewers' Comments and Conclusions

The Primary Efficacy Endpoint

It was noticed that there was a significant number of patients (n=139) discontinued the study early without a identified treatment failure, and more patients from paliperidone palmitate group (n=81, 35.8%) discontinued early than those from oral antipsychotic group (n=58, 26.6%), which is very concerning to us. Most frequently reported reason for early discontinuation were "lost to follow up" (15% in paliperidone palmitate and 11.9% in oral antipsychotics), "withdrawal by subject" (11.5% in paliperidone palmitate and 7.3% in oral antipsychotics) and other (6.2% in paliperidone palmitate and 5.4% in oral antipsychotics). The more detailed information regarding why these patients withdrew or

lost follow up was not provided in the submission. Clearly, these patients were not followed diligently after discontinuation. The outcomes of these patients were unknown to the sponsor. Potentially they could be arrested/incarcerated or hospitalized. Based on the pre-specified criteria for treatment failure, these patients were counted as censored, not an event.

This sNDA were brought to CDER Regulatory Briefing on March 13, 2015 because the proposed claim, study population, and the open label, "real world" study design. The panel was very concerned interpretability of the efficacy data from this study because of the large early drop-out, especially the fact that more patients dropped out in paliperidone palmitate group than those in the oral antipsychotic group and the outcome of these patients after discontinuation was not followed. The panel pointed out in the meeting that in this kind of open-label, "real world" setting, if the sponsor did not follow-up the outcome of these patients who dropped out earlier, these patients should be categorized as the event, not censored during efficacy analysis.

Our statistician, Ququan Liu, PhD, did the following additional sensitive analyses on the primary efficacy endpoint using eITT set:

1. included all 139 patients who discontinued study early without event as treatment failure, and
2. included 102 patients who discontinued study because of "lost to follow-up" or "withdrawal by subject" as treatment failure.

Both analyses showed that there was no statistically significant difference in delaying time to treatment failure tween two treatment groups (p=0.28 and p=0.19, respectively). The analyses results were summarized in Table 2 and Table 3.

Table 2. Sensitivity Analysis of Time to First Treatment Failure (by treating all 139 early discontinuations as an event)

Time to Event	Paliperidone Palmitate	Oral Antipsychotics
Number assessed	226	218
Event	171	175
Censored	55	43
Kaplan-Meier Median, Days (95% CI)	143 (124, 190)	134 (94, 164)
Log-Rank Test P-value	0.2805	
HR (95% CI)	0.891 (0.721, 1.100)	

Source: Dr. Liu's review

Table 3. Sensitivity Analysis of Time to First Treatment Failure (by treating 102 early discontinuations for reason of lost to follow-up or patient withdrawal as an event

Time to Event	Paliperidone Palmitate	Oral Antipsychotics
Number assessed	226	218
Event	150	159
Censored	76	59
Kaplan-Meier Median, Days (95% CI)	268 (185, 386)	179 (129, 243)
Log-Rank Test P-value	0.1885	
HR (95% CI)	0.861 (0.689, 1.077)	

Source: Dr. Liu's review

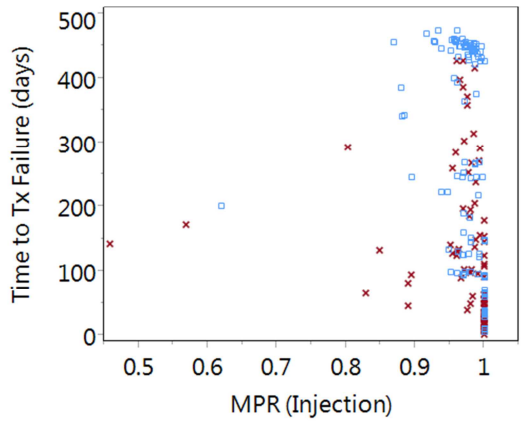
Key Secondary Endpoints

Among 4 proposed key secondary endpoints, only the 1st key secondary endpoint, time to first psychiatric hospitalization or arrest/incarceration, was statistically significantly in favor of paliperidone palmitate treatment. The rest 3 were considered negative findings. PSP and CGI-S are global functional assessments. There was no trend in these two measures favoring paliperidone palmitate treatment during the entire course of the trial. Because a large proportion of patients dropped the study earlier, the competing risks could potentially confound the analyses. Therefore, we consider the analyses for key secondary endpoints exploratory.

The Relationship between Medication Possession Ratio and Time to Treatment Failure

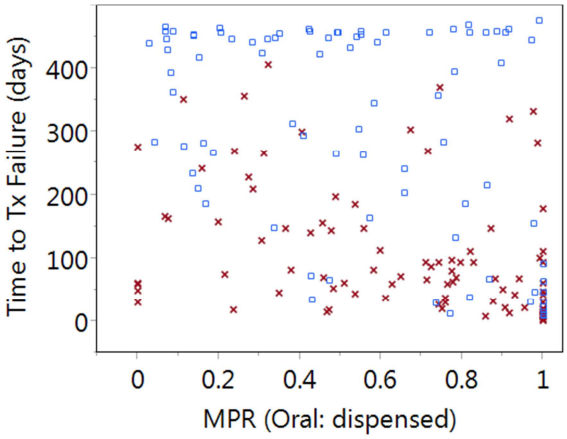
Our statisticians also explored the relationship between medication possession ratio (MPR, percentage of days covered by study medication) and time to treatment failure. No association between MPR and time to treatment failure was identified in both paliperidone palmitate and oral antipsychotic group, in either censored patients or those who had an event (see Figure 2 &3).

Figure 2. Time to Treatment Failure vs. MPR (paliperidone palmitate)



Source: Yang's slide in Reg. Briefing on 3/13/2015

Figure 3. Time to Treatment Failure vs MPR (oral antipsychotics)



Source: Yang's slide in Reg. Briefing on 3/13/2015

Efficacy Conclusion

Based on the sponsor's analyses, Study R092670-SCH-3006 appeared a positive trial—patients with paliperidone palmitate treatment had treatment failure later than patients who were on oral antipsychotic. However, once we included the patients who discontinued study early or discontinued study early due to "lost to follow-up" or "withdrawal by subject" as the events (treatment failure) in our analyses, paliperidone palmitate treatment was no longer superior to the oral antipsychotic treatment in delaying the time to treatment failure. Three out of 4 key secondary endpoints did not support that paliperidone palmitate treatment was superior to the oral antipsychotic treatment including 2 global functional measurements, PSP and CGI-S. Additionally, analysis on the relationship of medication possession ratio and the time to treatment failure did not see any trend either, i.e., the timing when patients had treatment failure was not related to whether patients received medication (percentages days covered by medication), or not in both treatment groups. We expected that patients who received or took medications most time would have treatment failure later. This also further question if the data from Study R092670-SCH-3006 are interpretable.

In summary, study R092670-SCH-3006 does not provide substantial evidence that paliperidone palmitate delays time to treatment failure compared to oral antipsychotic treatment in adults with schizophrenia who have been incarcerated.

The sponsor should consider conducting another confirmatory study with similar design addressing our concern regarding early discontinuation and diligently follow-up early drop-out patients. If the second study turned out a clear positive study, data from Study R092670-SCH-3006 could be used as supportive evidence.

SAFETY REVIEDW

The safety review is performed on Study R092670-SCH-3006 only. Because the study was an open label, flexible dosed, "real world" study, patients were allowed to take many concomitant medications during the study. Additionally the study completion rate was relatively low, significant number patients dropped study early, and high percentage of patients who were in oral antipsychotic arm were not compliant with their medications. Given all these reasons, the value of this safety review is limited. Glenn Mannheim MD is the medical reviewer. Please refer to his review for more information.

Exposure

A total of 448 patients were included in ITT set, the completion rate was 41% in the in the paliperidone palmitate group and 40.4% in the oral antipsychotics group.

The mean duration of exposure appeared similar between the 2 treatment groups (266.6 days for paliperidone palmitate and 271.5 days for the oral antipsychotic group). Exposure calculations for the oral antipsychotics group may have been overestimated, as data were based on prescription records.

Medication adherence was analyzed. There is a large disparity between availability and actual use with oral antipsychotics. Based on injection records (paliperidone palmitate) or prescriptions (oral antipsychotics), 95.2% of subjects in the paliperidone palmitate group and 78.6% of subjects in the oral antipsychotics group had a medication possession ratio (MPR) of >80%, and the mean medication gap (percentage of days not covered by study medication) was 5.3% and 10.9%, respectively - suggesting that a majority of subjects were prescribed adequate therapy. When the analysis was based on injection or refill (medication dispensed) records, however, 95.2% of subjects in the paliperidone palmitate group, but only 24.3% of subjects in the oral antipsychotics group, had a MPR >80%, and the mean medication gap was 5.3% and 48.2%, respectively.

Major Safety Results

Deaths

There was 1 death reported in Study R092670-SCH-3006. A 34 years old male patient in the paliperidone palmitate group died suddenly on Day 445 while (b) (6). An autopsy was performed on an unspecified date, reported that "a blood clot had moved from his leg". The investigator assessed the sudden death as doubtfully related to the study drug.

Serious Adverse Events

Serious treatment emergent adverse events (TEAEs) were reported for 18.6% of subjects in the paliperidone palmitate group and 24.3% of subjects in the oral antipsychotics

group. The majority of serious TEAEs in both treatment groups were related to patient underline psychiatric disorders, such as psychotic disorder, schizophrenia, suicidal ideation, and paranoid type schizophrenia.

Discontinuations Resulting from Adverse Events

TEAEs led to discontinuation from the study for 2.7% of subjects in the paliperidone palmitate group and 1.8% of subjects in the oral antipsychotics group. No individual TEAE led to study discontinuation in more than 1 subject in the paliperidone palmitate group.

Common Adverse Events

The safety profiles of paliperidone and paliperidone palmitate, and its parent compound risperidone, were well characterized and had been adequately described in product labelings, the scientific and medical literature. There was no new safety signals were identified from study R092670-SCH-3006.

Adverse events occurred more in paliperidone palmitate treatment than that in oral antipsychotics are:

- The frequency of body weight gain of ≥7% from baseline to the end of treatment was higher for paliperidone palmitate.
- Larger increases in serum prolactin levels were observed for paliperidone palmitate and the frequency of prolactin-related TEAEs was also higher among subjects treated with paliperidone palmitate. No differences were seen in clinician-rated SSEQ ratings of sexual side effects typically associated with increased prolactin levels.
- Injection site pain was only reported as a TEAE in subjects treated with paliperidone palmitate.
- Other TEAEs reported more frequently (≥ 2% difference) in the paliperidone palmitate group than in the oral antipsychotics group were insomnia, akathisia, anxiety, erectile dysfunction, fatigue, increased appetite, libido decreased, back pain, salivary hyper-secretion, nasal congestion, semen volume decreased, oropharyngeal pain, and galactorrhoea.

It is worth to mention that the oral antipsychotic group had poor medication adherence. Only 24.3% of subjects in the oral antipsychotics group had a MPR >80%. Relatively lower reported rate of adverse event in the oral antipsychotic group may be associated to poor medication adherence.

Safety Summary

No new safety signal associated with paliperidone palmitate was identified from Study R092670-SCH-3006. There were more adverse events reported in weight gain, prolactin-related TEAEs and increased prolactin levels, and akathisia in patients with paliperidone

palmitate treatment. But, as I mentioned earlier, oral antipsychotic group had poor medication adherence and the relatively lower reported adverse event rate in the oral antipsychotic group may be associated to poor medication adherence.

5. OSI Inspection

The Office of Scientific Investigations (OSI) inspected selected data from 3 clinical study sites: Jesse M. Carr, MD (Site 019, 23 subjects enrolled), Paul W. Murphy, M.D. (Site 007, 26 subjects enrolled) and Mary L. Stedman, MD (Site 016, 30 subjects enrolled).

At all three study sites, no significant deficiencies were observed and a Form FDA 483 was not issued. Minor deficiency observations were verbally discussed. The study conduct at all inspected study sites appeared adequate, including IRB oversight and sponsor monitoring of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the three inspected study sites appear reliable as reported in the NDA. The OSI reviewer, John Lee, M.D., concluded that data from these sites are reliable for further agency review.

6. Labeling

No labeling recommendation is necessary at this time because of the recommendation of non-approval action.

7. Pediatric Plan

No pediatric studies will be required.

8. Post Marketing Commitments or Requirements

No post marketing commitments are deemed necessary.

9. Risk Minimization Action Plan

No Risk Minimization Action Plan deemed necessary for this submission.

10. Conclusion and Recommendation

I agree with the conclusion from Drs. Glenn Mannheim MD, and Ququan Liu, PhD., that study R092670-SCH-3006 did not provide substantial evidence to demonstrate that paliperidone palmitate is superior to oral antipsychotics in delaying time to treatment failure in adults with schizophrenia who have been incarcerated. With current available data, I recommend that the Division takes a non-approval action on this sNDA.

I agree that improving medication adherence is an unmet medical need among schizophrenia patients, especially in incarcerated population. It is legitimate to study this population. However, we need substantial evidence to demonstrate the efficacy and we did not see it in this submission. The sponsor should consider conducting another

confirmatory study with similar design addressing our concern regarding early discontinuation and diligently follow-up these early drop-out patients. If the second study turns out a clear positive study, data from Study R092670-SCH-3006 can be used as supportive evidence.

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/s/

JING ZHANG
04/27/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	22264s015
Priority or Standard	Standard
Submit Date(s)	06/20/2017
Received Date(s)	06/20/2017
PDUFA Goal Date	12/20/2017
Division/Office	DPP / ODE1
Reviewer Name(s)	Daniel J. Lee, MD
Review Completion Date	12/18/2017
Established/Proper Name	paliperidone palmitate
(Proposed) Trade Name	Invega Sustenna
Applicant	Janssen Research & Development, LLC
Dosage Form(s)	39mg, 78mg, 117mg, 156mg, 234mg
Applicant Proposed Dosing Regimen(s)	39mg, 78mg, 117mg, 156mg, 234mg
Applicant Proposed Indication(s)/Population(s)	Maintenance treatment of schizophrenia
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Maintenance treatment of schizophrenia

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Paliperidone palmitate is an injectable atypical antipsychotic originally approved on July 31, 2009 (NDA 21999). It is currently approved for the treatment of adult and adolescent schizophrenia and schizoaffective disorder. Approved dosages of monthly paliperidone palmitate include 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg.

With this resubmission, the Applicant seeks to add results from the completed 15-month, schizophrenia relapse-prevention trial to the clinical trials section of the U.S. package insert (USPI). The Applicant proposed [redacted] (b) (4) During the first review cycle, discussion occurred regarding [redacted] (b) (4) paliperidone palmitate's schizophrenia maintenance indication by describing the trial in labeling. Trial data submitted in this application represent a "real-world" application of paliperidone palmitate's approved indication for schizophrenia maintenance to the unique and underserved patient population of recently incarcerated individuals with schizophrenia. This is notable because recently incarcerated individuals are often excluded from clinical trials due to chaotic living situations after release from confinement and higher likelihood of being lost to follow up.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant conducted Study SCH-3006 using approved reference drug in dosages approved for commercial sale. Paliperidone palmitate demonstrated substantial evidence of efficacy against an active control within the target population. The Applicant observed greater durability of treatment effect with paliperidone palmitate for schizophrenia maintenance than was observed with active control. Benefit obtained with paliperidone palmitate was statistically significant and clinically meaningful versus active control at all follow up time points.

Recognizing the challenges associated with a long-term, "real world" trial involving recently incarcerated individuals, we accepted the composite endpoint of treatment failure a priori. Unfortunately, disparities between the frequency and clinical importance of individual outcomes included in treatment failure confounded primary endpoint data and significantly limited the conclusions which could be drawn using the primary endpoint (1-7). To mitigate data confounding, I broke the primary endpoint into its components and analyzed the Applicant's data using different statistical methods. I noted superiority of paliperidone palmitate versus the amalgamation of seven oral antipsychotics when comparing:

- absolute risk reduction for individual and grouped outcomes beyond the risk reduction established by oral antipsychotics
- time to treatment failure endpoint
- number of participants reaching treatment failure by 15 months
- number of participants arrested or incarcerated by 15 months
- number of participants psychiatrically hospitalized by 15 months
- number of participants discontinuing treatment due to loss of efficacy by 15 months

All my experimental analyses supported the Applicant's primary conclusion. Paliperidone palmitate's superiority to the amalgamation of seven oral antipsychotics likely resulted from better adherence to treatment. Adherence rates favored paliperidone palmitate by 71% (95% vs 24%).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Schizophrenia is a severe psychiatric illness with an estimated prevalence of 0.7%-1% worldwide (8). Absent continuous treatment with an antipsychotic, psychotic episodes typically become more difficult to treat, requiring higher doses of antipsychotic or polypharmacy to control (9-14). Untreated schizophrenia often leads to cognitive disorders and permanent disability, particularly for individuals with severe negative symptoms upon emergence of initial symptoms or individuals with severe negative symptoms persisting despite treatment with an antipsychotic (9-14). Despite knowledge of disease progression without treatment, patients with schizophrenia are often poorly adherent to antipsychotic medication (9-14). The Applicant's finding of 24% adherence to daily oral antipsychotic medication at 15 months is similar to adherence rates observed in clinical trials focused on adherence (9-14).

Patients treated with paliperidone palmitate in SCH-3006 demonstrated statistically significant and clinically meaningful benefit over benefit observed for participants treated with one of seven daily oral antipsychotics at all follow up time points. Superiority was noted when comparing absolute risk reduction for individual outcomes beyond the risk reduction established by active control, number of participants reaching treatment failure by 15 months, number of participants arrested or incarcerated by 15 months, number of participants psychiatrically hospitalized by 15 months, and number of participants discontinuing treatment due to loss of efficacy by 15 months. Drug satisfaction and quality of life measurements were similar between groups.

Paliperidone palmitate's superiority to active control likely resulted from better adherence to treatment. Adherence rates favored paliperidone palmitate by 71% (95% vs 24%). Results of this application validate current clinical practice. No unanticipated safety concerns emerged during this trial beyond concerns already summarized in paliperidone palmitate's label. Given the absence of new safety concerns and the significant clinical benefit experienced by participants treated with paliperidone palmitate, I deemed submitted data to support approval and incorporation into labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Schizophrenia is a severe, progressive neurodegenerative psychiatric illness affecting roughly 0.7% of the world's population (8). • Left untreated, schizophrenia often leads to cognitive decline and disability (8). • Patients treated early in the disease process and patients remaining adherent to pharmacological treatment experience better outcomes (9-14). • Clinicians cannot predict schizophrenia prognosis at the time of initial diagnosis (8). Approximately 20% of individuals with schizophrenia experience favorable courses and 80% experience worsening of symptoms, treatment resistance, or progression of disease (8). • Very few individuals with schizophrenia recover completely (8-14). Symptoms often wax and wane throughout the lives of individuals with schizophrenia	• Epidemiologic and clinical trials observe that relapse through non-adherence decreases rates of response to treatment, particularly response to previously effective drugs (8-14). • Antipsychotic adherent patients with schizophrenia are less likely to require polypharmacological treatment for control of symptoms (9-14). • Expanding interventions that improve adherence to prescribed antipsychotics is critically important to the public health.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(8-14). • Symptoms such as delusions, hallucinations, grossly disorganized behavior, disorganized speech, and avolition profoundly influence an individual's ability to maintain proper self-care, employment, and interpersonal relationships (8). • The cause of schizophrenia is unknown (8). • Approximately 5-6% of individuals with schizophrenia die by suicide and approximately 20% attempt suicide at least once (8). • Poor adherence to pharmacological treatment is common in this patient population (9-14).	
Current Treatment Options	• FDA-approved long-acting formulations of antipsychotic drugs include haloperidol, fluphenazine, risperidone, paliperidone, aripiprazole, aripiprazole lauroxil, and olanzapine. • Antipsychotics, particularly in the doses necessary to treat schizophrenia, are associated with significant side effect burden and poor tolerability. • Required frequency of long-acting parenteral antipsychotic administration ranges from weekly to quarterly. • Administration of a long-acting antipsychotic requires a trained clinician for administration and post-injection monitoring. • Adherence to depot antipsychotics is relatively easy to monitor, as clinicians know when they administered the injection. • FDA-approved oral formulations of antipsychotic drugs include	• Successful treatment of schizophrenia requires early treatment and long-term adherence to antipsychotic drugs in most cases (8-14). • Poor antipsychotic tolerability often drives non-adherence. • Without adequate control of positive symptoms (delusions, hallucinations, etc.), psychotherapy and rehabilitation targeted at negative symptoms (avolition, cognitive deficits, etc.) are ineffective. • Reduced antipsychotic effectiveness from non-adherence often leads to need for higher antipsychotic drug dosing, polypharmacy, and ECT to achieve symptom control. • Higher doses of antipsychotic medication and polypharmacy significantly increase risk of harm from long-term exposure. • The advantage of using long-acting antipsychotics is the predictable timeframe in which clinicians and caregivers know repeat dosing is required.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, prochlorperazine, thioridazine, thiothixene, trifluoperazine, aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. • Adjunctive treatment options for patients with schizophrenia include interpersonal psychotherapy, social skills training, family psychotherapy, vocational rehabilitation and supported employment (8). • Clinicians sometimes use electroconvulsive therapy (ECT) in patients not responsive to antipsychotic drugs. However, ECT response rates in these patients are generally poor (9-14).	
Benefit	• Antipsychotic drugs control symptoms of schizophrenia in most patients and are thought to prevent disease progression (8-14). • Control of schizophrenia symptoms and prevention of disease progression leads to better quality of life, higher rates of employment, and better interpersonal function (8-14). • In the submitted trial, participants treated with paliperidone palmitate demonstrated 71% better adherence to treatment versus oral antipsychotics (95% vs 24%). • Extrapolating from the submitted trial, treatment with paliperidone palmitate potentially prevents an additional 8% of recidivism cases, an additional 5% of worsening mental illness cases, and an additional 4% of loss of efficacy cases beyond those prevented by commonly	• Paliperidone palmitate likely prevented adverse outcomes in SCH-3006 by improving treatment adherence. • Reductions in the rate of hospitalization, disease worsening, and incarceration translate into greater life stability for many patients with schizophrenia. • Routine use of long-acting antipsychotics, like paliperidone palmitate, in this sub-population likely translates into wider availability of mental health resources at the population level. Individuals in this sub-population are likely to be high volume consumers of health care resources, particularly when they are non-adherent to treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	used oral antipsychotics in a population of recently incarcerated individuals with schizophrenia • Schizophrenia outcomes are improved by antipsychotic treatment (8-14).	
Risk and Risk Management	• Rates of paliperidone palmitate discontinuation due to loss of tolerability and unsafe side effects are double observed discontinuation rates for patients randomized to oral antipsychotic treatment. While this is likely an artifact of oral antipsychotic non-adherence, it demonstrates the poor tolerability of available antipsychotics. • Chronic exposure to antipsychotics increases the risk of developing tardive dyskinesia, metabolic disorder, and other side effects. • The safety of chronic paliperidone exposure is well-characterized due to long-term clinical trials and post-marketing surveillance.	• While once widely accepted that parenterally administered depot antipsychotics improved treatment adherence, recent trials cast doubt upon this assertion (9-13). Newer trials suggest parentally administered depot antipsychotics merely delay non-adherence (9-13). • Chronic exposure to oral antipsychotics carries the similar risks associated with chronic exposure to long-acting injectable antipsychotics. • Monitoring for chronic antipsychotic-related adverse effects is widespread and well understood. Guidelines exist for monitoring of metabolic adverse events and tardive dyskinesia.

1.4. Patient Experience Data

The Applicant submitted no patient experience data.

2. Therapeutic Context

2.1. Analysis of Condition

Please see *Section 1.3 Risk Benefit Assessment* for condition details pertaining to this application.

2.2. Analysis of Current Treatment Options

Please see *Section 1.3 Risk Benefit Assessment* for current treatment details pertaining to this application.

Table 1: Summary of FDA-Approved Long-Acting Antipsychotics

Product (s) Name	Relevant Indication	Dosing/ Administration
haloperidol decanoate	Schizophrenia	50 mg or 100 mg injection monthly
fluphenazine decanoate	Schizophrenia	12.5 mg to 100 mg injection monthly
risperidone	Schizophrenia and Bipolar I Disorder	12.5 mg, 25 mg, 37.5 mg, or 50 mg injection every two weeks
paliperidone palmitate (1-month formulation)	Schizophrenia and Schizoaffective Disorder	39 mg, 78 mg, 117 mg, 156 mg, or 234 mg injection monthly
paliperidone palmitate (3-month formulation)	Schizophrenia	273 mg, 410 mg, 546 mg, or 819 mg injection quarterly
aripiprazole	Schizophrenia and Bipolar I Disorder	300 mg or 400 mg injection monthly
aripiprazole lauroxil	Schizophrenia and Bipolar I Disorder	441 mg, 662 mg, or 882 mg injection monthly; 882 mg injection every six weeks; 1064 mg injection every two months
olanzapine pamoate	Schizophrenia	150 mg-300 mg injection every two weeks; 405 mg injection monthly

Source: Reviewer Constructed

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Paliperidone received U.S. approval for the acute treatment of adults with schizophrenia in December, 2006, and for maintenance treatment of adults with schizophrenia in April, 2007, (NDA 21999). These indications broadened to include adjunctive treatment for adults with schizoaffective disorder in August, 2009, and treatment of adolescents aged 12-17 in April, 2011.

A monthly depot formulation received U.S. approval for acute and maintenance treatment of adults with schizophrenia in July, 2009 (NDA 22264). This indication was subsequently shortened to schizophrenia in August, 2012. A quarterly depot formulation received U.S. approval for the treatment of schizophrenia in clinically stable patients adequately treated with monthly paliperidone palmitate for at least four months in May 2015 (NDA 207946). FDA-approved paliperidone dosing ranges from 3mg-12mg per day for the oral formulation. Specific dosages of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg received approval for the monthly depot formulation. Approved dosages for the quarterly depot formulation are directly determined by the last-used monthly depot dosage. Monthly injections of 78 mg, 117 mg, 156 mg, and 234 mg translate into quarterly injections of 273 mg, 410 mg, 546 mg, and 819 mg, respectively. Currently-approved paliperidone formulations include oral extended-release tablets and two different aqueous suspensions intended for intermuscular injection.

3.2. Summary of Presubmission/Submission Regulatory Activity

This application is a Class 2 resubmission for Supplement 015 to NDA 022264. The Applicant's original submission was received on July 11, 2014. Following the initial review cycle, the Division issued a Complete Response (CR) letter in May 2015. The CR letter expressed concern regarding the higher rate of drop-out in the paliperidone palmitate arm versus the oral antipsychotic arm. The Division observed that if attrition differed between groups due to outcomes of interest, such as suicide, hospitalization, or incarceration, the potential for a negative clinical trial result still existed.

Subsequently, the Division met with the Applicant on January 14, 2016, to discuss methods of addressing missing data in preparation for re-submission. The Division recommended that the Applicant clarify the disposition of participants lost to follow up. Agreement was reached that the Applicant would attempt to contact participants, responsible friends, or participant families again. Individuals who could not be reached would be cross-referenced with publicly available police records and death records. The Applicant submitted its plan and design questions for addressing missing data to the Division on May 26, 2016, and received concurrence from the Division regarding the plan on July 17, 2016.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

From the prospective of OSI, the Applicant adequately responded to all deficiencies laid out in the Complete Response letter at the time of re-submission.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable.

4.5. Clinical Pharmacology

Not applicable.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Table of Clinical Trials

Phase	Trial	Participants	Trial Design	Duration
4	**SCH-3006**	**450**	**randomized, controlled, open-label**	**15 months**

Source: Reviewer Constructed

5.2. Review Strategy

As stated above, I focused on paliperidone palmitate's absolute risk reduction for individual pre-specified adverse outcomes beyond the risk reductions observed with active control. I calculated absolute risk reduction for individual adverse outcomes and then grouped data by clinically meaningful adverse outcomes. My rationale for grouping data by clinically meaningful adverse outcomes was mitigation of treatment effect dilution created by dividing data into overly narrow categories.

In my view, the Applicant's data logically combines into four over-arching categories: (1) recidivism, (2) worsening of mental illness, (3) loss of treatment efficacy, and (4) loss of treatment tolerability. This is because:

- There is little clinical distinction between patients being arrested or incarcerated. Clinicians typically respond similarly to these outcomes by focusing on lowering the probability that their patient(s) will have future negative interactions with law enforcement.
- Suicide attempts, suicidal ideation, need for psychiatric hospitalization, and need for more intensive psychiatric services all signal that psychiatric symptoms are not controlled and intensification of treatment is needed. Clinicians typically respond similarly to these outcomes by providing more psychiatric care than was being provided previously.
- Discontinuation of an antipsychotic due to inadequate treatment response and the addition of a second antipsychotic due to inadequate response both signify the loss of treatment efficacy.
- Discontinuation of an antipsychotic for safety reasons and discontinuation of an antipsychotic due to a significant side effect both signify the loss of treatment tolerability.

Prior to intensive review of outcome data, I visually inspected initial demographic, clinical, and adverse outcome data side-by-side to determine if participants lost to follow up differed

fundamentally from other trial participants in any way. Next, I moved to comparing recidivism, worsening of mental illness, loss of treatment efficacy, and loss of treatment tolerability between treatment and control separately for the original data and the drop-out data. I did not combine the original data with the drop-out data because the Applicant collected these data at different times and in a different manner than was done with the original data; I anticipated the introduction of confounding with any attempt to combine them. Instead, I focused on analyzing data from the first review cycle if drop-out data agreed with the original data. Ultimately, I found no contradictions or differing trends between the original data and the drop-out data and no exploratory analyses were needed.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated (SCH-3006)

6.1.1. Study Design

***Note: Trial design received prior review on April 22, 2015, by Glenn Mannheim, MD. Details pertinent to this re-submission are discussed below.**

Overview and Objective

The Applicant performed a 15-month, open-label, equipoise-stratified, multi-site, randomized clinical trial using recently incarcerated individuals with schizophrenia. After participant randomization to long-acting antipsychotic or one of seven oral antipsychotics, investigators monitored participants for pre-specified adverse outcomes and time to adverse outcomes to determine if antipsychotic formulation impacted time to occurrence of adverse outcomes.

Trial Design

The Applicant randomized 450 participants to monthly paliperidone palmitate injections or daily oral aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone tablets. Oral drugs were assigned by a computer program using only drugs the participant deemed acceptable. Randomization took place following a wash-out and confirmation of diagnosis phase. Investigators adjusted dosages of both paliperidone palmitate and oral antipsychotic based on tolerability and efficacy per clinical convention within the protocol-specified range during the trial.

A Treatment Failure Event Monitoring Board (TFEMB) blinded to participant group assignment determined the occurrence and date of first treatment failure event used in creating the primary composite endpoint. The Applicant performed secondary analyses using first treatment failure events identified by investigators.

Primary Study Endpoint

Treatment Failure, which was a composite endpoint comprised of arrest, incarceration, psychiatric hospitalization, suicide, need for increased psychiatric services, need for a second antipsychotic, treatment discontinuation due to loss of efficacy, treatment discontinuation for safety, and treatment discontinuation due to side effect or intolerance.

Secondary Study Endpoints

- time to first psychiatric hospitalization [Key Secondary Endpoint per Applicant]
- time to either first psychiatric hospitalization or first recidivism [Key Secondary Endpoint per Applicant]
- time to first recidivism
- change from baseline using the Personal and Social Performance Scale (PSP) total score
- change from baseline using the Clinical Global Impression-Severity (CGI-S) score

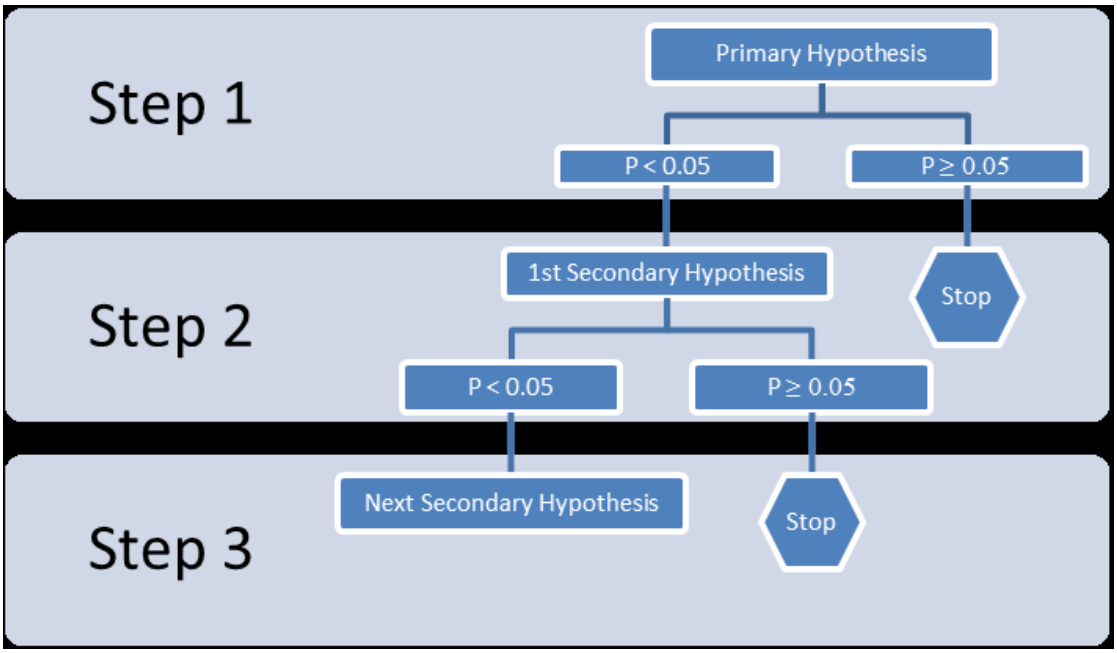
Statistical Analysis Plan

FDA agreed to the Applicant's final statistical plan. The Applicant controlled the Type I error rate for testing of primary and key secondary hypotheses at the 2-sided 0.05 significance level using a fixed-sequence gatekeeper approach as recommended in *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. The Applicant tested all other exploratory hypotheses at the 2-sided 0.05 significance level without adjustments for multiplicity.

The Applicant estimated time to treatment failure using the Kaplan-Meier method and both calculated the 95% confidence intervals and estimated hazard ratios using a Cox proportional hazards model with treatment as a fixed factor. In the event a proportional hazard assumption did not hold, a switch to the generalized Wilcoxon test for testing the primary hypothesis was permitted.

The Applicant defined the intention-to-treat (ITT) population as including all participants receiving at least one dose or injection of assigned drug. Analyses using only trial completers did not occur and were not planned. The Applicant accounted for missing data using last observation carried forward (LOCF).

Figure 1: The Applicant's Planned Analysis of Endpoints for Trial SCH-3006



Source: Applicant Document R092670: Statistical Analysis Plan R092670-SCH-3006

Protocol Amendments

The protocol for SCH-3006 received three major amendments, dated July 7, 2010; March 15, 2011; and April 12, 2012. These amendments focused on:

- enhancing data acquisition for participants lost to follow up
- clarifying methods for re-starting treatment for participants lost to follow up for several months
- clarifying procedures for treatment failure data acquisition and documentation for participants attending all established follow up appointments
- clarifying how data were to be reported to the Applicant
- common sense expansions of inclusion criteria
- permitting supplementary oral paliperidone for participants randomized to paliperidone palmitate and requiring a higher dose than originally permitted prior to the third injection
- increasing the recommended maintenance dose for paliperidone palmitate
- clarifying the definitions of individual primary and secondary endpoints

Changes made to paliperidone and paliperidone palmitate dosing had the greatest potential to impact trial results. It appears some participants received sub-therapeutic doses of paliperidone palmitate for much of the trial's first year, increasing the probability of committing a Type II error. Clarification of endpoint definitions occurred soon after trial initiation and likely had a

minor impact on trial results due to potential for confounding from differing outcome criteria definitions. Other changes made are unlikely to have significantly impacted trial results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests to conducting SCH-3006 in accordance with good clinical practices (GCP).

Financial Disclosure

For details regarding the Applicant's one reported disclosure, please see the first clinical review of this product by Glenn Mannheim, dated April 22, 2015.

Protocol Violations/Deviations

***Note: Data quality received prior review on April 22, 2015, by Glenn Mannheim. That review opines that "Sample case report forms and reported adverse event information appeared to be consistent." Due to the focus on missing data and the Complete Response letter, discussion of protocol violations and deviations did not appear in the 2015 review.**

SCH-3006 experienced a higher than anticipated number of major protocol deviations and violations (Table 3). In total, 33% of enrolled participants experienced one or more major protocol deviations. Protocol revisions likely played a role in the high rate of protocol deviations; SCH-3006 had three major protocol amendments in three years which altered outcome monitoring, drug dosing, and data reporting during the trial. Additionally, the Applicant excluded six randomized participants from the intention-to-treat (ITT) analysis due to protocol violations found during routine audit of one clinical site. Significant protocol deviations included:

- Participants enrolling without confirmation a schizophrenia diagnosis (10%)
- Participants receiving the wrong treatment or dose (1%)
- Participants completing end of trial final assessment prior to the scheduled end of the trial (7%)
- Improper refrigeration of paliperidone palmitate (2% in the paliperidone palmitate arm)
- Assessments being performed by an unqualified individual (2%)
- Missed assessment of primary endpoint event, missed lab draw, or missed psychometric scale (11%)

While potentially counterintuitive, the large number of protocol deviations strengthen my conclusions regarding paliperidone palmitate efficacy. The deviations and errors reported

increased the probability of the Applicant committing Type II error by undermining paliperidone palmitate's statistical ability to differentiate from oral antipsychotics. Specifically:

- Recruiting individuals without schizophrenia leads to lower baseline symptom scores and decreased ability to demonstrate differing change between arms over time
- Assessing final outcomes prior to 15 months decreases the amount of time afforded to treatment to differentiate from control
- Improper refrigeration of paliperidone results in administration of less effective treatment drug
- Accounting for missing data using LOCF typically results in smaller effect sizes than other methods such as random effects or linear regression
- Failure to conduct an oral paliperidone tolerance test or obtain documented evidence of paliperidone tolerance prior to administration of paliperidone palmitate increases the risk of adverse events for treatment-naïve individuals. Increased drug-related adverse events typically increase drop-out in the offending group. Because adverse events with long-acting antipsychotics are prolonged, drop-out in this group is more likely, reducing power to demonstrate an effect versus control

Table 3: Major Protocol Deviations for SCH-3006

Major Protocol Deviation Summary						
Intervention	**Total N**	**# with a major deviation**	**Entered trial without meeting entry criteria**	**Received wrong treatment or incorrect dose**	**Received excluded concomitant drug**	**Other***
Paliperidone Palmitate	**226**	**73 (32.3%)**	**18 (8%)**	**3 (1.3%)**	**1 (0.4%)**	**58 (25.7%)**
Oral Antipsychotics	**218**	**73 (33.5%)**	**25 (11.5%)**	**1 (0.5%)**	**0 (0%)**	**55 (25.2%)**
Total	**444**	**146 (32.9%)**	**43 (9.7%)**	**4 (0.9%)**	**1 (0.2%)**	**113 (25.5%)**
***Breakdown of Notable Protocol Deviations Classified as "Other"**						
Intervention	**Final visit <458 days after baseline**	**Missing study visit or visit out of window**	**Drug kit not stored within required temperature range**	**MINI or assessment performed by unqualified individual**	**Oral tolerance test not done or antipsychotic taper done incorrectly**	**Treatment failure, lab draw, or other assessment not performed at visit**
Paliperidone Palmitate	**15 (6.6%)**	**4 (1.8%)**	**4 (1.8%)**	**1 (0.4%)**	**1 (0.4%)**	**23 (5.2%)**
Oral Antipsychotics	**15 (6.9%)**	**5 (2.3%)**	**0 (0%)**	**8 (3.7%)**	**4 (1.8%)**	**26 (11.9%)**
Total	**30 (6.8%)**	**9 (2.0%)**	**4 (0.9%)**	**9 (2.0%)**	**5 (1.1%)**	**49 (11.0%)**

Source: Reviewer Constructed

Demographic Information

Table 4: Table of Demographic Characteristics

Drop-Out Population Demographics												
	N	Mean Age (Years)	Male Gender	Female Gender	White Race	Black / AA Race	Other Race	Days Since Last Incarcer-ation	Lifetime Hospital-izations	Mean Total PSP	Mean CGI-S	History of SA
Paliperi-done Palmitate	81	37.2 (10.13)	67 (82.7%)	14 (17.3%)	22 (27.2%)	57 (70.4%)	2 (2.4%)	33.1 (33.78)	9 (26.08)	55.8 (12.77)	3.7 (0.78)	71 (87.7%)
Active Control	58	37.9 (9.99)	50 (86.2%)	8 (13.8%)	22 (37.9%)	33 (56.9%)	3 (5.2%)	39.4 (32.18)	4.7 (4.23)	54.3 (13.55)	3.8 (0.67)	51 (87.9%)
Total	139	37.5 (10.04)	117 (84.2%)	22 (15.8%)	44 (31.7%)	90 (64.7%)	5 (3.6%)	35.8 (33.15)	7.2 (19.93)	55.2 (13.07)	3.7 (0.73)	122 (87.8%)
Original Submission Trial Population Demographics												
	N	Mean Age (Years)	Male Gender	Female Gender	White Race	Black / AA Race	Other Race	Days Since Last Incarcer-ation	Lifetime Hospital-izations	Mean Total PSP	Mean CGI-S	History of SA
Paliperi-done Palmitate	226	37.7 (10.57)	193 (85.4%)	33 (14.6%)	73 (32.3%)	145 (64.2%)	8 (3.5%)	38.9 (50.29)	7.3 (16.42)	54.8 (12.82)	3.8 (0.80)	209 (92.5%)
Active Control	218	38.6 (10.36)	190 (87.2%)	28 (12.8%)	74 (34.1%)	130 (59.9%)	13 (6.0%)	45.7 (53.04)	5.7 (5.58)	54.9 (12.74)	3.9 (0.70)	204 (93.6%)
Total	444	38.1 (10.47)	383 (86.3%)	61 (13.7%)	147 (33.2%)	275 (62.1%)	21 (4.7%)	42.2 (51.71)	6.5 (12.35)	54.9 (12.76)	3.8 (0.75)	413 (93.0%)

Abbreviations: African American (AA); Personal and Social Performance scale (PSP); Clinical Global Impression of Severity (CGI-S); Substance Abuse (SA); Source: Reviewer Constructed

No significant demographic or disease severity differences existed between the original submission trial population and the drop-out population. The greatest distinction between the full trial and the drop-out population was a one week difference in mean days since last incarceration with the drop-out population having been more recently incarcerated. I do not believe this difference impacted drop-out in any way.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Please see *Table 4: Table of Demographic Characteristics* for full details.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

***Note: Due to the focus on missing data and the Complete Response letter, discussion of treatment compliance, concomitant medication, and rescue medication did not appear in the 2015 review.**

A. Compliance

The Applicant evaluated treatment adherence by computing medication possession ratio (MPR) and medication gap for each intervention. The Applicant defined MPR as the number of days participants potentially received treatment based upon prescribed medication divided by the total number of days within a given treatment interval. For example, if a participant received a prescription for 30 once-daily tablets of aripiprazole and waited one week to fill the prescription, the participant's 30-day MPR equates to 77% [23 out of 30].

Medication gap evaluated the inverse of MPR. The Applicant defined medication gap as the number of days between refills or injections in the observation period, divided by time between the first and the last fills of the randomized oral antipsychotic or injection. In the above example, the participant's medication gap equates to 23% [7 out of 30]. Positive and negative medication gaps existed due to potential for early and late refill.

Ninety-five percent of participants randomized to paliperidone palmitate demonstrated MPRs >80% based on injection records. Participants randomized to oral antipsychotics demonstrated differing percentages of MPRs >80% based on method of confirmation. Seventy-nine percent demonstrated MPRs >80 based on written prescriptions. Rates fall to 24% of participants if refill records are used. Mean medication gaps observed using prescriptions were 5.3% for paliperidone palmitate and 10.9% for oral antipsychotics, respectively. Mean medication gaps observed using refill records were 5.3% for paliperidone palmitate and 48.2% for oral antipsychotics, respectively.

B. Concomitant Medications

Table 5: Concomitant Medications During Trial SCH-3006

Concomitant Medications by Group Assignment			
Concomitant Medication Drug Class	**Paliperidone Palmitate (n=226)**	**Active Control (n=218)**	**Total (n=444)**
# with Concomitant Psychoactive Medication	**168 (74.3%)**	**175 (80.3%)**	**343 (77.3%)**
Typical Anti-psychotic	**25 (11.1%)**	**28 (12.8%)**	**53 (11.9%)**
Atypical Anti-psychotic	**101 (44.6%)**	**111 (50.9%)**	**212 (47.7%)**
Depot Anti-Psychotic	**4 (1.8%)**	**9 (4.1%)**	**13 (2.9%)**
Anti-depressant	**84 (37.2%)**	**90 (41.3%)**	**174 (39.2%)**
Mood Stabilizer	**39 (17.3%)**	**37 (17.0%)**	**76 (17.1%)**
Anti-seizure (Not Mood Stabilizer)	**52 (23%)**	**42 (19.3%)**	**94 (21.2%)**
Benzo-diazapine	**45 (19.9%)**	**49 (22.5%)**	**94 (21.2%)**
Non-Benzo-diazepine Anxiolytic	**33 (14.6%)**	**23 (10.6%)**	**56 (12.6%)**
Beta Blocker	**33 (14.6%)**	**27 (12.4%)**	**60 (13.5%)**
Stimulant	**4 (1.8%)**	**0 (0%)**	**4 (0.9%)**
Anti-histamine	**45 (19.9%)**	**55 (25.2%)**	**100 (22.5%)**

Source: Reviewer Constructed

C. Rescue Medication Use

Not applicable.

Efficacy Results – Primary Endpoint

Overall, results favored paliperidone palmitate in all major outcomes measured except for rates of adverse events necessitating treatment discontinuation. Paliperidone palmitate demonstrated an absolute risk reduction (ARR) between 0.07 and 0.08 for recidivism, 0.05 for worsening of mental illness, and 0.04 for treatment changes required by loss of efficacy compared with active control. It is important to emphasize that paliperidone palmitate demonstrated these effects versus other FDA-approved drugs for the same indication. Paliperidone palmitate reduced the risk of participants experiencing specific pre-specified adverse outcomes by 4-8% beyond the statistically significant risk reduction observed in the amalgamation group of seven FDA-approved oral antipsychotics.

I am reasonably confident that much of paliperidone palmitate's performance in the trial is attributable to improved treatment adherence. The Applicant reports verifying adherence using pharmacy refills and prescriptions written with measured adherence rates favoring paliperidone palmitate by 71% (95% vs 24%). Improved treatment adherence also provides a plausible explanation for the higher rates of adverse event-related treatment discontinuations with paliperidone palmitate. I would not expect non-adherent participants to derive benefit or experience adverse events from a drug they are not taking.

I am also reasonably confident that missing data did not occur because of differential occurrence rates of suicide, psychiatric hospitalization, incarceration, or arrest between groups. While the exact cause of disproportionate drop-out in the paliperidone palmitate group versus active control is uncertain, potential explanations include the higher rate of documented adverse events in the paliperidone palmitate group or improved function in the paliperidone palmitate group due to better treatment adherence. Improved function in interpersonal relationships and occupational functioning often leads to fuller schedules and more items competing for participant time and interest. Submitted data is unhelpful in distinguishing between the two potential explanations because no difference was found between groups for satisfaction with treatment, global impression of severity, or global impression of improvement.

Results Obtained by Breaking Treatment Failure into Clinically Meaningful Outcomes

Table 6: Paliperidone Palmitate Absolute Risk Reduction Grouped by Clinically Meaningful Outcome

First Adverse Event from Randomization to Any Time Post Treatment or Discontinuation Grouped by Clinically Meaningful Outcome						
Clinically Meaningful Outcome	**Paliperidone Palmitate (ITT N=226 / Drop-Out N=81)**	**Oral Antipsychotic (ITT N=218 / Drop-Out N=58)**	**Total (ITT N=444 / Drop-Out N=139)**	**Risk Ratio (95% CI)**	**Absolute Risk Reduction vs. Oral Antipsychotics**	**Absolute Risk Increase vs. Oral Antipsychotics**
Total Recidivism (Original ITT)	**48 (21.2%)**	**64 (29.4%)**	**112 (25.2%)**	**0.72 (0.52-1.00)**	**0.08**	**-**
Total Recidivism (Drop-Out Analysis)	**31 (38.3%)**	**26 (44.8%)**	**57 (41.0%)**	**0.85 (0.57-1.27)**	**0.07**	**-**
Total Worsening of Mental Illness (Original ITT)	**21 (9.3%)**	**30 (13.7%)**	**51 (11.5%)**	**0.68 (0.40-1.14)**	**0.05**	**-**
Total Worsening of Mental Illness (Drop-Out Analysis)	**2 (2.5%)**	**4 (6.9%)**	**6 (4.3%)**	**0.36 (0.07-1.89)**	**0.05**	**-**
Total Loss of Efficacy (Original ITT)*	**6 (2.6%)**	**15 (6.9%)**	**21 (4.8%)**	**0.39 (0.12-0.98)**	**0.04**	**-**
Total Loss of Tolerability (Original ITT)*	**15 (6.6%)**	**8 (3.7%)**	**23 (5.2%)**	**1.81 (0.78-4.18)**	**-**	**0.03**
Missing Data in Drop-Out Analysis	**13 (16.0%)**	**4 (6.9%)**	**17 (12.2%)**	**2.33 (0.80-6.78)**	**-**	**0.09**

*Not tracked in drop-out population; Abbreviations: Intent-to-Treat (ITT), Confidence Interval (CI); Source: Reviewer Constructed. Computations Performed Using Applicant's Raw Data.

Results Obtained by Breaking Treatment Failure into Individual Sponsor Proposed Outcomes

Table 7: Paliperidone Palmitate Absolute Risk Reduction Grouped by Individual Outcome

First Adverse Outcome from Randomization to Any Time Post Treatment or Discontinuation Grouped by Individual Sponsor Proposed Outcomes						
Outcome	**Paliperidone Palmitate (ITT N=226 / Drop-Out N=81)**	**Oral Antipsychotic (ITT N=218 / Drop-Out N=58)**	**Total (ITT N=444 / Drop-Out N=139)**	**Risk Ratio (95% CI)**	**Absolute Risk Reduction**	**Absolute Risk Increase**
Arrest/Incarceration (Original ITT)	**48 (21.2%)**	**64 (29.4%)**	**112 (25.2%)**	**0.72 (0.52-1.00)**	**0.08**	**-**
Arrest/Incarceration (Drop-Outs)	**31 (38.3%)**	**26 (44.8%)**	**57 (41.0%)**	**0.85 (0.57-1.27)**	**0.07**	**-**
Hospitalization (Original ITT)	**18 (8.0%)**	**26 (11.9%)**	**44 (9.9%)**	**0.67 (0.38-1.18)**	**0.04**	**-**
Hospitalization (Drop-Outs)	**2 (2.5%)**	**4 (6.9%)**	**6 (4.3%)**	**0.36 (0.07-1.89)**	**0.05**	**-**
Suicide (Original ITT)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**N/A**	**N/A**	**N/A**
Suicide (Drop-Outs)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**N/A**	**N/A**	**N/A**
Need for Increased Psychiatric Services (Original ITT)*	**3 (1.3%)**	**4 (1.8%)**	**7 (1.6%)**	**0.72 (0.16-3.20)**	**0.01**	**-**
Treatment Discontinuation Due to Loss of Efficacy (Original ITT)*	**1 (0.4%)**	**9 (4.1%)**	**10 (2.3%)**	**0.11 (0.01-0.84)**	**0.04**	**-**
Need for a Second Antipsychotic (Original ITT)*	**5 (2.2%)**	**6 (2.8%)**	**11 (2.5%)**	**0.80 (0.25-2.60)**	**0.01**	**-**
Treatment Discontinuation for Safety or Tolerability (Original ITT)*	**15 (6.6%)**	**8 (3.7%)**	**23 (5.2%)**	**1.81 (0.78-4.18)**	**-**	**0.03**
Missing Data in Drop-Out Analysis	**13 (16.0%)**	**4 (6.9%)**	**17 (12.2%)**	**2.33 (0.80-6.78)**	**-**	**0.09**

Abbreviations: Intent-to-Treat (ITT), Confidence Interval (CI); Source: Reviewer Constructed. Computations Performed Using Applicant's Raw Data.

The results of my exploratory analyses support the Applicant's primary conclusion using the composite endpoint of treatment failure. Statistical reviewers Yang Wang, Ph.D. and Peiling Yang, Ph.D. could reproduce all statistical analyses performed by the Applicant. The fact that all statistical analyses yielded similarly positive results bolsters my confidence in the conclusions being drawn.

Data Quality and Integrity

No concerns regarding data quality are noted.

Efficacy Results – Secondary and other relevant endpoints

I repeated the Applicant's analyses of secondary endpoints and obtained the same result as the Applicant. Specific analyses performed included:

- Mixed model repeated measures analysis of MSQ score mean difference
- Mixed model repeated measures analysis of CGI-S score mean difference
- Mixed model repeated measures analysis of PSP score mean difference
- Kaplan-Meier estimate of time to first psychiatric hospitalization, time to first arrest or incarceration, and time to first psychiatric hospitalization, arrest, or incarceration

Pre-specified Key Secondary Endpoints

Paliperidone palmitate demonstrated superiority to active control in delaying first psychiatric hospitalization, arrest, or incarceration with an ARR of 0.11 compared to reductions attributable to active control. The median time to first psychiatric hospitalization, arrest, or incarceration was beyond the 450-day trial duration in the paliperidone palmitate group and 274 days in the active control group.

Other Prespecified Secondary Endpoints

Neither the Applicant nor I observed statistically significant differences in mean total personal and social performance (PSP) scores (p=0.69) or mean CGI-S scores (p=0.30) between groups.

Dose/Dose Response

During the trial, the Applicant raised the recommended maintenance dosage of paliperidone palmitate from 117 mg monthly to 156 mg monthly, added provisions for flexible paliperidone palmitate dosing, and removed the 39 mg monthly dosage entirely due to higher than anticipated rates of treatment ineffectiveness at lower doses. The Applicant also eliminated defining the need for supplemental pharmacotherapy beyond paliperidone palmitate 234 mg monthly as a treatment failure due to the number of participants requiring >234 mg monthly of paliperidone for control of symptoms. While some participants responded to paliperidone

palmitate 78 mg and 117 mg monthly, most participants required dosages between 156 mg monthly and 234 mg monthly for adequate control of symptoms. Specific data pertaining to dosages utilized and duration of treatment is found in *Section 8.2.1 Overall Exposure*.

Durability of Response

Paliperidone palmitate is effective for the treatment of schizophrenia while therapeutic blood levels are maintained. No treatment effect continues after an antipsychotic is discontinued or an individual becomes non-adherent. Durability of response requires continuous adherence to antipsychotic treatment. SCH-3006 demonstrated that the treatment effect is maintained over 15 months when individuals maintain continuous drug adherence.

Additional Analyses Conducted on the Individual Trial

Not applicable.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Sections 7.1.1-7.1.5 were deleted due to there being one trial in this application.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-Market Setting

This trial validates current clinical practice.

7.2.2. Other Relevant Benefits

None beyond what has already been discussed.

7.3. Integrated Assessment of Effectiveness

Not applicable due to there being one new trial in this application.

8. Review of Safety

Safety data did not change significantly between the first review cycle and re-submission. Please see the safety review of SCH-3006 by Glenn Mannheim, dated April 22, 2015, for details.

8.1. Safety Review Approach

Safety data was reviewed by Glenn Mannheim on April 22, 2015.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Paliperidone: The mean number of paliperidone palmitate injections was 9.5 and 33.2% of subjects received at least 16 injections. The mean dose of paliperidone palmitate was 181.3 mg. The mean duration of exposure to paliperidone palmitate was 266.2 days and duration of exposure was > 360 days for 44.2% of subjects. The most frequently used doses of paliperidone palmitate were 156 mg and 234 mg, both for the first maintenance dose (i.e., the third dose) (63.8% and 19.7%, respectively) and for the final maintenance dose (45.7% and 31.9%, respectively).

Oral Antipsychotics: Equipoise-stratification led to following assignments: aripiprazole (n=33), haloperidol (n=15), olanzapine (n=36), paliperidone (n=48), perphenazine (n=20), quetiapine (n=29), and risperidone (n=37). The mean number of oral antipsychotic prescriptions during the trial was 9.0. The mean duration of exposure to the randomized oral antipsychotic was 271.5 days and duration of exposure was > 360 days for 43.2% of subjects.

Sections 8.2.2-8.2.3 were deleted due to being reviewed by Glenn Mannheim, MD on April 22, 2015.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Data integrity and submission quality were sufficient to facilitate clinical review. I noted no issues or irregularities.

8.3.2. Categorization of Adverse Events

Safety data was reviewed by Glenn Mannheim on April 22, 2015.

8.3.3. Routine Clinical Tests

I note no concerns with the routine psychometric instrument administrations, clinical assessments, and laboratory draws as administered in the final protocol.

8.4. Safety Results

Sections 8.4-8.10 were deleted because safety data for Trial SCH-3006 was reviewed by Glenn Mannheim on April 22, 2015 and broader safety issues related to paliperidone palmitate were adjudicated during approval of paliperidone palmitate for the indication of schizophrenia maintenance. The proposed product has been widely available for sale within the U.S. for eight years; post-marketing surveillance for the proposed product is ongoing.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this supplemental application. Evaluation of the safety data revealed no safety issues that were unexpected for this drug class. I noted no concerns with the design and results of this trial.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Inclusion of the submitted trial into the Clinical Trials Section of the USPI is currently being negotiated with the Applicant.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required.

12. Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments are required.

13. Appendices

13.1. References

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12. Markowitz M, Fu D, Levitan B, Gopal S, Turkoz I, Alphs L. Long-acting injectable paliperidone palmitate versus oral paliperidone extended release: a comparative analysis from two placebo-controlled relapse prevention studies. Ann Gen Psychiatry. 2013;12(22):http://www.annals-general-psychiatry.com/content/12/1/22.
13. McEvoy J, Byerly M, Hamer R, Dominik R, Swartz M, Rosenheck R, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA. 2014;311(19):1978-87.
14. Paliperidone palmitate for schizophrenia [Internet]. Cochrane Database of Systemic Reviews. 2012.

13.2. Financial Disclosure

The Applicant adequately disclosed clinical investigator financial interests as recommended in FDA guidance for industry, *Financial Disclosure by Clinical Investigators*. For details regarding the Applicant's one reported disclosure, please see the initial clinical review by Glenn Mannheim, dated April 22, 2015.

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

/s/

DANIEL J LEE
12/18/2017

JAVIER A MUNIZ
12/18/2017

CLINICAL REVIEW

Application Type	Supplement
Application Number(s)	NDA 22-264, S015
Priority or Standard	Standard
Submit Date(s)	July 11, 2014
Received Date(s)	July 11, 2014
PDUFA Goal Date	May 11, 2015
Division / Office	OND-I/DPP
Reviewer Name(s)	Glenn B. Mannheim, MD
Review Completion Date	April 03, 2015
Established Name	INVEGA SUSTENNA (paliperidone palmitate) Extended-Release Injectable Suspension
Therapeutic Class	Anti-Psychotics
Applicant	Janssen Pharmaceuticals, Inc.
Formulation(s)	Intramuscular
Dosing Regimen	39, 78, 117, 156, 234 mg
Indication(s)	Comparison with Oral Antipsychotics in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated
Intended Population(s)	Previously Incarcerated Schizophrenics

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The data examined and discussed at FDA's Regulatory Briefing suggests that the current data is inconclusive at present to recommend approval. Despite, paliperidone palmitate suggesting superiority to treatment with oral antipsychotics in delaying time to first treatment failure in subjects with schizophrenia who had been incarcerated (primary endpoint), the presence of 31.3 % of the patients discontinuing early and being lost to follow-up, make such an interpretation unproven. In addition, there was a larger percent of patients who discontinued in the paliperidone palmitate group, and they were not completed followed up. No trend in favor of the paliperidone palmitate arm was demonstrated in terms of PSP total score and in CGI-S at month 15.

Implicitly, one would assume that giving injectable antipsychotics to non-compliant patients would be of more benefit than if they were asked to take oral antipsychotics. However, the present study does not clearly demonstrate this.

An additional study is recommended.

1.2 Risk Benefit Assessment

No clear benefit could be established in delaying time to first treatment failure in subjects with schizophrenia who had been incarcerated (primary endpoint). Risks associated with paliperidone and other second-generation antipsychotics include weight gain, dyslipidemias, glycemic abnormalities, hyperprolactinemia, movement disorders and cardiovascular events. Extrapyramidal motor side effects, tardive dyskinesia, etc. are also present. At present, based upon the current study, benefits cannot be said to exceed risks (b) (4).

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

None are recommended at this time.

1.4 Recommendations for Postmarketing Requirements and Commitments

None are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Paliperidone (9- hydroxyrisperidone) is the active metabolite of risperidone, which has been widely used in the treatment of schizophrenia since 1994. It is a selective, mono-aminergic antagonist with dopamine type 2 (D2) and serotonin (5-hydroxy-trptamine [5-HT]) type 2A (5HT2A) antagonism with a receptor-binding profile similar to risperidone. Paliperidone has a higher affinity for 5HT2A than for D2 receptors. The binding affinity of paliperidone for both the 5HT2A and D2 receptors and for α1- and α2-receptors and the H1 receptor is similar to that of risperidone.

It is available as a prolonged release oral formulation (INVEGA Extended Release (ER) tablets, once daily dosing) as well as a long-acting intramuscular (i.m.) injectable formulation (INVEGA SUSTENNA, paliperidone palmitate, 1-month dosing interval).

INVEGA was approved by FDA for the acute treatment of schizophrenia (December 2006, NDA 21-999), maintenance treatment of schizophrenia (April 2007), and treatment of schizophrenia in adolescents aged 12 to 17 years (April 2011). INVEGA was approved for the "acute treatment of schizoaffective disorder as monotherapy" and "acute treatment of schizoaffective disorder as an adjunct to mood stabilizers and/or antidepressants", which was received on July 31, 2009 (NDA 21-999). The indications wording was subsequently modified to "treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants" on April 6, 2011. INVEGA SUSTENNA (PPIM) was approved for the acute and maintenance treatment of schizophrenia in adults in July 31, 2009 (NDA 22-264). This was subsequently modified to "treatment of schizophrenia" (August 29, 2012).

The present submission to NDA 22-264 is S 015. It consists of a single study, protocol R092670-SCH-3006, entitled "A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated". This study forms the basis for requesting revisions to the (b) (4) Clinical Studies sections of the INVEGA SUSTENNA PI to include information on a comparative effectiveness claim for paliperidone palmitate in schizophrenic adult's patients with a history of incarceration.

2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed comparative efficacy claim for a long acting intramuscular injection (INVEGA SUSTENNA, paliperidone palmitate) versus oral antipsychotics in delaying time to treatment failure (e.g. preventing arrest/incarceration; psychiatric hospitalization, etc) in subjects with schizophrenia with a history of recent incarceration is unique. (b) (4)

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Paliperidone is a combined dopamine Type 2 receptors combined serotonin (5-hydroxytryptamine Type 2A) antagonist that is the active metabolite of risperidone. Two formulations (paliperidone ER-tablets: INVEGA; monthly paliperidone palmitate IM injection: INVEGA SUSTENNA) are currently available and marketed in the US.

2.4 Important Safety Issues with Consideration to Related Drugs

Paliperidone (9- hydroxyrisperidone) is second-generation antipsychotics which reportedly cause less extrapyramidal motor side effects and tardive dyskinesia than first-generation antipsychotics. Second-generation antipsychotics, however, appear to generally cause more weight gain and cardiometabolic adverse effects compared to first-generation antipsychotics. The most common adverse events associated with second-generation antipsychotics were weight gain, dyslipidemias, glycemic abnormalities, hyperprolactinemia, movement disorders and cardiovascular events,

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Type C Meeting took place between Janssen Research, Division of Psychiatry Products (Division, DPP) and Office of Prescription Drug Promotion on May 24, 2012 to discuss the adequacy of Study R092670-SCH-3006 to support proposed revisions to the INVEGA SUSTENNA USPI. The Division provided comments on the protocol and indicated that: 1) they did not object to the design of the study; 2) they agreed to the proposed definition of the primary endpoint of treatment failure and the plan to use a blinded Event Monitoring Board (EMB) as the adjudicator of treatment failure for the primary endpoint; and 3) assuming positive results, they were willing to discuss how the information might be characterized in labeling. (b) (4) it was felt that the Division would certainly take the issue to an Advisory Committee to obtain further expert opinion on how to interpret the results.

The Statistical Analysis Plan (SAP) for Study R092670-SCH-3006 was submitted to the Division on 11 October 2013 (IND 67,356; serial no. 431). The Division's statistical team provided their feedback on SAP on November 25, 2013.

A pre-sNDA meeting was scheduled with the Division on 28 May 2014. Based on the preliminary comments made by the Division dated May 21, 2014, the meeting was canceled. In their comments, the Division reiterated their willingness to consider revisions to the INVEGA SUSTENNA USPI sections based on review of this sNDA. The Division also provided feedback on the Sponsor's proposed content of the sNDA. It was agreed that this supplement will rely on the Chemistry, Manufacturing and Controls information that supported the approval of NDA 22-264 (022264/0000/Module 3) and would not be re-submitted in this sNDA given that there were no new significant CMC

differences between the product used in R092670-SCH-3006 and that approved in NDA 22-264.

As recommended by the Division, an environmental analysis was to be included in the current submission (Module 1.12.14/Environmental Analysis). This submission will also rely on nonclinical data previously submitted in NDA 22-264 given that no new nonclinical data were generated to support this study (NDA 22-264, Module 2.4).

Agreement was reached that the results of single study, R092670-SCH-3006 be provided in a Clinical Study Report (CSR) and that a Summary of Clinical Safety/Integrated Summary of Safety and an integrated Summary of Clinical Efficacy/Integrated Summary of Efficacy would not be required.

Other information to be provided as part of the sNDA submission consisted of: 1) a review of postmarketing data (limited to fatal cases, important potential risks, specific populations, relevant drug interactions and medication errors)of INVEGA SUSTENNA in the schizophrenia population; 2) a summary and bibliography relevant to the safety of all formulations of paliperidone (extended-release tablets and injectables).

Since the Division designated this submission as a labeling supplement with new clinical data; PREA was not triggered; and, hence no justification for waiver of pediatric studies was required.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Sample case report forms and reported adverse event information appeared to be consistent.

3.2 Compliance with Good Clinical Practices

Office of Scientific Investigation (OSI) inspections were conducted at the following sites which were involved in Study R092670SCH3006. Number of subjects in each site is noted.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects
Site # 001019 Carr, Jesse M., M.D. 230 N. Maryland Avenue #207 Glendale, CA 91206 USA	R092670SCH3006	23
Site # 001007 Murphy, Paul W., M.D. 1100 North St. Francis Suite 300 Wichita, KS 67214 USA	R092670SCH3006	26
Site # 001016 Stedman, Mary L., M.D. 3212 Cove Bend Drive Tampa, FL 33613 USA	R092670SCH3006	30

OSI found no significant deficiencies at all 3 sites. The study conduct at all inspected study sites appeared adequate, including IRB oversight and sponsor monitoring of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the three inspected study sites was felt to be reliable as reported in the NDA,

3.3 Financial Disclosures

Financial disclosures submitted were for the following individuals in Study R092670SCH3006:

(b) (6),
(b) (6)
SITE NO: (b) (6)
(b) (6)
(b) (6)

Disclosure: The investigator received compensation in the form of honoraria and consulting fees in excess of $25,000 from the sponsor during the course of the covered clinical trials.

Steps Taken to Minimize Investigator Bias: A Treatment Failure Event Monitoring Board (EMB) that was blinded to individual subject treatment assignment determined the occurrence and date of the first treatment failure event. In addition, all case report forms were collected and data analyzed by Janssen Research and Development. Site (b) (6) enrolled 20 out of the total of 450 randomized subjects.

Form FDA 3454, Certification of the Financial Interests and Arrangements of Clinical Investigators was submitted, and lists clinical investigators who participated in Study

R092670-SCH3006. It identifies them as having no disclosable financial arrangements with Janssen Research and Development.

A list of the Investigators is identified in the Appendix of this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

It was determined in the pre-sNDA meeting comments, dated May 21, 2014, that this supplement will rely on the Chemistry, Manufacturing and Controls information that supported the approval of NDA 22-264 (022264/0000/Module 3) and will not be re-submitted in this sNDA given that there are no new significant CMC differences between the product used in R092670-SCH-3006 and that approved in NDA 22-264.

4.2 Clinical Microbiology

No microbiology data was provided.

4.3 Preclinical Pharmacology/Toxicology

It was determined in the pre-sNDA meeting comments, dated May 21, 2014, that this supplement will not be resubmitted with the current sNDA. The original data (Modules 2.4 and 4.2.3.2) previously submitted on October 25, 2007 for NDA 22-264, INVEGA® SUSTENNA® (paliperidone palmitate intramuscular injection) for the treatment of schizophrenia is referenced.

4.4 Clinical Pharmacology

The present sNDA provides no new information to Clinical Pharmacology and the Summary of Biopharmaceutic Studies and Associated Analytical Methods (022264/0000/Module 2.7.1) and The Summary of Clinical Pharmacology (022264/0000/Module 2.7.2) submitted on October 25, 2007 for NDA 22-264, paliperidone palmitate for the treatment of schizophrenia is to be referenced.

5 Sources of Clinical Data

In addition, no new biopharmaceutics or clinical pharmacology studies have been performed for this study. Therefore, this sNDA relies on Module 2.7.1 previously

submitted on October 25, 2007 for NDA 22-264, INVEGA® SUSTENNA® (paliperidone palmitate intramuscular injection) for the treatment of schizophrenia.

5.1 Tables of Studies/Clinical Trials

Single Study: A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated

Alternative Study Name: PRIDE

5.2 Review Strategy

The efficacy review focused on a single, open label flexible dose, Phase 4, trial. The safety review involved an examination of deaths, serious adverse events, and premature discontinuations secondary to adverse events, other dropouts/discontinuations, sponsors postmarketing adverse event review and sponsors literature review. Supportive safety information (common adverse events, available labs, etc.) was also review

5.3 Discussion of Individual Studies/Clinical Trials

The review of efficacy was based on the individual study report for the single phase 4 study (Protocol R092670SCH3006).

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Primary Objective: To compare the efficacy of paliperidone palmitate with oral antipsychotic treatment in delaying time to first treatment failure over 15 months, in subjects with schizophrenia who had been incarcerated.

Treatment failure was a composite endpoint consisting of any of the following events: arrest/incarceration; psychiatric hospitalization; suicide; discontinuation of antipsychotic treatment due to inadequate efficacy; treatment supplementation with another antipsychotic due to inadequate efficacy; discontinuation of antipsychotic treatment due to safety or tolerability; or increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization.

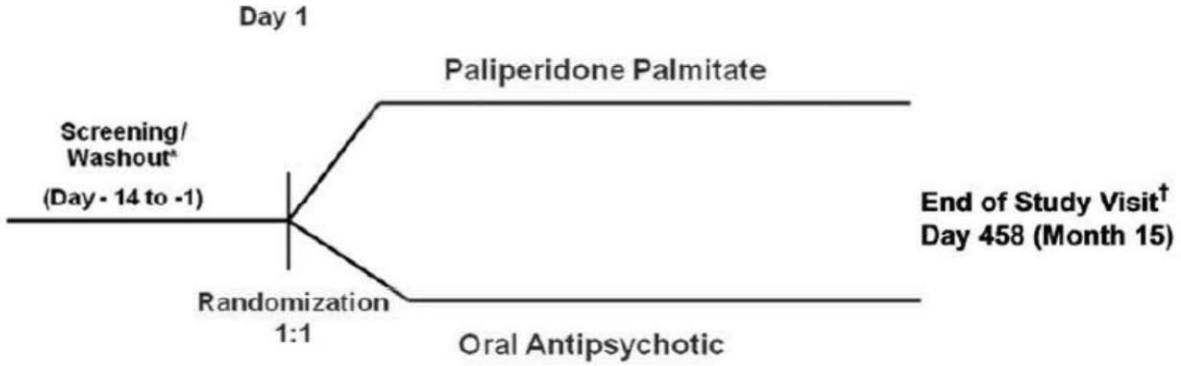
Major Secondary Objectives: To compare the efficacy of paliperidone palmitate with oral antipsychotic treatment in:

- time to first psychiatric hospitalization or arrest/incarceration;
- subject functioning as measured by change from baseline in Personal and Social Performance Scale (PSP) total score;
- time to first psychiatric hospitalization;
- symptom improvement as measured by change from baseline in Clinical Global Impression-Severity (CGI-S) score.

6.1.1 Methods

This was a 15-month, randomized, prospective, open-label, active controlled, parallel group, multicenter study comparing paliperidone palmitate treatment with oral antipsychotic treatment in the prevention of a treatment failure in subjects with schizophrenia. The study consisted of an up-to-14- day screening period and a 15-month open-label treatment period.

The study design is depicted below.



For subjects without source documentation of exposure to paliperidone, paliperidone palmitate, or risperidone, a 2-day oral tolerability test with a daily dose of 1 mg risperidone was conducted during the screening period, and was completed prior to randomization.

6.1.2 Demographics

Demographics and key baseline characteristics in the ITT analysis are summarized by the sponsor in the baseline demographics table copied and pasted below (Sec. 6.1.3 Subject Disposition).

Average age of all subjects was 38.1 (10.47) years; of whom, 86.3 % were males; 62.1 % were black or African American; with 42.2 (51.71) days since release from last incarceration. Of these 59.3% were on probation, 36.4% were on paroles, 87.8 % were

unemployed, 70.2% had a monthly income of less than $ 750.0, 43.8 % had no medical insurance, and 45.7% lived in a house or apartment with others, and 67.3% had no appointment for outpatient psychiatric care provided by the jail release program. Sponsor's table of baseline socio-demographics is copied and pasted below.

Table 6: Baseline Socio-demographics
ITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects	226	218	444
Highest Level of Education			
N	221	210	431
College or other post-high school training or education	42 (19.0%)	23 (11.0%)	65 (15.1%)
High school graduate or GED	87 (39.4%)	97 (46.2%)	184 (42.7%)
Less than either High School or GED	92 (41.6%)	90 (42.9%)	182 (42.2%)
Where the Subject Has Been Living Since Released From Jail?			
N	221	210	431
In a house or apartment alone (with no professional mental health supports)	19 (8.6%)	18 (8.6%)	37 (8.6%)
In a house or apartment with others (e.g., parents, sibling, spouse, friend, children)	105 (47.5%)	92 (43.8%)	197 (45.7%)
In a house, apartment, or boarding home where a mental health professional such as a counselor or case manager visits regularly	21 (9.5%)	24 (11.4%)	45 (10.4%)
In a treatment program or boarding home where a mental health professional such as a counselor or case manager is there all or almost all of the time	28 (12.7%)	21 (10.0%)	49 (11.4%)
On the streets or in an emergency shelter for the homeless	28 (12.7%)	34 (16.2%)	62 (14.4%)
Other	10 (4.5%)	5 (2.4%)	15 (3.5%)
Transitional facility	10 (4.5%)	16 (7.6%)	26 (6.0%)
Medical Insurance Coverage Since Released From Jail			
N	208	203	411
Medicaid	77 (37.0%)	65 (32.0%)	142 (34.5%)
Medicare	32 (15.4%)	34 (16.7%)	66 (16.1%)
Commercial	6 (2.9%)	5 (2.5%)	11 (2.7%)
Veteran's or Military Medical Benefits	3 (1.4%)	1 (0.5%)	4 (1.0%)
None	83 (39.9%)	97 (47.8%)	180 (43.8%)
Other	24 (11.5%)	19 (9.4%)	43 (10.5%)
Highest Monthly Income Over The Last 12 Months			
N	213	206	419
Less than $750	149 (70.0%)	145 (70.4%)	294 (70.2%)
$750 to $1,000	43 (20.2%)	41 (19.9%)	84 (20.0%)
$1,001 to $1,500	12 (5.6%)	13 (6.3%)	25 (6.0%)
more than $1,500	6 (2.8%)	7 (3.4%)	13 (3.1%)
Not applicable (Patient Refused)	3 (1.4%)	0	3 (0.7%)
Employment Status 12 Month Prior To The Last Incarceration			
N	221	210	431
Full-time	8 (3.6%)	17 (8.1%)	25 (5.8%)
Intermittent Work	17 (7.7%)	27 (12.9%)	44 (10.2%)
Not employed (includes student with no additional job)	182 (82.4%)	154 (73.3%)	336 (78.0%)
Part-time	14 (6.3%)	12 (5.7%)	26 (6.0%)

Employment Status Since Released From Jail			
N	217	208	425
Full-time	4 (1.8%)	2 (1.0%)	6 (1.4%)
Intermittent Work	10 (4.6%)	17 (8.2%)	27 (6.4%)
Not employed (includes student with no additional job)	194 (89.4%)	179 (86.1%)	373 (87.8%)
Part-time	9 (4.1%)	10 (4.8%)	19 (4.5%)

6.1.3 Subject Disposition

693 patients were screened, of which, 450 were randomized to either paliperidone palmitate (n = 230) or oral antipsychotics (n = 220).

The ITT analysis set included 444 subjects (226 paliperidone palmitate, 218 oral antipsychotics). Six 6 subjects were excluded from the ITT set included (4 subjects randomized to paliperidone palmitate, but not treated, and 2 subjects, randomized to oral antipsychotics) at site 001054 who were excluded due to audit findings.

181 patients completed the 15-month visit (Visit 18), 41.2% of subjects in the paliperidone palmitate group and 40.4% of subjects in the oral antipsychotics group. There were 263 subjects who discontinued from the study early; among those, nearly half (124 subjects; 47.1%) had already reached the primary endpoint (Table 1). The most frequently reported reasons for those early discontinuations without an event in the paliperidone palmitate and the oral antipsychotics groups were lost to follow-up (15.0%, 11.9%), withdrawal by subject (11.5%, 7.3%), and other (6.2%, 5.5%), respectively.

Table 1 Patient Disposition, All Randomized Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects Screened			693
Number of Screen Failures			243
Number of Subjects Randomized	230	220	450
Number of Subjects in the ITT Analysis Set [a]	226	218	444
Number of Subjects Completed Study	93 (41.2%)	88 (40.4%)	181 (40.8%)
With event [b]	38 (16.8%)	45 (20.6%)	83 (18.7%)
Without event [b]	55 (24.3%)	43 (19.7%)	98 (22.1%)
Number of Subjects Discontinued Study Early			
Total	133 (58.8%)	130 (59.6%)	263 (59.2%)
Adverse Event	5 (2.2%)	4 (1.8%)	9 (2.0%)
Death	1 (0.4%)	0	1 (0.2%)
Lack of Efficacy	0	0	0
Lost to Follow-Up	53 (23.5%)	55 (25.2%)	108 (24.3%)
Withdrawal by Subject	37 (16.4%)	27 (12.4%)	64 (14.4%)
Noncompliance with Study Drug	0	3 (1.4%)	3 (0.7%)
Physician Decision	5 (2.2%)	4 (1.8%)	9 (2.0%)
Protocol Violation	0	1 (0.5%)	1 (0.2%)
Other [c]	32 (14.2%)	36 (16.5%)	68 (15.3%)
With event [b]	52 (23.0%)	72 (33.0%)	124 (27.9%)
Adverse Event	4 (1.8%)	4 (1.8%)	8 (1.8%)
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-Up	19 (8.4%)	29 (13.3%)	48 (10.8%)
Withdrawal by Subject	11 (4.9%)	11 (5.0%)	22 (5.0%)
Noncompliance with Study Drug	0	2 (0.9%)	2 (0.5%)
Physician Decision	0	2 (0.9%)	2 (0.5%)
Protocol Violation	0	0	0
Other [c]	18 (8.0%)	24 (11.0%)	42 (9.5%)
Without event [b]	81 (35.8%)	58 (26.6%)	139 (31.3%)
Adverse Event	1 (0.4%)	0	1 (0.2%)
Death	1 (0.4%)	0	1 (0.2%)
Lack of Efficacy	0	0	0
Lost to Follow-Up	34 (15.0%)	26 (11.9%)	60 (13.5%)
Withdrawal by Subject	26 (11.5%)	16 (7.3%)	42 (9.5%)
Noncompliance with Study Drug	0	1 (0.5%)	1 (0.2%)
Physician Decision	5 (2.2%)	2 (0.9%)	7 (1.6%)
Protocol Violation	0	1 (0.5%)	1 (0.2%)
Other [c]	14 (6.2%)	12 (5.5%)	26 (5.9%)

[a] ITT subjects are those that were randomized and treated.
[b] Event refers to the EMB-determined treatment failure event – the primary study endpoint.
[c] Verbatim reasons for "other" included custody (incarcerated, jail,) for 40 subjects (18 paliperidone palmitate, 22 oral antipsychotics) and subject relocation for 8 subjects (4 paliperidone palmitate, 4 oral antipsychotics).
Four subjects randomized to Paliperidone Palmitate were not treated; 2 subjects randomized to Oral Treatment from site 001054 were excluded from ITT analysis set due to audit findings.
Note: All percentages are based on the ITT population.

2) Patient Demographic and Baseline Characteristics

The demographic and baseline characteristics were similar in both treatment arms. Mean age was 38 years, majority were males, black or African American. Mean time since release from the last incarceration was 42 days (Table 2).

Table 2 Patient Demographic and Baseline characteristics, eITT Population

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects	226	218	444
Age (years)			
N	226	218	444
Mean (SD)	37.7 (10.57)	38.6 (10.36)	38.1 (10.47)
Median	39.0	40.0	40.0
Range	(18; 61)	(19; 61)	(18; 61)
18-25	39 (17.3%)	32 (14.7%)	71 (16.0%)
26-50	161 (71.2%)	161 (73.9%)	322 (72.5%)
51-60	25 (11.1%)	24 (11.0%)	49 (11.0%)
>60	1 (0.4%)	1 (0.5%)	2 (0.5%)
Gender			
N	226	218	444
Male	193 (85.4%)	190 (87.2%)	383 (86.3%)
Female	33 (14.6%)	28 (12.8%)	61 (13.7%)
Race			
N	226	217	443
White	73 (32.3%)	74 (34.1%)	147 (33.2%)
American Indian or Alaska Native	2 (0.9%)	3 (1.4%)	5 (1.1%)
Black or African American	145 (64.2%)	130 (59.9%)	275 (62.1%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	1 (0.5%)	2 (0.5%)
Asian	2 (0.9%)	1 (0.5%)	3 (0.7%)
Other	1 (0.4%)	6 (2.8%)	7 (1.6%)
Multiple	2 (0.9%)	2 (0.9%)	4 (0.9%)
Ethnicity			
N	226	218	444
Hispanic or Latino	31 (13.7%)	36 (16.5%)	67 (15.1%)
Not Hispanic or Latino	185 (81.9%)	176 (80.7%)	361 (81.3%)
Unknown	2 (0.9%)	1 (0.5%)	3 (0.7%)
Not Reported	8 (3.5%)	5 (2.3%)	13 (2.9%)
Time Since Release from the Last Incarceration (days)			
N	226	217	443
Mean (SD)	38.9 (50.29)	45.7 (53.04)	42.2 (51.71)
Median	28.0	35.0	31.0
Range	(1; 575)	(1; 446)	(1; 575)

6.1.4 Analysis of Primary Endpoint(s)

Sponsor's Analysis: Time to first treatment failure was statistically significantly longer in the group with paliperidone palmitate compared to the group with an oral antipsychotic (p-value = 0.011), with a hazard ratio (95% CI) of 1.43 (1.09, 1.88). A total of 90 (39.8%) subjects in the paliperidone palmitate group and 117 (53.7%) subjects in the oral antipsychotics group had a treatment failure event. The estimated median time (95% CI) to first treatment failure was 416 days (285, not estimable [could not be reliably estimated due to study duration]) for subjects treated with paliperidone palmitate, compared with 226 days (147, 304) for subjects treated with oral antipsychotics.

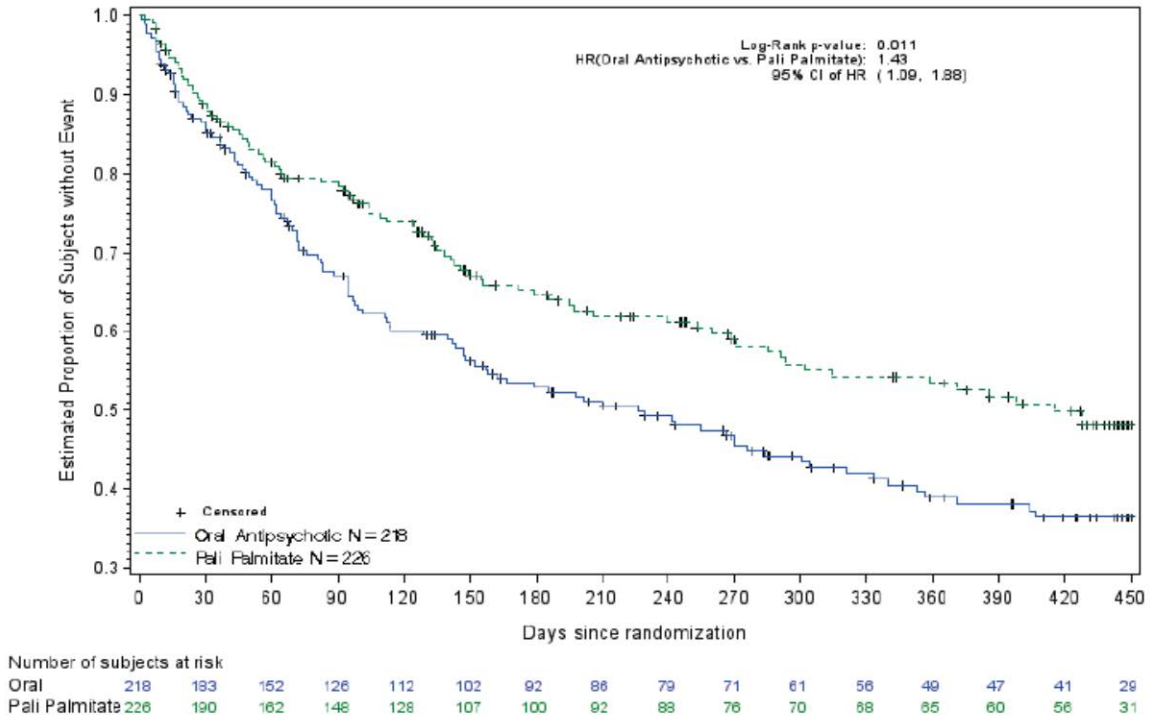
Table 16: Kaplan-Meier Analysis of Time to First Treatment Failure - per EMB Determination; eITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event[a]		
Number assessed	226	218
Event	90 (39.8%)	117 (53.7%)
Censored	136 (60.2%)	101 (46.3%)
Kaplan-Meier 25th Percentile, Days	109	62
(95% CI)	(63, 143)	(47, 82)
Kaplan-Meier Median, Days	416	226
(95% CI)	(285, -)	(147, 304)
Kaplan-Meier 75th Percentile, Days	-	-
(95% CI)	(-, -)	(-, -)
Cumulative Probability of Event[a]		
Month 3	0.22	0.33
(95% CI)	(0.16, 0.27)	(0.26, 0.39)
Month 6	0.35	0.47
(95% CI)	(0.29, 0.42)	(0.40, 0.54)
Month 9	0.41	0.55
(95% CI)	(0.34, 0.48)	(0.47, 0.62)
Month 12	0.47	0.61
(95% CI)	(0.39, 0.54)	(0.54, 0.69)
Month 15	0.52	0.64
(95% CI)	(0.44, 0.60)	(0.56, 0.71)
Log-Rank Test p-value[b]	0.011	
Wilcoxon Test p-value[b]	0.014	
Hazard Ratio From Cox Regression		
Treatment Group, Oral vs. Pali Palmitate	1.43	
(95% CI)	(1.09, 1.88)	
p-value	0.011	

[a] Quartiles and cumulative probabilities are based on Kaplan-Meier estimates.
[b] P-values are for testing difference between paliperidone palmitate and oral antipsychotic treatment.

[TEFTFKM01E.rtf] [JNJ-16977831\SCH3006\DBR_FINAL\RE_CSR\teftfkm01e.sas] 19FEB2014, 10:08

Figure 4: Kaplan-Meier Estimates of Time to First Treatment Failure Per EMB Determination; eITT Analysis Set (Study R092670-SCH-3006)



Frequency distribution of type of first treatment failure event in the eITT analysis set is presented in sponsor's table, copied and pasted below. All component events occurred more frequently in subjects treated with oral antipsychotics than in subjects treated with paliperidone palmitate, except for discontinuation due to safety or tolerability (6.6% paliperidone palmitate, 3.7% oral antipsychotics). The most prevalent component was arrest/incarceration (48 in the paliperidone palmitate group vs. 64 in the oral antipsychotic group based on the eITT analysis set).

Table 17: Frequency Distribution of Component Events of First Treatment Failure, per EMB Determination; eITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
First treatment failure			
Number of Subjects	226	218	444
Any Event	90 (39.8%)	117 (53.7%)	207 (46.6%)
Arrest/incarceration	48 (21.2%)	64 (29.4%)	112 (25.2%)
Discontinuation of antipsychotic treatment due to inadequate efficacy	1 (0.4%)	9 (4.1%)	10 (2.3%)
Suicide	0	0	0
Discontinuation of antipsychotic treatment due to safety or tolerability	15 (6.6%)	8 (3.7%)	23 (5.2%)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	7 (1.6%)
Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	44 (9.9%)
Treatment supplementation with another antipsychotic due to inadequate efficacy	5 (2.2%)	6 (2.8%)	11 (2.5%)

Analyses of time to individual components were explored, which also suggested that the statistically significant finding in the composite primary endpoint was mainly driven by the arrest/incarceration component. However, these analyses were exploratory.

Biometrics Review: Please refer to Drs. Liu's review for statistical assessments. Her analysis showed that there was no statistically significant difference in delaying time to treatment failure between treatment groups (p=0.2805, p=0.1885)

6.1.5 Analysis of Secondary Endpoints(s)

Time to First Psychiatric Hospitalization or Arrest/Incarceration:
Treatment with paliperidone palmitate was superior to treatment with an oral antipsychotics in delaying time to first psychiatric hospitalization or arrest/incarceration (p = 0.019), with a hazard ratio (95% CI) of 1.43 (1.06, 1.93). A total of 76 (33.6%) subjects in the paliperidone palmitate group and 98 (45.0%) subjects in the oral antipsychotics group had a psychiatric hospitalization or an arrest/incarceration.

The median time to first psychiatric hospitalization or arrest/incarceration was not estimable (> 450 days) in the paliperidone palmitate group and 274 days in the oral antipsychotics group.

Table 19: Kaplan-Meier Analysis of Time to First Psychiatric Hospitalization or Arrest/Incarceration; eITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event[a]		
Number assessed	226	218
Event	76 (33.6%)	98 (45.0%)
Censored	150 (66.4%)	120 (55.0%)
Kaplan-Meier 25th Percentile (95% CI), Days	139 (99, 206)	88 (62, 120)
Kaplan-Meier Median (95% CI), Days	NE	274 (202, 407)
Kaplan-Meier 75th Percentile, Days	NE	NE
Cumulative Probability of Event[a] (95% CI)		
Month 3	0.18 (0.12, 0.23)	0.26 (0.19, 0.32)
Month 6	0.30 (0.23, 0.36)	0.40 (0.32, 0.47)
Month 9	0.37 (0.30, 0.45)	0.49 (0.42, 0.57)
Month 12	0.43 (0.35, 0.51)	0.55 (0.47, 0.63)
Month 15	0.47 (0.39, 0.56)	0.60 (0.52, 0.68)
Log-Rank Test p-value[b]	0.019	
Hazard Ratio (95% CI) From Cox Regression, Oral vs. Pali Palmitate	1.43 (1.06, 1.93)	

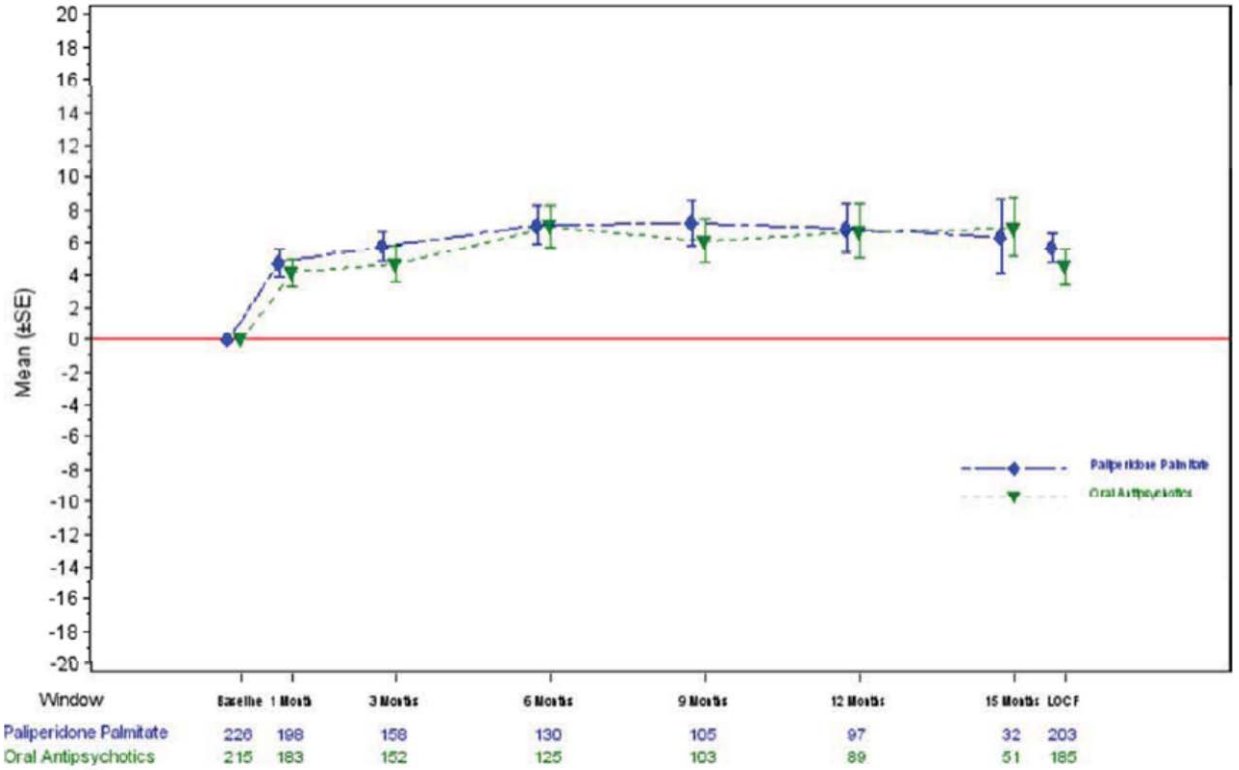
NE = not estimable.
[a] Quartiles and cumulative probabilities are based on Kaplan-Meier estimates.
[b] P-values are for testing difference between paliperidone palmitate and oral antipsychotic treatment.

Table 20: Mixed Model Repeated Measures Results for PSP Total Score: Overall Treatment Effect; eITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Difference
PSP Total Score			
Overall Treatment Effect			
LS Mean	60.33	59.94	0.39
SE	0.690	0.690	0.976
95% CI	(58.98;61.69)	(58.58;61.30)	(-1.53;2.31)
p-value [a]	<.0001	<.0001	0.6891
LS Mean - Change from Baseline	5.75	5.36	0.39
SE	0.690	0.690	0.976
95% CI	(4.40;7.11)	(4.00;6.72)	(-1.53;2.31)
p-value [a]	<.0001	<.0001	0.6891

[a] p-value based on repeated measures model that includes baseline value, treatment, time, and treatment by time interaction. An unstructured variance-covariance matrix was used to model the correlations among repeated measures from individual subject.

Figure 7: PSP Total Score: Mean ±SE Change from Baseline Over Time and LOCF; eITT Analysis Set (Study R092670-SCH-3006)



Personal and Social Performance (PSP)

There was no significant difference in overall mean change from baseline PSP total scores between paliperidone palmitate and oral antipsychotic treatment (p = 0.689).

Table 20: Mixed Model Repeated Measures Results for PSP Total Score: Overall Treatment Effect; eITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Difference
PSP Total Score			
Overall Treatment Effect			
LS Mean	60.33	59.94	0.39
SE	0.690	0.690	0.976
95% CI	(58.98;61.69)	(58.58;61.30)	(-1.53;2.31)
p-value [a]	<.0001	<.0001	0.6891
LS Mean - Change from Baseline	5.75	5.36	0.39
SE	0.690	0.690	0.976
95% CI	(4.40;7.11)	(4.00;6.72)	(-1.53;2.31)
p-value [a]	<.0001	<.0001	0.6891

[a] p-value based on repeated measures model that includes baseline value, treatment, time, and treatment by time interaction. An unstructured variance-covariance matrix was used to model the correlations among repeated measures from individual subject.

Time to Psychiatric Hospitalization
There was no statistically significant finding in favor of paliperidone palmitate (p-value =0.551).

Mean Change from Baseline in CGI-S to Month 15
There was no statistically significant difference between treatment groups at month 15

Biometrics Review: Please refer to Drs. Liu's review for statistical assessments. Her analysis showed that "a large proportion of patients discontinued early before reaching a treatment failure, the competing risks could potentially confound the analyses of these secondary endpoints whether based on the eITT or pITT analysis set. Hence, these results should be considered exploratory."

3.2.8 Conclusions

The trial seemed to demonstrate superiority of paliperidone palmitate based on the pre-specified primary endpoint. However, the additional analyses performed by Dr. Liu suggest that there was no statistically significant difference in delaying time to treatment failure between treatment groups (p=0.2805, p=0.1885). This may be related to a large proportion of patients discontinuing early.

7 Review of Safety

Safety Summary

Study R092670-SCH-3006 compared paliperidone palmitate with atypical oral antipsychotics commonly used in clinical practice. Paliperidone palmitate and these oral antipsychotics appeared to have a similar safety and tolerability profile in this 15-month study, with the exceptions noted below:

- The frequency of body weight gain of ≥7% from baseline to the end of treatment was higher for paliperidone palmitate.
- Larger increases in serum prolactin levels were observed for paliperidone palmitate and the frequency of prolactin-related TEAEs was also higher among subjects treated with paliperidone palmitate. No differences were seen in clinician-rated SSEQ ratings of sexual side effects typically associated with increased prolactin levels.
- Injection site pain was only reported as a TEAE in subjects treated with paliperidone palmitate.
- Other TEAEs reported more frequently (≥ 2% difference) in the paliperidone palmitate group than in the oral antipsychotics group were insomnia, akathisia, anxiety, erectile dysfunction, fatigue, increased appetite, libido decreased, back pain, salivary hypersecretion, nasal congestion, semen volume decreased, oropharyngeal pain, and galactorrhoea.

One subject in the paliperidone palmitate group died and the investigator considered the event of sudden death as doubtfully related to the study drug. However, the narrative indicates that that an autopsy was performed which indicated a blood clot moving from the leg.

Serious TEAEs were reported for 42 (18.6%) of subjects in the paliperidone palmitate group and 53 (24.3%) of subjects in the oral antipsychotics group. The majority of serious TEAEs in both treatment groups coded to Psychiatric Disorders [psychotic disorder (4.9% paliperidone palmitate; 3.2% oral antipsychotics), etc].

Treatment-emergent adverse events led to study discontinuation for 6 (2.7%) subjects in the paliperidone palmitate group and 4 (1.8%) subjects in the oral antipsychotics group.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study R092670-SCH-3006 comparing paliperidone palmitate with 7 atypical oral antipsychotics (from aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone) commonly formed the primary safety database for this review.

7.1.2 Categorization of Adverse Events

The sponsor examined adverse events of clinical interest (extrapyramidal-related and prolactin-related) and incidence of adverse events by subgroups. Extrapyramidal and prolactin related adverse events are discussed below (Sec 7.3.4: Significant Adverse Events).

TEAE's were summarized by age, baseline BMI, sex and race, and no clinically meaningful increased risk was detected in any of the subgroups evaluated by the sponsor.

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

Given that this sNDA is based on a single clinical study (R092670-SCH-3006), the Division agreed that a Summary of Clinical Safety/Integrated Summary of Safety and an integrated Summary of Clinical Efficacy/Integrated Summary of Efficacy were not required for the sNDA

7.2 Adequacy of Safety Assessments

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

The first dose of paliperidone palmitate was 234 mg, given on Day 1 of the treatment period. The second dose was 156 mg, given on Day 8 (#4 days). Starting on Day 38, flexible monthly maintenance dosing of paliperidone palmitate within the range of 78 to 234 mg was allowed. For the population in this trial, the recommended maintenance dose was 156 mg; however, based on previous clinical history of tolerability and/or efficacy, some subjects could benefit from lower or higher maintenance doses of the other available strengths (78 mg, 117 mg, and 234 mg). Decisions to increase or decrease the dose were made at the investigator's discretion based on clinical judgment.

After Day 15, subjects who were determined by the investigator to require a higher dose of paliperidone palmitate could receive supplemental oral paliperidone (3 or 6 mg) daily until the dose of paliperidone palmitate could be increased at the next injection day. Supplemental oral paliperidone was discontinued when the subject received an injection with the new, higher dose of paliperidone palmitate.

Subjects randomly assigned to the oral antipsychotic treatment group received one of the oral antipsychotics allowed in the study (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone). The IVRS randomly selected 1 of the medications that the investigator had specified as appropriate for the subject. The investigator selected a dose appropriate for the subject and provided a prescription and voucher for the assigned medication that the subject could present at a local pharmacy. Subjects who were randomly assigned to the oral antipsychotic treatment group began their assigned drug on Day 1.

Investigators were encouraged to use the randomly assigned oral antipsychotic as monotherapy and to adjust the dose for management of symptoms/tolerability at any

time. The sponsor provided remuneration in the form of a voucher for only 1 of the 7 protocol-specified oral antipsychotic medications at any one time. Subjects generally were treated within the approved dosage ranges for all antipsychotics

7.2.2 Explorations for Dose Response.

Study R092670-SCH-3006 was not designed to assess a dose-response of the efficacy of paliperidone palmitate due to the flexible dose nature of its design.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing were done for this study.

7.2.4 Routine Clinical Testing

Clinical laboratory testing, prolactin levels, urine drug screen, urinalysis, physical examination and ECG were done at screening. Laboratory testing was repeated at visit 18 (month 15). Urine drug testing was repeated at baseline and at visit 18 (month 15). ECG studies were not repeated. (Appendix: Schedule of Events for Screening, Treatment and Re-Initiation Phases)

7.2.5 Metabolic, Clearance, and Interaction Workup

None were done for this study.

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

In study R092670-SCH-3006, paliperidone palmitate was compared with atypical oral antipsychotics commonly used in clinical practice. Paliperidone palmitate and these oral antipsychotics appear to have a similar safety and tolerability profile in this 15-month study, with the exceptions identified by the sponsor below:

- The frequency of body weight gain of ≥7% from baseline to the end of treatment was higher for paliperidone palmitate.
- Larger increases in serum prolactin levels were observed for paliperidone palmitate and the frequency of prolactin-related TEAEs was also higher among subjects treated with paliperidone palmitate.
- Injection site pain was only reported as a TEAE in subjects treated with paliperidone palmitate.

7.3 Major Safety Results

7.3.1 Deaths

There was 1 death in Study R092670-SCH-3006. A subject in the paliperidone palmitate group died due to an unknown event as per the sponsor. A copy of the subject narrative is in the Appendix of this review indicates that an autopsy was performed which indicated “a blood clot moved from his leg.”

There was also an event of fetal death in the oral antipsychotics group. The female partner of a male subject in this group became pregnant while the male subject was on study (subject treated on study with risperidone), and subsequently gave birth to a full term infant who was dead at birth with the umbilical cord around its neck.

7.3.2 Serious Adverse Events

Serious TEAEs were reported for 42 (18.6%) of subjects in the paliperidone palmitate group and 53 (24.3%) of subjects in the oral antipsychotics group. The majority of serious TEAEs in both treatment groups coded to Psychiatric Disorders (event rates of 13.3% and 17.4%, respectively) and the most common individual events (≥ 2% in either group) were psychotic disorder (4.9% paliperidone palmitate; 3.2% oral antipsychotics), schizophrenia (1.8% vs 5.0%, respectively), suicidal ideation (2.2% vs 5.0%, respectively), paranoid type schizophrenia (1.8% vs 2.3%, respectively), depression (1.8%, 0.5%), suicide attempt (0.4%, 1.4%), and homicidal ideation (0%, 1.4%). Sponsor’s Table of Treatment Emergent Serious Adverse Events is copied and pasted in the Appendix.

7.3.3 Dropouts and/or Discontinuations

A total of 28 (12.4%) subjects in the paliperidone palmitate group and 19 (8.7%) subjects in the oral antipsychotics group experienced one or more TEAEs that led to discontinuation of study medication.

TEAEs led to discontinuation from the study for 6 (2.7%) of subjects in the paliperidone palmitate group and 4 (1.8%) of subjects in the oral antipsychotics group. No individual TEAE led to study discontinuation in more than 1 subject in the paliperidone palmitate group.

7.3.4 Significant Adverse Events

Extrapyramidal-related Adverse Events: 58 (25.7%) subjects in the paliperidone palmitate group and 43 (19.7%) in the oral antipsychotics group experienced EPS-related TEAEs. Akathisia occurred more frequently (≥ 2% difference) in the paliperidone palmitate group than in the oral antipsychotics group (11.5% vs 7.8%); no EPS-related

TEAE occurred more frequently in the oral antipsychotics group than in the paliperidone palmitate group. This is shown in sponsors table copied and pasted into the Appendix of this review.

Prolactin-Related Adverse Events: A total of 57 (25.2%) subjects in the paliperidone palmitate group and 11 (5.0%) subjects in the oral antipsychotics group experienced at least one prolactin related TEAE.

Among women in the p ITT analysis set (Refer to Table in Appendix), TEAEs potentially related to prolactin were reported for 11 of 33 women (33.3%) in the paliperidone palmitate group and 2 of 28 women (7.1%) in the oral antipsychotics group. The most frequently reported prolactin-related adverse events in the paliperidone palmitate group were as follows (paliperidone palmitate, oral antipsychotics): amenorrhea (15.2%, 3.6%), galactorrhea (15.2%, 0.0%), menstruation irregular (6.1%, 3.6%), hyperprolactinemia (6.1%, 3.6%), and blood prolactin increased (6.1%, 0.0%).

Among men in the p ITT analysis set (Refer to Table in Appendix), TEAEs potentially related to prolactin were reported for 46 of 193 men (23.8%) in the paliperidone palmitate group and 9 of 190 men (4.7%) in the oral antipsychotics group. The most frequently reported prolactin-related TEAEs in men were as follows (paliperidone palmitate, oral antipsychotics): erectile dysfunction (8.8%, 0.5%), libido decreased (6.7%, 1.6%), and blood prolactin increased (4.7%, 1.1%).

Specific Primary Safety Concerns

Based upon a review of the AE data from the Study R092670-SCH-3006, a total of 12 new ADRs were identified for paliperidone palmitate that are not currently listed in the INVEGA SUSTENNA USPI: abnormal weight gain; libido decreased; loss of libido; semen volume decreased; ejaculation failure; injection site discomfort; injection site irritation; injection site movement impairment; breast enlargement; breast pain; breast swelling; and cogwheel rigidity.

The following changes to the INVEGA SUSTENNA USPI are proposed by the sponsor:

- ADRs of libido decreased (also reflecting the similar ADR term of loss of libido), breast enlargement/breast swelling, and ejaculation disorder (which subsumes the ADR terms of ejaculation failure and semen volume decreased) will be added to the *Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA* subsection of the USPI. The ADR term, retrograde ejaculation, is also included under the broader ADR term of ejaculation disorder and will be removed from the *Adverse Reactions Reported in Clinical Trials with Oral Paliperidone* subsection of the USPI.
- The ADRs of breast tenderness/breast pain and cogwheel rigidity, while not previously identified as ADRs based on clinical experience with paliperidone palmitate, had previously been identified as ADRs for paliperidone ER. Therefore,

these ADRs will be moved from the *Adverse Reactions Reported in Clinical Trials with Oral Paliperidone* subsection of the USPI to the *Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA* subsection.

- No change to the INVEGA SUSTENNA USPI will be made regarding the ADR of abnormal weight gain as this ADR is considered sufficiently similar to the listed ADR of weight increased in the current USPI.
- No change to the INVEGA SUSTENNA USPI will be made regarding the ADRs of injection site discomfort, injection site irritation, or injection site movement impairment as these ADRs are considered to be part of the grouped listed ADR term of injection site reactions in the current USPI.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, treatment-emergent adverse events (TEAEs) were reported for 195 (86.3%) of subjects in the paliperidone palmitate group and 178 (81.7%) of subjects in the oral antipsychotics group. They led to study discontinuation for 6 (2.7%) subjects in the paliperidone palmitate group and 4 (1.8%) subjects in the oral antipsychotics group. Sponsor's table copied and pasted below summarizes this.

Table 26: Overall Summary of Treatment-Emergent Adverse Events; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects	226	218	444
Subjects with Treatment-Emergent Adverse Event	195 (86.3%)	178 (81.7%)	373 (84.0%)
Possibly related TEAE [a]	157 (69.5%)	113 (51.8%)	270 (60.8%)
TEAE leading to death	1 (0.4%)	0	1 (0.2%)
1 or more serious TEAE	42 (18.6%)	53 (24.3%)	95 (21.4%)
TEAE leading to treatment discontinuation [b]	28 (12.4%)	19 (8.7%)	47 (10.6%)

[a] Study drug relationship of possible, probable, and very likely are included in this category.
[b] Including subjects who discontinued during Treatment Phase with AE action taken as DRUG WITHDRAWN, but the onset of AE was in the Treatment Phase.
Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Reported dictionary version: MedDRA 12.0.

The TEAEs that were reported more frequently (≥ 2% difference) in the paliperidone palmitate group than in the oral antipsychotics group were: injection site pain (18.6%, 0.0%), erectile dysfunction (7.5%, 0.5%), insomnia (18.6%, 12.4%), weight increased (13.3%, 7.3%), fatigue (7.5%, 2.8%), libido decreased (5.8%, 1.4%), blood prolactin increased (4.9%, 0.9%), akathisia (11.5%, 7.8%), increased appetite (7.1%, 3.7%), abnormal weight gain (4.9%, 1.8%), salivary hypersecretion (3.1%, 0.0%), anxiety (11.1%, 8.3%), semen volume decreased (2.2%, 0.0%), nasal congestion (2.7%, 0.5%), oropharyngeal pain (2.2%, 0.0%), galactorrhea (2.2%, 0.0%), and back pain (5.8%, 3.7%). Sponsor's table showing TEAE's ≥ 2 % of subjects in any treatment group by preferred term is copied and pasted into the Appendix of this review.

A TEAE of weight increased was reported for 13.3% of subjects in the paliperidone palmitate group and 7.3% of subjects in the oral antipsychotics group in the pITT analysis set (Appendix).

A total of 58 (25.7%) subjects in the paliperidone palmitate group and 43 (19.7%) subjects in the oral antipsychotics group experienced EPS-related TEAEs.

A total of 57 (25.2%) subjects in the paliperidone palmitate group and 11 (5.0%) subjects in the oral antipsychotics group experienced at least one prolactin-related TEAE. The most frequently reported prolactin-related adverse events in the paliperidone palmitate group were amenorrhea, galactorrhea, menstruation irregular, hyperprolactinemia, and blood prolactin increased in women; and erectile dysfunction, libido decreased, and blood prolactin increased in men. At the final visit, 69.7% of women and 65.0% of men in the paliperidone palmitate group and 14.8% of women and 17.2% of men in the oral antipsychotics group had treatment-emergent prolactin concentrations above the upper limit of normal.

7.4.2 Laboratory Findings

Based on mean changes from baseline and the occurrence of treatment-emergent markedly abnormal values and associated TEAEs, the effects of paliperidone palmitate on the results of chemistry and hematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) showed no clinically relevant findings.

Clinically noteworthy mean changes from baseline in the pITT analysis set were as follows:

ALT:

- Screening: The mean (SD) concentration was 29.6 (23.95) U/L in the paliperidone palmitate group and 29.8 (27.30) U/L in the oral antipsychotics group
- Final Visit: It was 29.6 (27.54) and 37.6 (58.56) U/L, respectively and the mean (SD) change from screening to the final visit was -1.7 (23.22) and 3.8 (53.31) U/L, respectively.

AST:

- Screening: The mean (SD) concentration at screening was 27.2 (15.75) U/L in the paliperidone palmitate group and 28.2 (27.22) U/L in the oral antipsychotics group
- Final Visit: it was 28.0 (21.19) and 36.3 (47.37) U/L, respectively and the mean (SD) change from screening to the final visit was 0.8 (18.64) and 5.8 (43.03) U/L, respectively.

CPK:

- Screening: The mean (SD) concentration at screening was 237.0 (192.95) U/L in the paliperidone palmitate group and 244.0 (225.49) U/L in the oral antipsychotics group
- Final Visit: It was 257.7 (314.55) and 258.1 (242.02) U/L, respectively and the mean (SD) change from screening to the final visit was 11.6 (335.24) and 16.4

Prolactin:

- Women: Mean (SD) prolactin in the pITT analysis set increased from 15.0 (16.1) µg/L at screening to 76.3 (56.1) µg/L at 15 months (LOCF) in the paliperidone palmitate group, compared with values of 27.3 (37.5) µg/L at screening and 27.4 (30.7) µg/L at 15 months (LOCF) in the oral antipsychotics group.

- Men: Mean (SD) prolactin in the pITT analysis set increased from 11.1 (12.4) µg/L at screening to 29.6 (15.9) µg/L at 15 months (LOCF) in the paliperidone palmitate group, compared with values of 10.2 (13.5) µg/L at screening and 11.2 (10.4) µg/L at 15 months (LOCF) in the oral antipsychotics group.

Individual Clinically Significant Abnormalities

Markedly abnormal chemistry values at the final visit (15 months LOCF) that occurred in 2 or more subjects in either treatment group (paliperidone palmitate, oral antipsychotics) were: high ALT (1 subject, 4 subjects), high AST (0 subjects, 3 subjects), high glucose (2 subjects, 1 subject), and high triglycerides (2 subjects, 0 subjects).

Serious Laboratory TEAE's

Two subjects had serious TEAEs due to laboratory abnormalities: 1 subject in the paliperidone palmitate group had a serious TEAE of hyponatremia and 1 subject in the oral antipsychotics group had a serious adverse event of hypoglycemia (Appendix, Table of Incidence of Serious Treatment Adverse Events). Neither event was considered by the investigator to be related to study treatment.

7.4.3 Vital Signs

A clinically notable increase in pulse rate (≥100 bpm with an increase of ≥15 bpm) was reported for a similar percentage of subjects in the paliperidone palmitate and oral antipsychotics groups (12.8% vs 11.0%, respectively). Fewer than 2% of subjects in the paliperidone palmitate group experienced a clinically notable increase or decrease in systolic or diastolic blood pressure.

Body Weight

Average BMI values at baseline indicated that approximately two-thirds of subjects in Study R092670-SCH-3006 were overweight (25 to <30 kg/m2) or obese (≥ 30 kg/m2) at study entry. The mean increase in body weight at the final visit was 3.3 kg for the paliperidone palmitate group compared with <1 kg for oral antipsychotics group, and starting at 1 month, subjects in the paliperidone palmitate group were more likely than subjects in the oral antipsychotics group to have abnormal weight gain (an increase ≥7%). These results were consistent with those reported for paliperidone palmitate in other studies. Portions of sponsors table, copied and pasted below, showing abnormal weight changes from start to study end.

Table 35: Incidence of Abnormal Weight Change; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Day 8			
N	204	193	397
Decrease >=7%	1 (0.5%)	1 (0.5%)	2 (0.5%)
Increase >=7%	3 (1.5%)	2 (1.0%)	5 (1.3%)
Final visit (15 Months LOCF)			
N	219	210	429
Decrease >=7%	26 (11.9%)	26 (12.4%)	52 (12.1%)
Increase >=7%	74 (33.8%)	39 (18.6%)	113 (26.3%)

Note: Percentages calculated with the number of subjects per parameter as denominator.

7.4.4 Electrocardiograms (ECGs)

Results of the ECG at the screening visit were not reported in the CRF unless they were deemed clinically significant and relevant by the investigator. No follow-up ECG's were apparently done.

7.5 Additional Submissions / Safety Issues

The sponsor examined clinically notable changes in vital signs for each treatment group, and for changes in Sexual Side Effects Questionnaire (SSEQ) and InterSePT Scale for Suicidal Thinking-Plus (ISST-Plus). There was no evidence of clinically meaningful changes from baseline to the final visit for any question on the SSEQ in either treatment group. For the ISST-Plus, at any visit, 2% or fewer subjects in either treatment group reported positively for most of the questions about suicidal ideation or attempts. No major shifts in the global suicidality rating were observed during the study.

In the pITT analysis set, a total of 28 (12.8%) subjects in the paliperidone palmitate group and 23 (11.0%) subjects in the oral antipsychotics group experienced a clinically notable pulse increase from baseline, and 3 (1.4%) and 9 (4.3%) subjects, respectively, experienced a clinically notable diastolic blood pressure increase from baseline.

Starting at 1 month, subjects in the paliperidone palmitate group were more likely than subjects in the oral antipsychotics group to have abnormal weight gain (an increase ≥ 7%) at each visit. At the final visit, the mean (SD) change from baseline in body weight in the pITT analysis set was 3.3 (8.90) kg in the paliperidone palmitate group and 0.9 (8.23) kg in the oral antipsychotics group.

8 Postmarketing Experience

A cumulative review of the spontaneous post-marketing adverse events reported to the sponsor's safety database, for paliperidone palmitate in the schizophrenic population was conducted by the sponsor up to February 28, 2014. They identified 3,165 spontaneous cases involving paliperidone palmitate either as suspect, co-suspect, or suspect-interacting drug. Of the 3,165 cases, 71 involved at least 1 PT with a fatal outcome. There were no cases reporting fatal neuroleptic malignant syndrome, rhabdomyolysis, or cancer. Six cases involving cardiovascular causes of death (not reporting sudden death) were either insufficiently documented or reported factors that confounded the assessment of the case. Of the 22 cases of sudden or unexplained deaths, none reported torsade de pointes or ventricular fibrillation. The vast majority of cases lacked important information including concomitant medications, medical history, latency, and/or details of the patient's death. Cardiac arrest was the cause of death reported in the 1 case reporting autopsy information. Five of the 22 cases reported antipsychotic polypharmacy, and cardiovascular risk factors were reported in slightly more than half of the cases (12/22, 54%). Six cases involved a latency of 14 days or less; however, 4 reported at least 1 cardiovascular risk factor, 2 of which also involved antipsychotic polypharmacy.

The sponsor states that there have been numerous reports in the literature of higher mortality rates among persons with schizophrenia compared with the general population with predominant causes being cardiovascular, unnatural deaths (including suicide), respiratory and cancer related. They further state that ischemic heart disease is underdiagnosed in this population and sudden cardiac death has been found to occur well above the general population rates. The cases involving reports of sudden death or cardiovascular disease did not reveal any new safety information regarding paliperidone palmitate. The sponsor states that their assessment of the causes of death in the remaining cases with fatal outcome was consistent with the causes of death reported within the schizophrenia population in the literature.

Sponsor's review of cases involving potential risks in the EU RMP did not change the assessment of these risks. Their review of events reported in cases of pregnancy exposure did not detect any emerging safety signals specific to paliperidone palmitate use in this population.

Sponsor's review of post-marketing cumulative data for paliperidone palmitate in the schizophrenic population through was generally consistent with the established safety profile of oral paliperidone. They identified no new significant safety issues.

9 Appendices

9.1 Literature Review/References

The sponsor provided a list of literature references and articles dealing with long acting injectable antipsychotics and its role in relapse prevention, incarceration in schizophrenia, clinical effectiveness trials, treatment adherence; prevalence of mental illness in jail detainees; and second generation antipsychotic drugs.

9.2 Labeling Recommendations

Since a CR action will be taken, no labeling should be considered until the specific deficiencies and corrective actions identified are corrected to place the application in a suitable condition for approval.

9.3 Advisory Committee Meeting

There are currently no plans to have an Advisory Committee Meeting to further discuss this application.

A Regulatory Briefing was conducted on January 30, 2015 at which time the present application was discussed. Some of the problems associated with this application were identified.

9.4 Other

List of Investigators

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
USA	001209 Received drug	Adams. Neal, M.D., MPH 1611 Telegraph Avenue Suite 100 & 1550 Oakland, CA 94612 USA	Kline, Howard, M.D. Bland, Farzana, PsyD (b) (6) Cottrell, K.I. M.D. (b) (6) Lalonde, Irene, R.N. Nanda, Simret, M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001061 Did Not Receive Drug	Alam, Mohammed, M.D. 1200 Harger Rd Oak Brook, IL 60523	Alam, Dinesh, M.D. Khadri, Syed, M.D. Khan, Farrah, M.D., MPH Pazhampally, Jose , MSW, MDSW Zusevics,Linda, PsyD	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001063 Received drug	Baber, Riaz, M.D. 1460 Bond Street Suite 130 Naperville, IL 60563 USA	Golewale, Mazhar Hasan, M.D. Gupta, Seema, M.D. Vita, Anthony J., M.D.	Sub-Investigator Sub-Investigator Sub-Investigator
USA	001054 Received drug	Bailey, Rahn, M.D. 1005 D B Todd Blvd Nashville, TN 37208 USA	Ali, Shahid, M.D. Jabeen, Shagufta, M.D.	Sub-Investigator Sub-Investigator
USA	001083 Received drug	Balkunas, Michael, M.D. 100 Grand Street New Britain, CT 06050 USA	Caratas, Mihai, M.D. (b) (6) (b) (6)	Sub-Investigator
USA	001082 Received drug	Bari, Mohammed, M.D. 1908 Sweetwater Rd. National City, CA 91950 USA	Dolnak, Douglas, D.O. Ishaque, Saleem, M.D. Jenkin, Frederick D., M.D. Vassilenko, Ekaterina, M.D. Williams, Jonathan, Ph.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001210 Received drug	Bell, Carl, M.D. 8704 S. Constance Ave. Chicago, IL 60617 USA	(b) (6)	
USA	001086	Bennett, Jeffrey		

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USA	001040 Received drug	Bhatia, Prakash, M.D. 710 E Grand Ave Escondido, CA 92025 USA	Allen, John, M.D. Brown, Harold T., PhD Deilgat, Jaclyn, MA Dennis, Tshekedi G., M.D. Paniccia, Gregory, M.D. Woodaman, Betty, RN Woodaman, Woody, MA	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001034 Received drug	Brauer, Robert, M.D. 35900 Euclid Avenue Willoughby, OH 44094 USA	Barley, Leonard, M.D. Christmyer, Luannn, RN Levicky, Marie Parran, Jr., Theodore V., M.D. Savioli, Wanda, RN MS, CCRP	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001011 Did not receive drug	Brenner, Ronald 74 Carman Avenue Cedarhurst, NY 11516 USA	Adler, David N., M.D. (b) (6) Bartha, Griselda, M.D. Brodsky, Ella, M.D. (b) (6)	Sub-Investigator Sub-Investigator Sub-Investigator
USA	001084 Received drug	Cai, Wen, M.D. 3615 North Prince Village Place Tuscon, AZ 85719 USA		
USA	001002 Received drug	Camacho, Alvaro, M.D. 2417 Marshall Ave, Ste 1 Imperial, CA 92251 USA	(b) (6) Ng, Bernardo, M.D. (b) (6) Wetherill, Paul, PA	 Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
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USA	001077 Did not receive drug	Chandra, Rakesh, M.D. 225 Medical Center Drive Suite 305 Paduca, KY 42003 USA	(b) (6) Wallace, Jesse, M.D.	Sub-Investigator
USA	001078 Received drug	Colon, Marc Andrew, M.D. 3202 William Ave. Shreveport, LA 71103 USA	Ahmad, Uzma, M.D. Amin, Shweta, M.D. Boykin, Barbara A., BA Claiborne, Jeremy R., M.D. Geller, Felix A., M.D. Guthrie, Joseph C., M.D. (b) (6) Huynh, Nga, M.D. Joe, Roger, M.D. Khalid, Ovais, M.D. Kumar, Dharmendra, M.D. Lee, Robert, M.D. (b) (6) Modi, Dhruv B., M.D. Narayana, Swamy Suresh Sabbenalli, M.D. Nguyen, Nhu, M.D. Paladugu, Anubha, M.D. Papaspyros, George, M.D. Purawat, Sapna, M.D. (b) (6) Roggero, Barbara, BA, CCRC Rowell, John P., RN Sangsura, Smink, M.D. (b) (6) Singh, Jasjit Kaur, M.D. Smith, Katie, M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
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			Su, Michael X.	Sub-Investigator
			Thanaseelan, Jayaselvi, M.D.	Sub-Investigator
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			O'Meara, Charles, RN	Sub-Investigator
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			Harris, Jimmie, D.o.	Sub-Investigator
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			(b) (6)	
USA	001098 Received Drug	Dubovsky, Steven L., M.D. 462 Grider Street Buffalo, NY 14215 USA	Cummings, Michael R., M.D.	Sub-Investigator
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USA	001025 Received Drug	Fils, Jean, M.D. (Current PI) Keefe, Brian (Former PI) 3515 East Fletcher Ave. Tampa, FL 33613 USA	Bannon, Yvonne, RN	Sub-Investigator
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			Marsh, Patrick J., M.D.	Sub-Investigator
			Santana, Carlos, M.D.	Sub-Investigator
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USA	001022 Received Drug	Frei, Karen, M.D. (Current PI) Edrozo, Johnny A., M.D. (Former PI) 1814 Commerce Center West San Bernadino, CA 92408 USA	Diaz, Maria Rosario	Sub-Investigator
			Edrozo, Johnny, M.D.	Sub-Investigator
			Frei, Karen	Sub-Investigator
			Sauber, Chris	Sub-Investigator
			Walters, Donald E.	Sub-Investigator
			Pugh, Renail, RN	Sub-Investigator
			Hatch, Lonnie, LVN	Sub-Investigator
			Pratcher, Katrina, PMHNP	Sub-Investigator
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			Nader, Joseph, MD	Sub-Investigator
USA	001091	Horne, Robert, M.D.	Breiland, Keith, M.D.	Sub-Investigator

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USA	001053	Iqbal, Javed 230 E Ridgewood Avenue Paramus, NJ 07652 USA	Cheema, Faiz, M.D. Ghaffar, Sadia, MD Montagnino, Joseph W., M.D. Nadeem, Ferhana, M.D. Noorani, Gulam, M.D. Penciu, Cristian, M.D. Vaks, Yakir, M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001012 Received Drug	Isacescu, Valentin, M.D. 3230 Waring Court Oceanside, CA 92056 USA	(b) (6) Lindamood, Timothy Evan, M.D. Sheth, Manish V., M.D., PhD Zalewski-Zaragoza, Robert A., M.D. Melden, Mark, D.O.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001204 Did not receive drug	Jamil, Shahid 27780 Novi Road, Suite 101 Novi, MI 48377 USA	(b) (6) Krstevska, Shana S., M.D. Schechter, Steven H., M.D.	Sub-Investigator Sub-Investigator
USA	001036 Received Drug	Kaczenski, Gregory, M.D. 801 Scott St Little Rock, AR 72201 USA	Ashby Christine Ballard Clarence, M.D. Davis Betty Evans Lauren Hammil Joyce Ellen Powell Andrew Reid Graham	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001024 Did not receive drug	Kansagra, Pravin, M.D. 1781 W Rumneya Dr #B Anaheim, CA 92801 USA	Rajani, Raj P., M.D.	Sub-Investigator
USA	001026 Received drug	Knesevich, Mary A., M.D., P.A. 4225 Wingren Plaza Suite 105 Irving, TX 75062 USA	Hudson, Jack S., MSSW, LCSW Bolen, Roger L. Liverman, R.E., D.O. Hodges, Ralph Gail, M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001062 Received Drug	Krefetz, David G., D.O. 1113 Hospital Dr Ste 202	Glass, Steven J., M.D. Hassman, Howard A., D.O.	Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
		Willingboro, NJ 08046 USA	Pinho, Maria, RN Steinerman, Joshua, M.D. Brown, Juliet, PhD	Sub-Investigator Sub-Investigator Sub-Investigator
USA	001027 Received Drug	Kwentus, Joseph, M.D. 3531 Lakeland Drive Brentwood Plaza Suite 1060 Flowood, MS 39232 USA	Hall, Sara, RN Nhema, Shungu, MS Rack, Sara K., M.D. Richardson, Karen S., PhD Rochelle, Danny	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001004 Received Drug	Lerman, Mark N., M.D. 1786 Moon Lake Blvd Ste 200 Hoffman Estate, IL 60169 USA	(b) (6) Judge, Lisa, R.N. Kumar, Siddhartha, M.D. (b) (6) Patel, Chinmay K., D.O. (b) (6) Schmidt, Karen L., Psy.D. (b) (6)	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001013 Received Drug	Lindenmayer, Jean-Pierre, M.D. Ward's Island Complex New York, NY 10035 USA	Augustin, Paul, M.D. (b) (6) Glen Dirk, BS Kaushik, Saurabh, M.D. (b) (6) Parak Mohan, M.D. Parker, Benedicto B., M.D. Saintu, Dharampaul, LPN Smith, Robert, M.D. El Gamal, Eman, M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001099 Received Drug	Lu, Brett Y., M.D. 1356 Lusitana St Fl 4 Honolulu, HI 96813 USA	Luk, Selene, D.O. Nishimura Stephanie, PhD	Sub-Investigator Sub-Investigator
USA	001057 Received Drug	Malcolm, Robert J., M.D. 67 President Street Charleston, SC 29425 USA	Barth, Kelly, D.O. Donovan, Jennifer, PhD Fields, Christopher Scott, M.D. Hamner, Mark, M.D. Hebbard, Amy, PharmD Jackson, Michelle, PharmD Nichols, Taylor, PharmD O'Rourke, Colleen, MD	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
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			Vandenberg, Amy, PharmD	Sub-Investigator
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USA	001208 Received Drug	Mantero-Atienza, Emilio, M.D., PhD 1300 SW 27Av Miami, FL 33145 USA	Grenier, Ernesto, M.D. Murillo, Abel, M.D.	Sub-Investigator Sub-Investigator
USA	001092 Received Drug	Mee-Lee, Denis 1286 Queen Emma Street Honolulu, HI 96813 USA	Brandon, Valerie, M.D.	Sub-Investigator
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USA	001006 Received drug	Mobley, Lawrence Edward, III, M.D. 1221 W. Lakeview Avenue Pensacola, FL 32501 USA	Cherian, Annie, M.D.	Sub-Investigator
USA	001007 Received drug	Murphy, Paul W., M.D. 1100 North St. Francis Suite 300 Wichita, KS 67214 USA	(b) (6) Williamson, Sheila K., M.D. (b) (6)	Sub-Investigator
USA	001073 Received drug	Mustafa, Syed Jamal 10634 East Riverside Drive Suite 100 Bothell, WA 90811 USA	Chaudhary, Narayan, M.D. Mustafa, Syed Kamal, M.D.	Sub-Investigator Sub-Investigator
USA	001058 Received drug	Novitsky, Mark A., M.D. 111 N 49Th St Ste 119	Gruener, Daniel, M.D. Kramer, Shirley, MA	Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
		Philadelphia, PA 19139 USA	(b) (6)	
USA	001066 Received drug	Patel, Nilesh J., M.D. 10119 US 59, Suite 100 Wharton, TX 77488	(b) (6) Brams Matthew, M.D.	Sub-Investigator
USA	001059 Received drug	Pean, Pierre, M.D. 4600 W. Commercial Blvd. Suite 1 Tamarac, FL 33319 USA		
USA	001205 Received drug	Peyton, Marvin Lane, M.D. 2601 N.W. Expressway Suite 602 West Oklahoma City, OK 73112 USA	Minatra Sue Skarky Steve, M.D. Tinsley Charlotte White Rebecca Hallett, Jennifer E.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001090 Received drug	Ramadan, Mohamed, M.D. 2580 Highway 95 Suite 215 Bullhead City, AZ 86442 USA	Denomme, Melissa Hobson, Sharon, RN Shumaker, Mary Wilson, Kristen, APRN	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001038 Received drug	Ramaswamy, Sriram, M.D. (Current PI) Wilson, Daniel, M.D. (Former PI) 3528 Dodge Street Omaha, NE 68131 USA	Bestha, Durga, M.D. (b) (6) Dickerson, Davin, NPC Domnitei, Diana, M.D. (b) (6) Jeevarakshagan, Shamala, M.D. Kinaan, Shannon, M.D. Madaan, Vishal, MD Farooq, Umer, M.D. Fahner, Jill, BS Singh, Harmit, M.D. Qadri, S. Faiz, M.D. Madabushi, Jayakrishna, M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001015 Did not receive drug	Riesenberg, Robert A., M.D. 811 Juniper Street NE Atlanta, GA 30308 USA	Atella, Maria K., BA Siddappa, D.S., M.D. Yang, Kendra S., BA, MA	Sub-Investigator Sub-Investigator Sub-Investigator
USA	001074 Received drug	Sajatovic, Martha, M.D. W.O. Walker Center- 7th Floor	Hahn, David Y., M.D. Ramirez, Luis F., M.D.	Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
		10524 Euclid Avenue Cleveland, OH 44106 USA		
USA	001043 Received drug	Saklad, Stephen R., PharmD, BCCP 7703 Floyd Curl Drive MC 6220 San Antonio, TX 78229 USA	Raj, Jeslina, PsyD Taylor, Sally B., M.D. Wallace, Christopher, M.D. Watson, Nicole, MS Martinez Jr., Cervando, M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001030 Received drug	Sfera, Adonis, M.D. 3400 W Ball Rd Ste 100B Anaheim,CA 92804 USA	Diaz, Maria Rosario Kaur, Jasit, M.D. Kong, Min Vu, Chuong Becerra, Vasthl Akulov, Anton	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001051 Received drug	Shiwach, Rajinder M.D.(Current PI) Brownlee, Ernest Jr., M.D. (Former PI) 1011 N. Cooper Street Arlington, TX 76011 USA	Shiwach, Rajinder M.D. Reddy, Tarakumar, M.D. (b) (6) Badea-Barothi, Paul Stelian, M.D.	Sub-Investigator Sub-Investigator (b) (6) Sub-Investigator
USA	001050 Received drug	Sommi, Roger, PharmD, BCCP, FCCP School of Pharmacy 4250 Health Sciences Bldg. 2464 Charlotte Street Kansas City, MO 64108 USA	Dellenbaugh, Timothy, M.D. (b) (6) Jarvis, Stephen, M.D. Nelson, Leigh Anne, PharmD Shelley, William C., M.D. Winans, Elizabeth, PharmD	Sub-Investigator (b) (6) Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001055 Received drug	St. Clair, Dwight S., D.O. 1709 South Rock Road Wichita, KS 67207 USA	(b) (6) Coyner, Laurie S., M.D. Denner, Danielle M., LPN Duncan, Sheri L., RN (b) (6) Hook, Kristen N. Keely, Deanna R. RN Klein, Terry D. M.D. Klein, Thomas C., M.D. Klein, Tracy R., M.D. Lingvai, Sonya, BA Meyers, Scott L., M.D. Nold, Joni J., RN Poling, Terry L., M.D.	(b) (6) Sub-Investigator Sub-Investigator Sub-Investigator (b) (6) Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
			Reed, Victoria L., PA-C	Sub-Investigator
			Rudick, Jessica M., BA	Sub-Investigator
			Stuckey, Lisa R., PA-C	Sub-Investigator
			Thome, Cindy N., RN	Sub-Investigator
			Turner, Gabrielle L., PA-C	Sub-Investigator
			Wheeler, Kristine M., RN	Sub-Investigator
			Kempke, Laynee L., LPN	Sub-Investigator
			Burden, Kelsey J., MS	Sub-Investigator
USA	001016 Received drug	Stedman, Mary L., M.D. 3212 Cove Bend Drive Tampa, FL 33613 USA	Herrero. Belen M., M.D. Carulli, Denise M., ARNP	Sub-Investigator Sub-Investigator
USA	001020 Received drug	Sunder, Rajagopal Keerthy, M.D. (Current PI) Chung, Lily S., M.D. (Former PI) Rajadhyaksha, Sadashiv, M.D. (Former PI) Dey, Samuel E. Jr., M.D. (Former PI) 5700 Division Street Suite 101 Riverside, CA 92506 USA	Simons, Jeffrey R., M.D. F.C.C.P. Dougan, Princess, M.D. (b) (6) Saied, Saied Ibrahim, M.D. Rajadhyaksha, Sadashiv, M.D. Benzor, Joanne M., M.D. Ramierez, Monica, CRC Kauffman, Renee	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001088 Received drug	Torres, Jose R., Dr. Highway 877 Km 1.6 Camino Las Lomas Rio Piedras, PR 00926	Pardo, Cecilio F., Dr.	Sub-Investigator
USA	001089 Received drug	Townsend, Mark H. 3450 Chestnut Street New Orleans, NO 20115 USA	Conrad, Erich J., M.D. Zibilich, Craig M., BS	Sub-Investigator Sub-Investigator
USA	001093 Received drug	Tran, John, M.D. 400 S Jefferson Street Suite 109 Spokane, WA 99204 USA	Davis, Joan, M.D. (b) (6) Smith, Lisa Marie, M.D. Snyder, Nicole Bland, Kathryn	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001037 Received drug	Tran-Johnson, Tram K., Pharm.D., PsyD. 446 26th Street 6th Floor San Diego, CA 92102	Benbow, Christopher H., M.D. Chen, James Y., M.D. Dahms, Eric B., M.D. Takamura, Michael M., M.D.	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator

Region	Site No.	Principal Investigator / Site Address	Other Participants	Role
		USA	Gutierrez, Aireen L., M.D. Torres, Randall P., PsyD. Bobo, Jerry C., M.D. (b) (6) Nguyen, Ngocbich T., M.D. (b) (6) Olonon, Christopher, M.D. Perkovic, Romina L., M.A. Bautista, Maria C., M.D. (b) (6)	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001069 Received drug	Valente, Thomas J., M.D. 2020 Tally Road Leesburg, FL 34749 USA		
USA	001045 Received drug	Vasiliu-Feltes, Ingrid (Current PI) Steinbook, Richard, M.D. (Former PI) 1120 NW 12th Street 14th Floor Miami, FL 33136 USA	Bellon, Alfredo, M.D. (b) (6) Rios, Juan, M.D. (b) (6) Strassnig, Martin T., M.D.	Sub-Investigator Sub-Investigator Sub-Investigator
USA	001046 Received drug	Volk, Stephen J., M.D. 1040 Elm Avenue Suites 309/204 Long Beach, CA 90813 USA	Apostle,Thomas, D.O. Badolian, Hagop (Jake) Gursky, Ellen Melson, Alexis Slomnski, Cindy L., M.D., MPH	Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator
USA	001070 Did not receive drug	Weisman, Robert, D.O. 2613 W. Henrietta Road Rochester, NY 14623 USA	Bilinski, Tamara, MA Lamberti, Steven J., M.D. Milligan, Jacqueline, MA (b) (6)	Sub-Investigator Sub-Investigator Sub-Investigator
USA	001039 Received drug	Woyshville, Mark J., M.D. 18660 Bagley Road Building II, Suite 205 Middleburg Heights, OH 44130 USA	Syed, Abu Nasir, M.D.	Sub-Investigator
USA	001018 Did not receive drug	Zaglul, Jose T., M.D. 2020 26th Avenue East Bradenton, FL 34208 USA	Carol, Jennifer, PsyD. Cutler,Andrew J., M.D.	Sub-Investigator Sub-Investigator

[**Instructions**: Include all investigators for whom information was submitted to the health authority. In the Site No. column, indicate whether the site "**received drug**" or "**did not receive drug**"]

TIME AND EVENTS SCHEDULE – SCREENING PHASE

Procedures	Study Phase: Day(s):	Screening -14 to -1
Informed consent and quiz		X
Pharmacogenomic informed consent[a]		X
Physical Examination, including height		X
Medical history		X
Psychiatric History		X
Inclusion/exclusion criteria		X
Vital signs and weight		X
Electrocardiogram[b]		X
Clinical laboratory sample collection		X
Prolactin blood sample collection		X
Urinalysis		X
Urine drug screen		X
Urine pregnancy test[c]		X
Mini International Neuropsychiatric Interview (M.I.N.I.)[d]		X
Prior and concomitant medication[e]		X
Adverse events		X
Oral tolerability test (OTT)[f]		X

Screening procedures may be initiated only after informed consent has been provided and the quiz completed/passed. Screening should begin no later than 90 days after a subject is released from custody and be completed within 14 days of the subject signing the informed consent form.

[a] The pharmacogenomics informed consent form may be signed at any time during the study; participation in the pharmacogenomics part of the study is optional and is, therefore, not required for participation in the main component of the study.

[b] Obtained locally.

[c] Women of childbearing potential, urine dipstick test

[d] The M.I.N.I.(Version 6.0) must be administered by medically qualified site personnel

[e] For subjects who enter screening while receiving more than 1 oral antipsychotic, the investigator will choose 1 medication for the subject to continue taking. The other medication(s) should be tapered down and discontinued over the first 3 days of screening and before Day 1. Subjects must be taking no more than 1 oral antipsychotic on the day before randomization.

[f] Subjects who do not have prior exposure to risperidone or paliperidone oral or injectable formulations must complete the OTT with risperidone.

Time and Events Schedule-Treatment Phase

TIME AND EVENTS SCHEDULE – TREATMENT PHASE

Phase:	Treatment																		
Visit:	1[a]	2[b]	3[b]	4[b,c]	5	6	7	8	9	10	11	12	13	14	15	16	17	18[d]	UV[e]
Month:	0	0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15[l]	
Day:	1	8	15	38	Monthly (30 Days) ±7 Days													458	
Procedure																			
Randomization[f]	X																		
Vital signs and weight	X	X	X	X		X			X			X			X			X	X
Clinical laboratory sample collection																		X	
Prolactin blood sample collection				X					X						X			X	
Pharmacogenomic sample collection[g]	X																		
Urine drug screen	X[h]																	X	O
Urine pregnancy test	X[h]																	X	O
Alcohol/Drug Use Questionnaire[i]	X								X									X	
CGI-S	X	X	X	X		X			X			X			X			X	X
PSP	X			X		X			X			X			X			X	X
RUQ	X					X			X			X			X			X	X
MSQ	X	X	X	X		X			X			X			X			X	X
Search public records for arrest						X			X			X			X			X	X
ISST-Plus	X		X			X			X			X			X			X	
ISST-Plus Short Form[j]		X		X	X		X	X		X	X		X	X		X	X		X
IADL	X			X	X	X			X			X			X			X	
ESRS-A	X	X							X									X	
SDS	X					X			X			X			X			X	
SSEQ	X			X					X						X			X	
Administer study drug or provide voucher[k]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Assessment for treatment failure		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

CGI-S=Clinical Global Impression-Severity; ESRS-A=Extrapyramidal Symptom Rating Scale-abbreviated; IADL=Instrumental Activities of Daily Living; ISST-Plus=InterSePT Scale for Suicidal Thinking-Plus; MSQ=Medication Satisfaction Questionnaire; O=Optional; PSP=Personal and Social Performance; RUQ=Resource Utilization Questionnaire; SDS=Sheehan Disability Scale; SSEQ=Sexual Side Effects Questionnaire; UV=Unscheduled Visit.

Footnotes can be found on the following page.

[a] Visit 1=Baseline

[b] Visit 2 should occur on Day 8±4 days, Visit 3 on Day 15±3 days, and Visit 4 on Day 38±7 days (if this window is exceeded, the Medical Monitor should be called).

[c] Visit 4 and all subsequent visits may occur ±7 days of the stated day.

[d] For all subjects, Visit 18 procedures will be completed at the end-of-study or at the time of early withdrawal from the study.

[e] Unscheduled visits should be performed, as necessary for the following reasons
1) Unscheduled visits that are clinically indicated: Unscheduled visits should be performed as necessary in the judgment of the physician for appropriate clinical care, including reasons of safety or tolerability.
2) Unscheduled visits for investigational purposes: Any subject who experiences a protocol defined treatment failure event before Visit 18 should undergo an unscheduled visit. This applies to every treatment failure episode; not just the initial. If an unscheduled visit can't be performed before the next scheduled protocol visit, applicable unscheduled visit procedures should be performed during the scheduled visit even when they are not normally part of the scheduled visit. Note that subjects who experience a treatment failure event should continue in the study.

[f] Contact the Interactive Voice Response System (IVRS) and, based on the investigator's clinical judgment, prespecify the oral antipsychotic for entry into the IVRS.

[g] Subjects who provide informed consent for the pharmacogenomics component of the study will have the 10-mL blood sample collected. The sample should be collected at the time that informed consent for participation in pharmacogenomic portion of the study is obtained. Collection of the blood sample should not be done until the subject is found to be eligible for entry into the treatment phase.

[h] Pregnancy and drug testing should be completed before the first administration of study drug. Additional urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy throughout the study.

[i] This questionnaire is derived from the Addiction Severity Index-lite (ASI-lite). At baseline, the full Drug and Alcohol section of the ASI-lite will be administered. A modification of this section will be administered at the subsequent visits at which this scale is administered (Visits 9 and 18).

[j] If suicidality is identified (ie, 'yes' is answered to questions 1.0, 2.2, 3.0, or 4.0 of the ISST-Plus Short Form) the full ISST-Plus should be administered.

[k] The IVRS should be contacted to either obtain the paliperidone palmitate kit number or confirm the subject is continuing on their randomized oral treatment. Subjects who are randomly assigned to receive paliperidone palmitate will receive injections after all screening assessments have been completed. After the initial 2 injections, injections may be given in a deltoid or gluteal muscle—alternating sides. Subjects who are randomly assigned to receive an oral antipsychotic will be provided a voucher to present at a local pharmacy to receive their assigned study drug.
If a subject receiving paliperidone palmitate is without an injection for more than 6 weeks, refer to Section 3.2.5, Re-Entry Following Missed Injections or Visits, for directions for reinitiation of injections.

[l] After Visit 4 (Day 38), all subsequent study visits are to occur monthly (+ 7 Days) from the previous study visit. In order to be considered to have completed the study a subject must have completed Visit 18 and have had a treatment period of at least 15 months (458 days).

a Visit 1=Baseline

TIME AND EVENTS SCHEDULE – RE-INITIATION VISIT

Up to Two Consecutive Injections or Visits Missed	
Visit[a]	Reinitiation Day 1[b]
Procedures	
CGI-S	X
PSP	X
RUQ	X
MSQ	X
Vital signs and weight	X
ESRS-A	X
Concomitant medication	X
ISST-Plus Short Form[e]	X
Adverse events	X
Contact IVRS[f]	X
Provide study drug or voucher	X
Assessment for treatment failure	X

Three or More Injections or Visits Missed		
Visit[a]	Reinitiation Screening[c]	Reinitiation Day 1[b]
Procedures		
Informed Consent	X	
CGI-S		X
PSP		X
RUQ		X
MSQ		X
Vital signs and weight	X	X
ESRS-A		X
Clinical laboratories	X	
Urine drug screen	X	
Urine pregnancy test[d]	X	
Prolactin blood sample collection	X	
Concomitant medication	X	X
ISST-Plus Short Form[e]		X
Adverse events	X	X
Contact IVRS[f]		X
Provide study drug or voucher		X
Assessment for treatment failure	X	X

CGI-S=Clinical Global Impression-Severity; ESRS-A=Extrapyramidal Symptom Rating Scale-abbreviated; IADL=Instrumental Activities of Daily Living; ISST-Plus=InterSePT Scale for Suicidal Thinking-Plus; MSQ=Medication Satisfaction Questionnaire; PSP=Personal and Social Performance; RUQ=Resource Utilization Questionnaire; SDS=Sheehan Disability Scale; SSEQ=Sexual Side Effects Questionnaire

[a] See Section 3.2.5, Re-Entry Following Missed Injections or Visits, for further explanation.
[b] Reinitiation Day 1 is required for subjects who are returning to the study after missing at least 1 paliperidone palmitate injection or 1 scheduled visit.
[c] Reinitiation screening is required for all subjects who are returning after missing 3 or more consecutive injections or visits and is to occur before the Reinitiation Day 1 visit. Reinitiation screening may last up to 7 days before a subject re-enters the treatment phase.
[d] Women of childbearing potential, urine dipstick test.
[e] If suicidality is identified (ie, 'yes' is answered to questions 1.0, 2.2, 3.0, or 4.0 of the ISST-Plus Short Form) the full ISST-Plus should be administered.
[f] Contact with the IVRS is for notification of reinitiation only, Subjects will NOT be re-randomly assigned to a study treatment. The IVRS does not need to be contacted for subjects who return while taking a nonprotocol-specified antipsychotic and who wish to remain on that medication.

Relevant Subject Narratives

Narrative 1 Subject R092670-SCH-3006-(b) (6)

- **REASON FOR NARRATIVE SELECTION**

  Serious adverse event (sudden death)
  Death (sudden death)

- **DEMOGRAPHICS AND BASELINE CHARACTERISTICS**

  □Study ID: R092670-SCH-3006
  □Baseline Height (cm): 182.9
  □Baseline Weight (kg): 79.1
  □Baseline BMI (kg/m2): 23.6
  □Age (yrs): 34
  □Sex: Male
  □Race: Black Or African American
  □Randomization Date: (b) (6)
  □Treatment Arm: PALIPERIDONE PALMITATE
  □Study End Date: (b) (6)
  □Standardized Disposition Term: DEATH

- **MEDICAL HISTORY ABNORMALITIES**

Body System	Term (verbatim)	Medical History Ongoing at Study Entry
Nervous system disorders	Bell's palsy	N
Injury, poisoning and procedural complications	(b) (6)	Y
Injury, poisoning and procedural complications		Y
Respiratory, thoracic and mediastinal disorders	Asthma	Y

- **PSYCHIATRIC HISTORY**

Parameter	Value
Age first psychiatric diagnosis (in years)	22
Age first pharmacological treatment psychiatric symptoms	22
Age at first psychiatric hospitalization	22
Num psych hospitalizations last 12 months	1
Prior psychiatric diagnoses	Schizophrenia

- **POSITIVE URINE DRUG SCREEN**

  No positive urine drug screen reported

- **EXPOSURE**

Category for Treatment	Name of Actual Treatment	Prescription/Injection Date	Dose	Dosing Frequency	Number of Tablets Prescribed
Paliperidone palmitate	Paliperidone	(b) (6)	234	Qw	-
Paliperidone palmitate	Paliperidone		156	Qm	-
Paliperidone palmitate	Paliperidone		234	Qm	-

Category for Treatment	Name of Actual Treatment	Prescription/Injection Date	Dose	Dosing Frequency	Number of Tablets Prescribed
Paliperidone palmitate	Paliperidone	(b) (6)	234	Qm	-
Paliperidone palmitate	Paliperidone		234	Qm	-
Paliperidone palmitate	Paliperidone		234	Qm	-
Paliperidone palmitate	Paliperidone		234	Qm	-
Paliperidone palmitate	Paliperidone		156	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-
Paliperidone palmitate	Paliperidone		117	Qm	-

■ CONCOMITANT THERAPY

Concomitant Term	Dose/Unit	CM Start Date CM End Date	Indication	AE	Treatment Ongoing
Paliperidone	9 mg	(b) (6)	Schizophrenia	-	-

■ SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS LEADING TO DISCONTINUATION

Dictionary-Derived Term Reported Term of the Adverse Event	Start Day End Day	Outcome of Adverse Event	Analysis Severity/Intensity	Causality	Serious Event	Action Taken with Study Treatment	Concomitant or Additional Treatment Given
Sudden death	445 -	Fatal	Severe	Doubtful	Y	Drug withdrawn	N

■ CONTACT WITH CRIMINAL JUSTICE SYSTEM

Reason for Arrest	Date of Arrest	Date Incarcerated	Date of Release from Incarceration
Drug charges	2011-05-05	2011-05-05	2011-07-25

■ NARRATIVE TEXT

Subject (b) (6) was a 34-year-old black or African American man with medical history of (b) (6) and asthma that were ongoing at the time of enrollment. His prior psychiatric history included schizophrenia. The subject was randomized to receive paliperidone palmitate.

On Day 445, *the subject died suddenly while* (b) (6) *the cause of death was unknown* (Source: CIOMS). The investigator assessed the sudden death as doubtfully related to the study drug. *An autopsy was performed on an unspecified date, and it was reported that "a blood clot had moved from his leg"* (Source: CIOMS).

[Manufacturer's Control No.: US-JNJFOC-20121106798(5)]

Incidence of Serious Treatment Adverse Events

Table 28: Incidence of Treatment-Emergent Serious Adverse Events; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of subjects	226	218	444
Subjects with Serious TEAE	42 (18.6%)	53 (24.3%)	95 (21.4%)
Body system / Preferred term			
Psychiatric Disorders	30 (13.3%)	38 (17.4%)	68 (15.3%)
Psychotic Disorder	11 (4.9%)	7 (3.2%)	18 (4.1%)
Suicidal Ideation	5 (2.2%)	11 (5.0%)	16 (3.6%)
Schizophrenia	4 (1.8%)	11 (5.0%)	15 (3.4%)
Schizophrenia, Paranoid Type	4 (1.8%)	5 (2.3%)	9 (2.0%)
Depression	4 (1.8%)	1 (0.5%)	5 (1.1%)
Suicide Attempt	1 (0.4%)	3 (1.4%)	4 (0.9%)
Acute Psychosis	1 (0.4%)	2 (0.9%)	3 (0.7%)
Alcohol Withdrawal Syndrome	2 (0.9%)	1 (0.5%)	3 (0.7%)
Homicidal Ideation	0	3 (1.4%)	3 (0.7%)
Agitation	2 (0.9%)	0	2 (0.5%)
Alcoholism	2 (0.9%)	0	2 (0.5%)
Hallucination, Auditory	1 (0.4%)	1 (0.5%)	2 (0.5%)
Paranoia	2 (0.9%)	0	2 (0.5%)
Aggression	0	1 (0.5%)	1 (0.2%)
Delusion	1 (0.4%)	0	1 (0.2%)
Depression Suicidal	1 (0.4%)	0	1 (0.2%)
Depressive Symptom	1 (0.4%)	0	1 (0.2%)
Factitious Disorder	0	1 (0.5%)	1 (0.2%)
Hallucination	0	1 (0.5%)	1 (0.2%)
Hallucinations, Mixed	1 (0.4%)	0	1 (0.2%)
Mania	1 (0.4%)	0	1 (0.2%)
Mental Status Changes	1 (0.4%)	0	1 (0.2%)
Polysubstance Dependence	0	1 (0.5%)	1 (0.2%)
Psychotic Behaviour	0	1 (0.5%)	1 (0.2%)
Schizoaffective Disorder Bipolar Type	0	1 (0.5%)	1 (0.2%)
Substance Abuse	1 (0.4%)	0	1 (0.2%)
Nervous System Disorders	3 (1.3%)	7 (3.2%)	10 (2.3%)
Akathisia	1 (0.4%)	0	1 (0.2%)
Cerebellar Ataxia	1 (0.4%)	0	1 (0.2%)
Convulsion	0	1 (0.5%)	1 (0.2%)
Dystonia	0	1 (0.5%)	1 (0.2%)
Encephalitis	1 (0.4%)	0	1 (0.2%)
Epilepsy	0	1 (0.5%)	1 (0.2%)
Facial Paresis	0	1 (0.5%)	1 (0.2%)
Ischaemic Stroke	0	1 (0.5%)	1 (0.2%)
Presyncope	0	1 (0.5%)	1 (0.2%)
Syncope	0	1 (0.5%)	1 (0.2%)
Infections And Infestations	4 (1.8%)	4 (1.8%)	8 (1.8%)
Cellulitis	2 (0.9%)	1 (0.5%)	3 (0.7%)
Pneumonia	1 (0.4%)	1 (0.5%)	2 (0.5%)
Acquired Immunodeficiency Syndrome	1 (0.4%)	0	1 (0.2%)
Cholecystitis Infective	0	1 (0.5%)	1 (0.2%)
H1N1 Influenza	1 (0.4%)	0	1 (0.2%)
HIV Infection	1 (0.4%)	0	1 (0.2%)
Otitis Media	0	1 (0.5%)	1 (0.2%)
Sepsis	1 (0.4%)	0	1 (0.2%)
Wound Infection	0	1 (0.5%)	1 (0.2%)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Injury, Poisoning And Procedural Complications	4 (1.8%)	4 (1.8%)	8 (1.8%)
Intentional Overdose	1 (0.4%)	1 (0.5%)	2 (0.5%)
Accidental Overdose	1 (0.4%)	0	1 (0.2%)
Alcohol Poisoning	1 (0.4%)	0	1 (0.2%)
Gun Shot Wound	0	1 (0.5%)	1 (0.2%)
Hip Fracture	0	1 (0.5%)	1 (0.2%)
Lower Limb Fracture	0	1 (0.5%)	1 (0.2%)
Overdose	1 (0.4%)	0	1 (0.2%)
Perirenal Haematoma	1 (0.4%)	0	1 (0.2%)
Traumatic Brain Injury	1 (0.4%)	0	1 (0.2%)
Traumatic Lung Injury	1 (0.4%)	0	1 (0.2%)
General Disorders And Administration Site Conditions	2 (0.9%)	3 (1.4%)	5 (1.1%)
Asthenia	0	1 (0.5%)	1 (0.2%)
Chest Pain	0	1 (0.5%)	1 (0.2%)
Drug Withdrawal Syndrome	0	1 (0.5%)	1 (0.2%)
Non-cardiac Chest Pain	1 (0.4%)	0	1 (0.2%)
Sudden Death	1 (0.4%)	0	1 (0.2%)
Renal And Urinary Disorders	1 (0.4%)	2 (0.9%)	3 (0.7%)
Renal Failure Acute	1 (0.4%)	2 (0.9%)	3 (0.7%)
Respiratory, Thoracic And Mediastinal Disorders	2 (0.9%)	1 (0.5%)	3 (0.7%)
Asthma	1 (0.4%)	1 (0.5%)	2 (0.5%)
Acute Respiratory Distress Syndrome	1 (0.4%)	0	1 (0.2%)
Pneumothorax	1 (0.4%)	0	1 (0.2%)
Pulmonary Embolism	1 (0.4%)	0	1 (0.2%)
Status Asthmaticus	0	1 (0.5%)	1 (0.2%)
Gastrointestinal Disorders	2 (0.9%)	0	2 (0.5%)
Haematemesis	1 (0.4%)	0	1 (0.2%)
Intestinal Obstruction	1 (0.4%)	0	1 (0.2%)
Vomiting	1 (0.4%)	0	1 (0.2%)
Metabolism And Nutrition Disorders	1 (0.4%)	1 (0.5%)	2 (0.5%)
Hypoglycaemia	0	1 (0.5%)	1 (0.2%)
Hyponatraemia	1 (0.4%)	0	1 (0.2%)
Vascular Disorders	1 (0.4%)	1 (0.5%)	2 (0.5%)
Deep Vein Thrombosis	1 (0.4%)	0	1 (0.2%)
Hypertension	0	1 (0.5%)	1 (0.2%)
Cardiac Disorders	0	1 (0.5%)	1 (0.2%)
Cardiac Failure Congestive	0	1 (0.5%)	1 (0.2%)
Coronary Artery Disease	0	1 (0.5%)	1 (0.2%)
Immune System Disorders	0	1 (0.5%)	1 (0.2%)
Hypersensitivity	0	1 (0.5%)	1 (0.2%)
Musculoskeletal And Connective Tissue Disorders	1 (0.4%)	0	1 (0.2%)
Rhabdomyolysis	1 (0.4%)	0	1 (0.2%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (0.4%)	0	1 (0.2%)
Gastric Cancer Stage III	1 (0.4%)	0	1 (0.2%)
Pregnancy, Puerperium And Perinatal Conditions	0	1 (0.5%)	1 (0.2%)
Stillbirth	0	1 (0.5%)	1 (0.2%)

Incidence of Treatment Emergent Adverse Events Leading to Discontinuation

Table 29: Incidence of Treatment-Emergent Adverse Events Leading to Study Discontinuation; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of subjects	226	218	444
Subjects with TEAE Leading to Study Discontinuation	6 (2.7%) [a]	4 (1.8%)	10 (2.3%) [a]
Body system / Preferred term			
Psychiatric Disorders	1 (0.4%)	3 (1.4%)	4 (0.9%)
Schizophrenia	0	2 (0.9%)	2 (0.5%)
Abnormal Dreams	1 (0.4%)	0	1 (0.2%)
Aggression	0	1 (0.5%)	1 (0.2%)
Nervous System Disorders	2 (0.9%)	1 (0.5%)	3 (0.7%)
Akathisia	1 (0.4%)	0	1 (0.2%)
Dizziness	0	1 (0.5%)	1 (0.2%)
Headache	1 (0.4%)	0	1 (0.2%)
General Disorders And Administration Site Conditions	1 (0.4%)	0	1 (0.2%)
Sudden Death	1 (0.4%) [a]	0	1 (0.2%) [a]
Reproductive System And Breast Disorders	1 (0.4%)	0	1 (0.2%)
Amenorrhoea	1 (0.4%)	0	1 (0.2%)
Skin And Subcutaneous Tissue Disorders	1 (0.4%)	0	1 (0.2%)
Psoriasis	1 (0.4%)	0	1 (0.2%)

[a] The subject in the paliperidone palmitate group with a treatment-emergent adverse event of sudden death was included in the total number of treatment-emergent adverse events leading to study discontinuation in this table, but not in Table 26.

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

Incidence of Treatment Emergent EPS Related Adverse Events

Table 30: Incidence of Treatment-Emergent EPS-Related Adverse Events Classified by EPS Group; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of subjects	226	218	444
Subjects EPS-Related Adverse Events	58 (25.7%)	43 (19.7%)	101 (22.7%)
EPS Group / Preferred term			
Hyperkinesia	30 (13.3%)	17 (7.8%)	47 (10.6%)
Akathisia	26 (11.5%)	17 (7.8%)	43 (9.7%)
Restlessness	4 (1.8%)	1 (0.5%)	5 (1.1%)
Parkinsonism	21 (9.3%)	14 (6.4%)	35 (7.9%)
Extrapyramidal Disorder	5 (2.2%)	4 (1.8%)	9 (2.0%)
Parkinsonism	4 (1.8%)	4 (1.8%)	8 (1.8%)
Musculoskeletal Stiffness	5 (2.2%)	1 (0.5%)	6 (1.4%)
Muscle Rigidity	3 (1.3%)	2 (0.9%)	5 (1.1%)
Bradykinesia	2 (0.9%)	1 (0.5%)	3 (0.7%)
Drooling	1 (0.4%)	1 (0.5%)	2 (0.5%)
Muscle Tightness	1 (0.4%)	1 (0.5%)	2 (0.5%)
Cogwheel Rigidity	1 (0.4%)	0	1 (0.2%)
Dystonia	8 (3.5%)	10 (4.6%)	18 (4.1%)
Dystonia	5 (2.2%)	6 (2.8%)	11 (2.5%)
Muscle Spasms	2 (0.9%)	3 (1.4%)	5 (1.1%)
Blepharospasm	1 (0.4%)	0	1 (0.2%)
Torticollis	0	1 (0.5%)	1 (0.2%)
Dyskinesia	8 (3.5%)	8 (3.7%)	16 (3.6%)
Dyskinesia	6 (2.7%)	4 (1.8%)	10 (2.3%)
Tardive Dyskinesia	1 (0.4%)	3 (1.4%)	4 (0.9%)
Muscle Twitching	1 (0.4%)	1 (0.5%)	2 (0.5%)
Tremor	5 (2.2%)	3 (1.4%)	8 (1.8%)
Tremor	5 (2.2%)	3 (1.4%)	8 (1.8%)

Percentages calculated with the number of subjects in each group as denominator.
Reported dictionary version: MedDRA 12.0.

Incidence of Treatment Emergent Prolactin Related Adverse Events for Females

Table 31: Incidence of Treatment-Emergent Prolactin-Related Adverse Events for Female Subjects; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of subjects	33	28	61
Subjects with Prolactin-Related Adverse Events	11 (33.3%)	2 (7.1%)	13 (21.3%)
Body system / Preferred term			
Reproductive System And Breast Disorders	10 (30.3%)	2 (7.1%)	12 (19.7%)
Amenorrhoea	5 (15.2%)	1 (3.6%)	6 (9.8%)
Galactorrhoea	5 (15.2%)	0	5 (8.2%)
Menstruation Irregular	2 (6.1%)	1 (3.6%)	3 (4.9%)
Breast Tenderness	1 (3.0%)	1 (3.6%)	2 (3.3%)
Endocrine Disorders	2 (6.1%)	1 (3.6%)	3 (4.9%)
Hyperprolactinaemia	2 (6.1%)	1 (3.6%)	3 (4.9%)
Investigations	2 (6.1%)	0	2 (3.3%)
Blood Prolactin Increased	2 (6.1%)	0	2 (3.3%)

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

Incidence of Treatment Emergent Prolactin Related Adverse Events for Males

Table 32: Incidence of Treatment-Emergent Prolactin-Related Adverse Events for Male Subjects; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of subjects	193	190	383
Subjects with Prolactin-Related Adverse Events	46 (23.8%)	9 (4.7%)	55 (14.4%)
Body system / Preferred term			
Reproductive System And Breast Disorders	22 (11.4%)	2 (1.1%)	24 (6.3%)
Erectile Dysfunction	17 (8.8%)	1 (0.5%)	18 (4.7%)
Breast Tenderness	3 (1.6%)	1 (0.5%)	4 (1.0%)
Gynaecomastia	4 (2.1%)	0	4 (1.0%)
Breast Pain	1 (0.5%)	0	1 (0.3%)
Sexual Dysfunction	1 (0.5%)	0	1 (0.3%)
Psychiatric Disorders	16 (8.3%)	3 (1.6%)	19 (5.0%)
Libido Decreased	13 (6.7%)	3 (1.6%)	16 (4.2%)
Anorgasmia	3 (1.6%)	0	3 (0.8%)
Loss of Libido	1 (0.5%)	0	1 (0.3%)
Investigations	9 (4.7%)	2 (1.1%)	11 (2.9%)
Blood Prolactin Increased	9 (4.7%)	2 (1.1%)	11 (2.9%)
Endocrine Disorders	5 (2.6%)	3 (1.6%)	8 (2.1%)
Hyperprolactinaemia	5 (2.6%)	3 (1.6%)	8 (2.1%)

Percentages calculated with the number of subjects in each group as denominator.
Reported dictionary version: MedDRA 12.0.

TEAE's in ≥ 2 % Subjects in Any Treatment Group by Preferred Term

Table 27: Treatment-Emergent Adverse Events in >=2% of Subjects in any Treatment Group by Preferred Term; pITT Analysis Set (Study R092670-SCH-3006)

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects	226	218	444
Number of Subjects with TEAE	195 (86.3%)	178 (81.7%)	373 (84.0%)
Psychiatric Disorders	104 (46.0%)	96 (44.0%)	200 (45.0%)
Insomnia	42 (18.6%)	27 (12.4%)	69 (15.5%)
Anxiety	25 (11.1%)	18 (8.3%)	43 (9.7%)
Depression	20 (8.8%)	18 (8.3%)	38 (8.6%)
Suicidal Ideation	8 (3.5%)	17 (7.8%)	25 (5.6%)
Schizophrenia	10 (4.4%)	16 (7.3%)	26 (5.9%)
Psychotic Disorder	12 (5.3%)	9 (4.1%)	21 (4.7%)
Hallucination, Auditory	4 (1.8%)	7 (3.2%)	11 (2.5%)
Agitation	7 (3.1%)	5 (2.3%)	12 (2.7%)
Schizophrenia, Paranoid Type	4 (1.8%)	5 (2.3%)	9 (2.0%)
Libido Decreased	13 (5.8%)	3 (1.4%)	16 (3.6%)
Nervous System Disorders	80 (35.4%)	88 (40.4%)	168 (37.8%)
Headache	17 (7.5%)	19 (8.7%)	36 (8.1%)
Sedation	15 (6.6%)	18 (8.3%)	33 (7.4%)
Akathisia	26 (11.5%)	17 (7.8%)	43 (9.7%)
Somnolence	10 (4.4%)	16 (7.3%)	26 (5.9%)
Dizziness	6 (2.7%)	11 (5.0%)	17 (3.8%)
Dystonia	5 (2.2%)	6 (2.8%)	11 (2.5%)
Dyskinesia	6 (2.7%)	4 (1.8%)	10 (2.3%)
Extrapyramidal Disorder	5 (2.2%)	4 (1.8%)	9 (2.0%)
Tremor	5 (2.2%)	3 (1.4%)	8 (1.8%)

Gastrointestinal Disorders	59 (26.1%)	63 (28.9%)	122 (27.5%)
Dry Mouth	15 (6.6%)	18 (8.3%)	33 (7.4%)
Toothache	11 (4.9%)	13 (6.0%)	24 (5.4%)
Constipation	7 (3.1%)	8 (3.7%)	15 (3.4%)
Diarrhoea	4 (1.8%)	7 (3.2%)	11 (2.5%)
Nausea	9 (4.0%)	6 (2.8%)	15 (3.4%)
Abdominal Discomfort	0	5 (2.3%)	5 (1.1%)
Vomiting	3 (1.3%)	5 (2.3%)	8 (1.8%)
Dyspepsia	7 (3.1%)	3 (1.4%)	10 (2.3%)
Salivary Hypersecretion	7 (3.1%)	0	7 (1.6%)
Infections And Infestations	53 (23.5%)	59 (27.1%)	112 (25.2%)
Nasopharyngitis	15 (6.6%)	14 (6.4%)	29 (6.5%)
Upper Respiratory Tract Infection	13 (5.8%)	11 (5.0%)	24 (5.4%)
Bronchitis	6 (2.7%)	5 (2.3%)	11 (2.5%)
Influenza	4 (1.8%)	5 (2.3%)	9 (2.0%)
Injury, Poisoning And Procedural Complications	25 (11.1%)	40 (18.3%)	65 (14.6%)
Laceration	4 (1.8%)	12 (5.5%)	16 (3.6%)
Joint Sprain	2 (0.9%)	6 (2.8%)	8 (1.8%)
Investigations	54 (23.9%)	32 (14.7%)	86 (19.4%)
Weight Increased	30 (13.3%)	16 (7.3%)	46 (10.4%)
Blood Prolactin Increased	11 (4.9%)	2 (0.9%)	13 (2.9%)
Semen Volume Decreased	5 (2.2%)	0	5 (1.1%)
Musculoskeletal And Connective Tissue Disorders	38 (16.8%)	32 (14.7%)	70 (15.8%)
Back Pain	13 (5.8%)	8 (3.7%)	21 (4.7%)
Pain in Extremity	9 (4.0%)	8 (3.7%)	17 (3.8%)
Arthralgia	7 (3.1%)	3 (1.4%)	10 (2.3%)
Musculoskeletal Stiffness	5 (2.2%)	1 (0.5%)	6 (1.4%)

	Paliperidone Palmitate	Oral Antipsychotics	Total
General Disorders And Administration Site Conditions	73 (32.3%)	24 (11.0%)	97 (21.8%)
Fatigue	17 (7.5%)	6 (2.8%)	23 (5.2%)
Irritability	4 (1.8%)	6 (2.8%)	10 (2.3%)
Pain	1 (0.4%)	5 (2.3%)	6 (1.4%)
Injection Site Pain	42 (18.6%)	0	42 (9.5%)
Metabolism And Nutrition Disorders	38 (16.8%)	19 (8.7%)	57 (12.8%)
Increased Appetite	16 (7.1%)	8 (3.7%)	24 (5.4%)
Abnormal Weight Gain	11 (4.9%)	4 (1.8%)	15 (3.4%)
Respiratory, Thoracic And Mediastinal Disorders	27 (11.9%)	18 (8.3%)	45 (10.1%)
Cough	7 (3.1%)	6 (2.8%)	13 (2.9%)
Nasal Congestion	6 (2.7%)	1 (0.5%)	7 (1.6%)
Oropharyngeal Pain	5 (2.2%)	0	5 (1.1%)
Vascular Disorders	3 (1.3%)	10 (4.6%)	13 (2.9%)
Hypertension	2 (0.9%)	8 (3.7%)	10 (2.3%)
Reproductive System And Breast Disorders	39 (17.3%)	9 (4.1%)	48 (10.8%)
Amenorrhoea	5 (2.2%)	1 (0.5%)	6 (1.4%)
Erectile Dysfunction	17 (7.5%)	1 (0.5%)	18 (4.1%)
Galactorrhoea	5 (2.2%)	0	5 (1.1%)
Endocrine Disorders	7 (3.1%)	5 (2.3%)	12 (2.7%)
Hyperprolactinaemia	7 (3.1%)	4 (1.8%)	11 (2.5%)

Percentages calculated with the number of subjects in each group as denominator.
Reported dictionary version: MedDRA 12.0.
Incidence is based on number of subjects, not the number of events. The subject's event with worst severity is used.

[TSFAE12P.rtf] [JNJ-16977831\SCH3006\DBR_FINAL\RE_CSR\tsfae12p.sas] 19FEB2014, 14:36

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/s/

GLENN B MANNHEIM
04/22/2015

JING ZHANG
04/22/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY Supplemental NDA REVIEW AND EVALUATION

Application number:	NDA 22264 Supplemental New Drug Application S-015 (efficacy supplement)
Supporting document/s:	SDN 469; Sequence No. 0135
Applicant's letter date:	July 11, 2014
CDER stamp date:	July 11, 2014
Product:	Invega Sustenna (paliperidone palmitate)
Indication:	Schizophrenia
Applicant:	Janssen Pharmaceuticals, Inc.
Review Division:	Division of Psychiatry Products
Reviewer:	Elzbieta Chalecka-Franaszek, Ph.D.
Supervisor/Team Leader:	Aisar Atrakchi, Ph.D.
Division Director:	Mitchel Mathis, M.D.
Project Manager:	Ann Sohn, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22264 Supplemental Application S-015 is owned by Janssen Pharmaceuticals, Inc. or are data for which Janssen Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22264 Supplemental Application S-015 that Janssen Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22264 Supplemental Application S-015.

1 Executive Summary

1.1 Introduction

Janssen Pharmaceuticals, Inc. submitted on July 11, 2014 supplement S-015 to the NDA 22264 for Invega Sustenna®. This supplement supports revisions to the product label based on findings from the clinical protocol R092670-SCH-3006 titled "A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated". The original protocol was submitted to IND 67,356 on 20 April 2010.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical data were generated to support the NDA 22264 supplement S-015. No new pharmacology/toxicology information was submitted and/or reviewed at present. This supplemental NDA relies on nonclinical data previously submitted to the NDA 22264. Please see pharmacology/toxicology review of the NDA 22264 dated August 25, 2008 for nonclinical findings from studies conducted with paliperidone palmitate.

1.3 Recommendations

1.3.1 Approvability

The nonclinical studies submitted in support of the NDA 22264 for Invega Sustenna (paliperidone palmitate) approved for the treatment of schizophrenia on July 31, 2009, are sufficient to recommend approval of the supplemental NDA 22264 S-015 from the pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

No changes from the labeling for Invega Sustenna are recommended in sections 8.1 (Pregnancy), 8.4 (Pediatric Use), 12.1 (Mechanism of action), 12.2 (Pharmacodynamics), and 13.1 (Carcionogenesis, Mutagenesis, Impairment of Fertility) from the pharmacology/toxicology perspective.

Elzbieta Chalecka-Franaszek, Ph.D., Pharmacologist *{see appended electronic signature page}*

Aisar Atrakchi, Ph.D., Supervisor *{see appended electronic signature page}*

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/s/

ELZBIETA CHALECKA FRANASZ
04/07/2015

AISAR H ATRAKCHI
04/07/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 22264
Supplement #:	S-15 resubmission
Drug Name:	INVEGA SUSTENNA® (paliperidone palmitate injection 1 month formulation)
Indication(s):	Adults with Schizophrenia Who Have Been Incarcerated
Applicant:	Janssen Research & Development, LLC
Date(s):	Letter date: Jun 20, 2017
	PDUFA due date: Dec 20, 2017
Review Priority:	Class 2 resubmission (6 months)
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Yang Wang, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph. D., Team Leader
	H.M. James Hung, Ph.D., Division Director
Medical Division:	Division of Psychiatry Products
Clinical Team:	Daniel Lee, M.D., Clinical Reviewer
	Javier Muniz, M.D., Clinical Team Leader
Project Manager:	Sandy Chang

Keywords:

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1. EXECUTIVE SUMMARY

This resubmission has provided additional information to account for the reasons for discontinuation of 139 patients (31.3%) without meeting the definition of a treatment failure, and includes the supplemental data analyses to address FDA's concerns regarding interpretation and justification of robustness of the primary efficacy analysis in the original submission.

The observed proportions of subjects with an event of treatment failure (TF), first arrest/incarceration, or first psychiatric hospitalization were numerically higher in the oral antipsychotic group than in the paliperidone palmitate injection group within 30 days, 60 days, 90 days of study drug discontinuation, and at any time post study drugs discontinuation. This is consistent with findings for the eITT analysis set in the original CSR.

Based on these post-hoc exploratory analyses, there seems no evidence that the higher rate of discontinuation in the paliperidone palmitate group compared to the oral antipsychotic group for the ITT analysis set was related to impending TF due to loss of efficacy or emerging intolerability.

Thus, the exploratory supplemental analyses of the dropout analysis set support the positive findings from the original submission in showing that treatment with paliperidone palmitate was statistically significantly superior to oral antipsychotics in delaying the time to first TF in adults with schizophrenia and a history of incarceration.

2. INTRODUCTION

2.1 Overview

INVEGA® SUSTENNA®, the long-acting 1-month injectable formulation, is approved for the acute and maintenance treatment of schizophrenia in adults (in December 2006 under NDA 21999) and for treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants (in July 2009 under NDA 22264).

Supplement S-15 was submitted to NDA 22264 on July 11, 2014, intended to support revisions to the product label for INVEGA® SUSTENNA® (PP1M). It consisted of results from study R092670-SCH-3006 entitled, "A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated.".

A Complete Response (CR) letter was issued on May 11, 2015, and determined that study R092670-SCH-3006 does not provide substantial evidence that PP1M delays time to treatment failure in adults with schizophrenia who have been incarcerated due to FDA's inability to interpret the study results. As noted in the CR letter:

A total of 139 patients (31.3%) discontinued the study early without meeting the definition of a treatment failure, and, importantly, there were more discontinuations in the paliperidone palmitate group (n=81, 35.8%) than in the oral antipsychotic group (n=58, 26.6%). Furthermore, in 60 patients (26.5%) in the paliperidone palmitate group and 42 patients (19.3%) in the oral antipsychotic group, the reasons for discontinuation reported in the case report forms were either "lost to follow-up" or "withdrawal by subject" in the case report forms. Thus, there is no way to know whether or not these patients experienced treatment failure, and the relatively large differences between treatment groups undermine the interpretability of the results.

There are 29 subjects with an Event Monitoring Board (EMB)-adjudicated treatment failure event that occurred after discontinuation of randomized treatment but was outside the protocol-defined primary period of interest. Their information could be used as reported in the original study. At the Type B meeting held on Jan 14, 2016, it was agreed that additional follow-up data should be collected for the remaining 110 subjects who discontinued early without knowledge of their treatment failure status to determine if the treatment failure events are roughly balanced between the two treatment groups in support of the primary efficacy result.

A general advice letter was issued with no objections on Jul 27, 2016, in response to Sponsor's plan for collection of additional data for study R092670-SCH-3006 submitted on May 26, 2016.

This resubmission includes a Clinical Study Report (CSR) Addendum for Study SCH-3006 which contains the complete results of all additional analyses for the subgroup of dropout subjects, in hope to address the FDA's concerns about the robustness of the primary study results.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
Protocol R092670SCH3006	*Phase 4*	*15-month open-label treatment period*	*N.A.*	*450 in total randomized to paliperidone palmitate (n=230) and oral antipsychotic (n=220)*	*subjects with schizophrenia*

2.2 Data Sources

The following data sources were considered in this review:
a) Applicant's study report
(\\CDSESUB1\evsprod\NDA022264\0175\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5351-stud-rep-contr\r092670sch3006)
b) Data sets
(\\CDSESUB1\evsprod\NDA022264\0175\m5\datasets\r092670sch3006\analysis\adam\datasets)
c) Software code
(\\CDSESUB1\evsprod\NDA022264\0175\m5\datasets\r092670sch3006\analysis\adam\program)
(\\CDSESUB1\evsprod\NDA022264\0177\m5\datasets\r092670sch3006\analysis\adam\programs
)
d) Response to FDA information request
(\\CDSESUB1\evsprod\NDA022264\0177\m1\us)

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

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

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

In the original submission, there were a total of 139 subjects who discontinued participation in Study SCH-3006 without having an explanatory intent-to-treat (eITT) treatment failure event during the period from randomization through the end of the randomized treatment period (28 days after the last injection of paliperidone palmitate or 1 day after the last dose of oral antipsychotic). They are referred to as the **dropout analysis set**. There were more discontinuations in the paliperidone palmitate group (n=81, 35.8%) than in the oral antipsychotic group (n=58, 26.6%).

The purpose of the additional data collection was to determine whether any of the 139 subjects who discontinued the study prematurely without an EMB-adjudicated treatment failure event experienced treatment failure event from the time of discontinuation to the end of planned study follow-up (Day 450 [Month 15] post randomization). The primary supplemental analysis for Study SCH-3006 focused on treatment failure events occurring closer to treatment discontinuation, defined as the 90-day interval following study treatment discontinuation as agreed upon at the Jan 14, 2016 meeting.

Of the 139 subjects, the FDA agreed with the Sponsor's proposal that no further data collection was necessary for 43 subjects:

- 29 subjects with an EMB-adjudicated treatment failure event that occurred after discontinuation of randomized treatment but was outside the protocol-defined primary period of interest (i.e., occurred >28 days after last dose of paliperidone palmitate or >1 day after last dose of oral antipsychotic) could be used as reported in the original study.

- 2 subjects who moved during the study due to social circumstances and 1 subject who died of a non-suicide-related death were considered not to have had a treatment failure, and treated as non-informative dropouts.

- 11 subjects with a treatment failure event (arrest and/or incarceration) reported by the principal investigator (PI) that was not adjudicated as a treatment failure by the EMB are

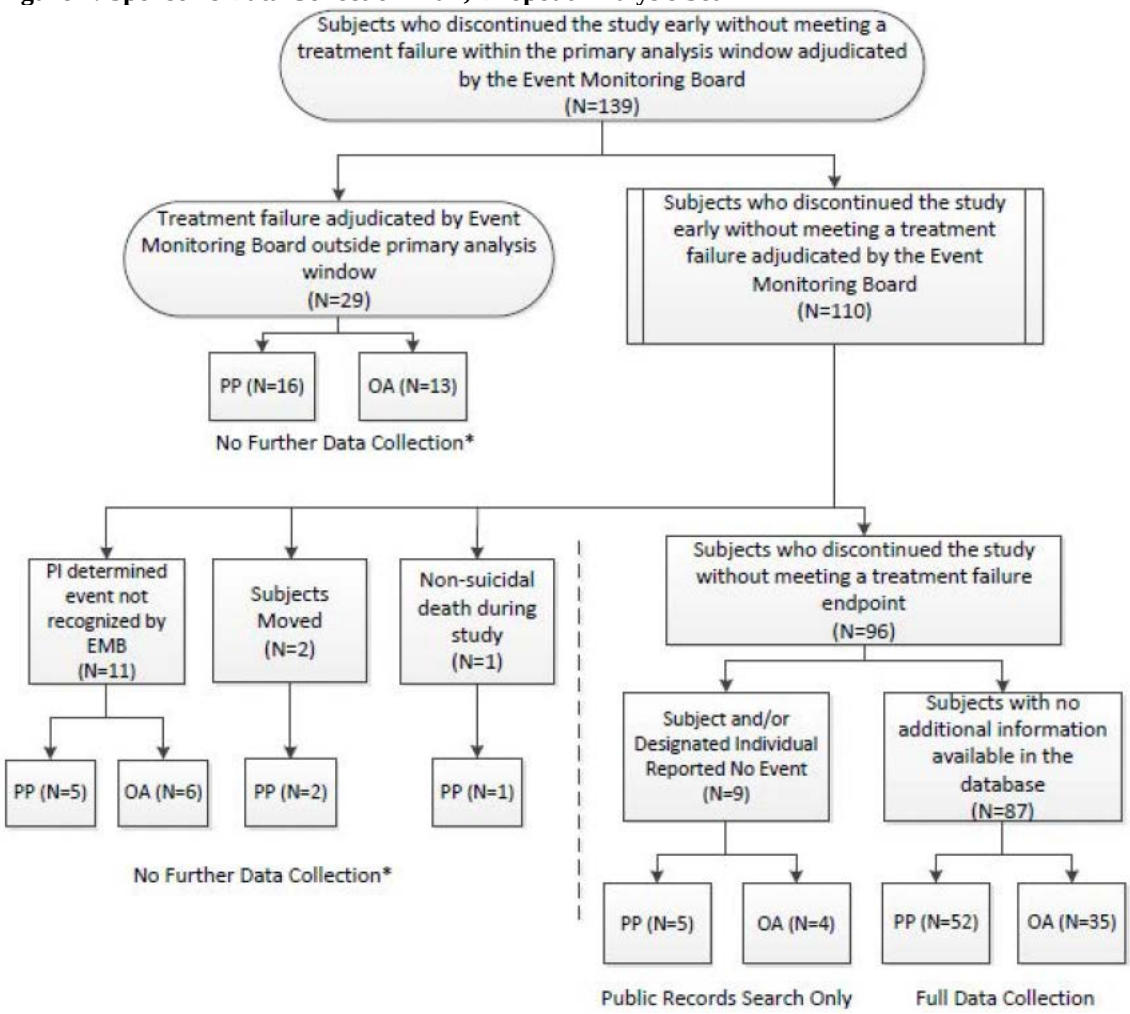
included in the supplemental analyses as treatment failures, consistent with process for treatment failure determination for the remainder of subjects in the dropout analysis set.

For the remaining 96 subjects (57 in the paliperidone palmitate group, 39 in the oral antipsychotic group), the supplementary data collection plan pursued treatment failure events of interest data focused on identification of 3 types of treatment failure events: psychiatric hospitalization, arrest and/or incarceration, and suicide, as these were considered objective events that were less likely to be influenced by recall biases:

- For the 9 subjects who had a documented report that no TF event occurred between the last on-site visit and the time of verbal contact with the subject or designated individual (interval ranging from 95 to 399 days), public records were searched for arrest, incarceration, and completed suicide for the period ranging from the last on-site visit to Day 450 post randomization.

- For the 87 subjects with no additional information in the study database, data collection activities to determine whether the aforementioned 3 types of treatment failure events occurred from the time of last on-site visit up to Day 450 post randomization included a search of public records, review of the principal investigator medical records, and attempts to locate and interview the subject and designated individual.

Figure 1: Sponsor's Data Collection Plan; Dropout Analysis Set



Source: figure 1 on page 10 of Sponsor's CSR.

The endpoints specified for the supplemental analyses are listed below and each endpoint was calculated for the intervals of 30 days, 60 days, 90 days, and at any time, relative to randomization and to study drug discontinuation:

- Proportion of subjects with a TF
- Proportion of subjects with arrest/incarceration
- Proportion of subjects with psychiatric hospitalization
- Time to first TF
- Time to first arrest/incarceration
- Time to first psychiatric hospitalization

3.2.2 Statistical Methodologies

3.2.2.1 Supplemental Analyses

The difference between the paliperidone palmitate and oral antipsychotic treatment groups in the proportion of subjects with an event within each specific time period of interest was tested using Chi-Square test.

The distribution of time to the first event was estimated by the Kaplan-Meier method for each treatment group.

The difference between the paliperidone palmitate and oral antipsychotic treatment groups with respect to the distribution of the time to first event endpoints was tested using a log-rank test.

The hazard ratio and its 95% CI were estimated using a Cox proportional hazards model with treatment group as a fixed factor.

3.2.2.2 Sample Size Determination

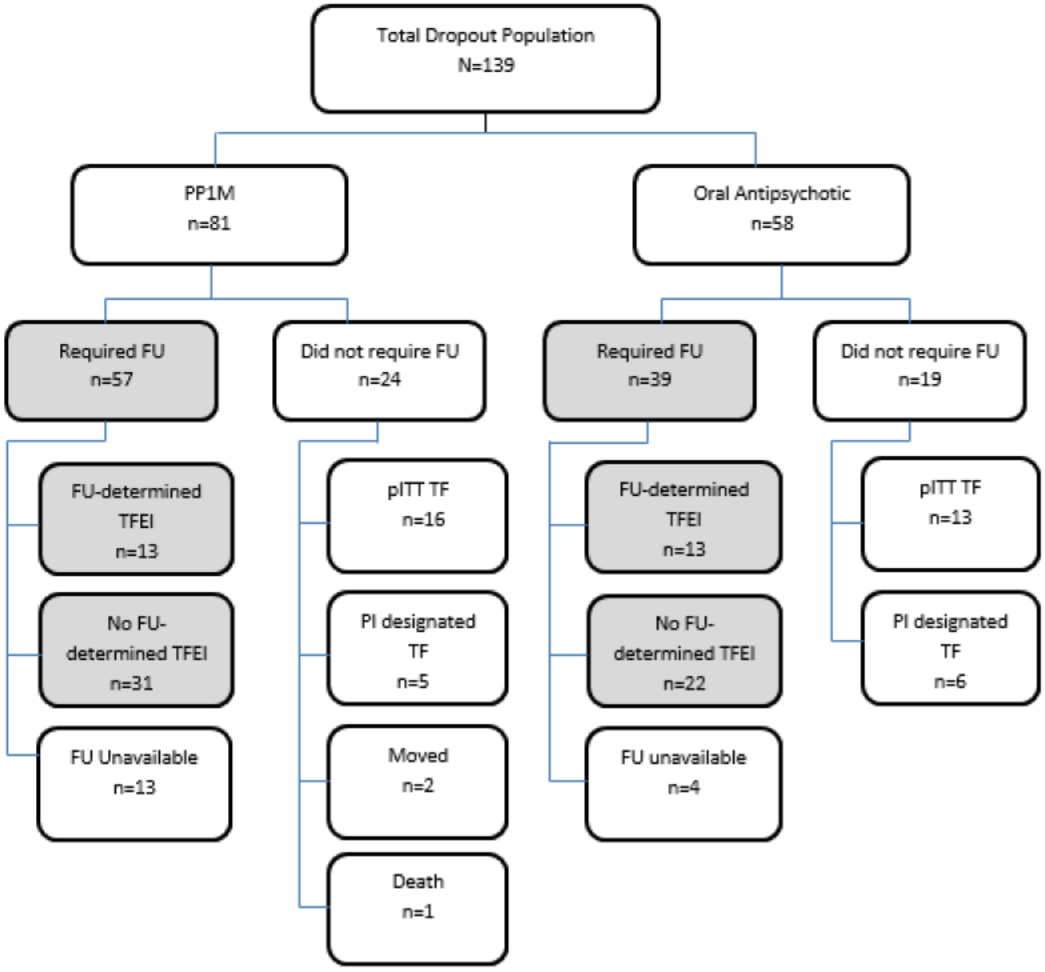
The supplemental analyses are based on the dropout analysis set of 139 subjects who discontinued without an event of treatment failure. It is a subset of subjects from the ITT population in the original submission. It should be noted that these supplementary analyses were not adequately powered for testing treatment group differences.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Only for 79 of these 96 subjects (82.3%), follow-up information was available and a determination could be made as to whether or not a treatment failure had occurred.

Figure 2: Subject Treatment Failure Follow-up Status; Dropout Analysis Set



Note: FU=follow-up; pITT=pragmatic intent-to-treat; PI=principal investigator; TFEI= treatment failure events of interest; TF=treatment failure

Source: figure 3 on page 16 of Sponsor's CSR.

Patient disposition by the type of the first treatment failure is shown in the following table:

Table 2: Frequency Distribution of 1st Treatment Failure by Type; Dropout Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics
Number of Subjects	81	58
Any Event	34 (42.0%)	32 (55.2%)
Arrest/incarceration	30 (37.0%)	25 (43.1%)
Suicide	0	0
Psychiatric hospitalization	1 (1.2%)	3 (5.2%)
Arrest and Psychiatric hospitalization	0	1 (1.7%)
Other	3 (3.7%)	3 (5.2%)

Source: table TEFTFTP01P on page 131 of Sponsor's CSR.

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Supplemental Analyses

3.2.4.1.1 Time from Randomization to First TF

Twenty-four (29.6%) of 81 subjects in the paliperidone palmitate group and 23 (39.7%) of 58 subjects in the oral antipsychotic group had a TF within 90 days of study drug discontinuation. Thirty-four (42.0%) of 81 subjects in the paliperidone palmitate group and 32 (55.2%) of 58 subjects in the oral antipsychotics group had a TF event at any time after study drug discontinuation.

The observed proportions of subjects with a TF event were generally higher in the oral antipsychotic group than in the paliperidone palmitate injection group in all 4 studied windows.

Reviewer's note: Statistical inference is not made by this reviewer based on these post-hoc supplemental analyses due to their exploratory nature. However, numerical comparisons in favor of paliperidone palmitate manage to support the robustness of the primary efficacy analysis from the original submission.

Table 3: Subject Treatment Failure Follow-up Status; Dropout Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics
Number of Subjects [a]	81	58
With TF event at any time post study drug discontinuation?		
No	47 (58.0%)	26 (44.8%)
Yes	34 (42.0%)	32 (55.2%)
With TF event within 30 days of study drug discontinuation?		
No	63 (77.8%)	42 (72.4%)
Yes	18 (22.2%)	16 (27.6%)
With TF event within 60 days of study drug discontinuation?		
No	61 (75.3%)	35 (60.3%)
Yes	20 (24.7%)	23 (39.7%)
With TF event within 90 days of study drug discontinuation?		
No	57 (70.4%)	35 (60.3%)
Yes	24 (29.6%)	23 (39.7%)

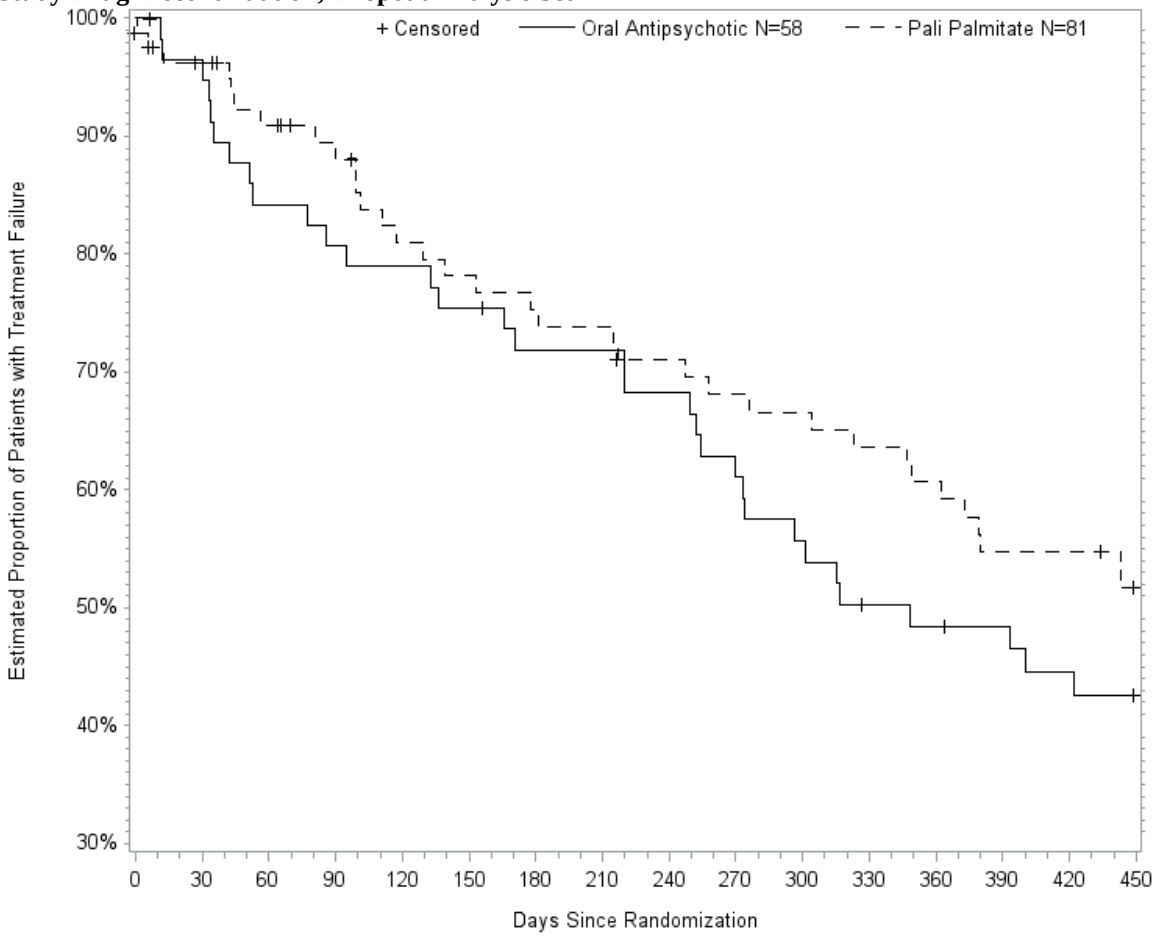
a Includes all 139 dropout subjects who did not had an explanatory ITT treatment failure event per EMB-determination

Note: All percentages are based on the number of subjects in the dropout analysis set.

Source: partial table 9 on page 35 of Sponsor's CSR.

The Kaplan-Meier curves of time to first treatment failure at any time post study drug discontinuation are displayed in the following figure.

Figure 3: Kaplan-Meier Estimates of Time from Randomization to 1st Treatment Failure at any time post Study Drug Discontinuation; Dropout Analysis Set



Source: reviewer's plot similar to figure 4 on page 38 of Sponsor's CSR.

3.2.4.1.2 Time from Randomization to First Arrest/Incarceration

A total of 31 (38.3%) of 81 subjects in the paliperidone palmitate group and 26 (44.8%) of 58 subjects in the oral antipsychotics group had an arrest/incarceration at any time post study discontinuation.

The observed proportions of subjects with an event of first arrest/incarceration were generally higher in the oral antipsychotic group than in the paliperidone palmitate injection group in all 4 studied windows. The findings are supported by the Kaplan-Meier estimates of time to first arrest/incarceration at any time post study drug discontinuation.

Table 4: Subject Arrest/Incarceration Follow-up Status; Dropout Analysis Set

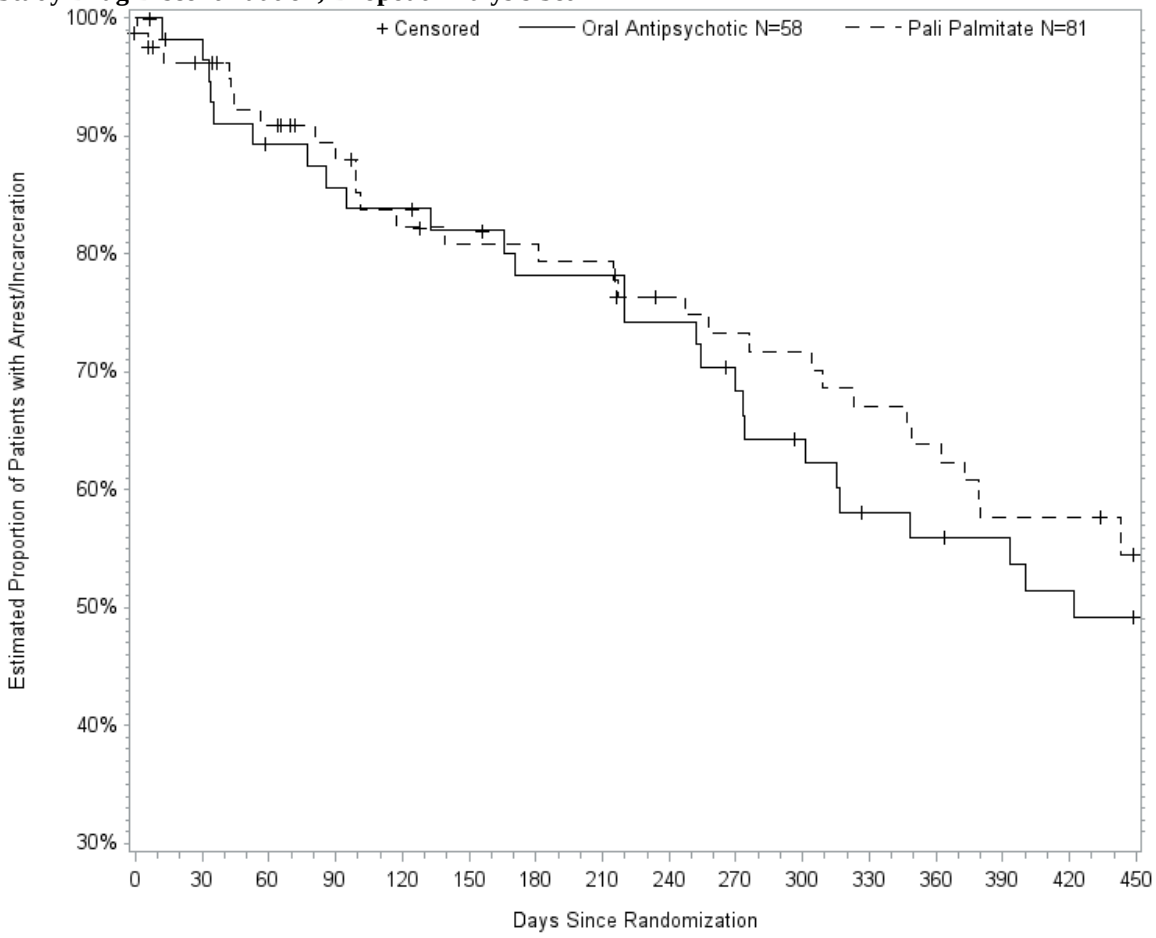
	Paliperidone Palmitate	Oral Antipsychotics
Number of Subjects [a]	81	58
With event at any time post study drug discontinuation?		
No	50 (61.7%)	32 (55.2%)
Yes	31 (38.3%)	26 (44.8%)
With event within 30 days of study drug discontinuation?		
No	67 (82.7%)	46 (79.3%)
Yes	14 (17.3%)	12 (20.7%)
With event within 60 days of study drug discontinuation?		
No	65 (80.2%)	41 (70.7%)
Yes	16 (19.8%)	17 (29.3%)
With event within 90 days of study drug discontinuation?		
No	61 (75.3%)	41 (70.7%)
Yes	20 (24.7%)	17 (29.3%)

a Includes all 139 dropout subjects who did not had an explanatory ITT treatment failure event per EMB-determination

Note: All percentages are based on the number of subjects in the dropout analysis set.

Source: table 12 on page 40 of Sponsor's CSR.

Figure 4: Kaplan-Meier Estimates of Time from Randomization to 1st Arrest/Incarceration at any time Post Study Drug Discontinuation; Dropout Analysis Set



Source: reviewer's plot similar to figure 5 on page 43 of Sponsor's CSR.

3.2.4.1.3 Time from Randomization to First Psychiatric Hospitalization

A total of 2 (2.5%) of 81 subjects in the paliperidone palmitate group and 4 (6.9%) of 58 subjects in the oral antipsychotics group had a psychiatric hospitalization at any time post study discontinuation.

The observed proportions of subjects with an event of first psychiatric hospitalization were generally higher in the oral antipsychotic group than in the paliperidone palmitate injection group in all 4 studied windows. The findings are supported by the Kaplan-Meier estimates of time to first psychiatric hospitalization at any time post study drug discontinuation.

Table 5: Subject Psychiatric Hospitalization Follow-up Status; Dropout Analysis Set

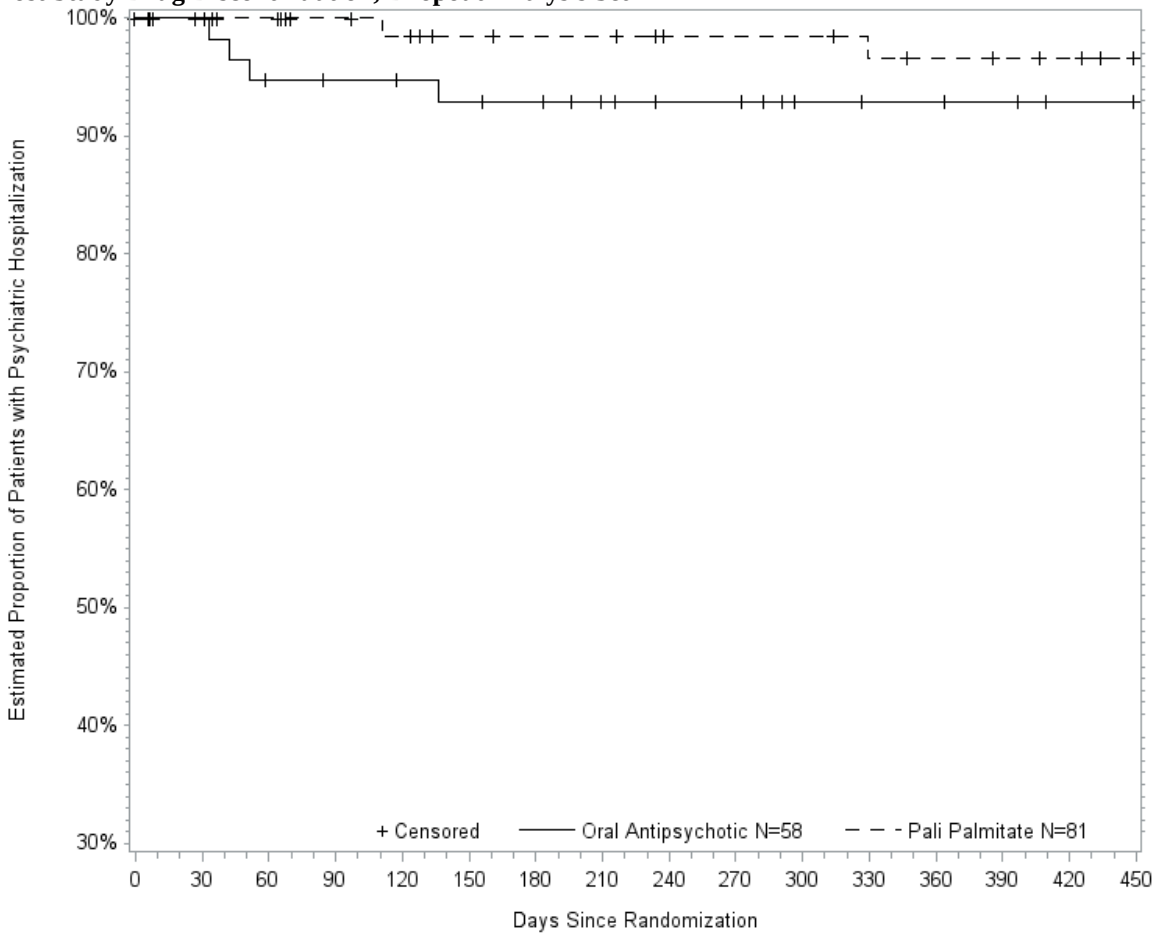
	Paliperidone Palmitate	Oral Antipsychotics
Number of Subjects [a]	81	58
With event at any time post study drug discontinuation?		
No	79 (97.5%)	54 (93.1%)
Yes	2 (2.5%)	4 (6.9%)
With event within 30 days of study drug discontinuation?		
No	80 (98.8%)	55 (94.8%)
Yes	1 (1.2%)	3 (5.2%)
With event within 60 days of study drug discontinuation?		
No	80 (98.8%)	54 (93.1%)
Yes	1 (1.2%)	4 (6.9%)
With event within 90 days of study drug discontinuation?		
No	79 (97.5%)	54 (93.1%)
Yes	2 (2.5%)	4 (6.9%)

a Includes all 139 dropout subjects who did not had an explanatory ITT treatment failure event per EMB-determination

Note: All percentages are based on the number of subjects in the dropout analysis set.

Source: table 15 on page 44 of Sponsor's CSR.

Figure 5: Kaplan-Meier Estimates of Time from Randomization to 1st Psychiatric Hospitalization at any time Post Study Drug Discontinuation; Dropout Analysis Set



Source: reviewer's plot similar to figure 6 on page 47 of Sponsor's CSR.

3.2.4.1.4 Time from Study Discontinuation to First TF

A higher proportion of subjects with a first TF event within 90 days of discontinuation and at any time post discontinuation was observed in the oral antipsychotic group compared to the paliperidone palmitate injection group.

Table 6: Summary of Time from study drug discontinuation to 1st Treatment Failure

Time to Event	Paliperidone Palmitate N=81	Oral Antipsychotics N=58	Paliperidone Palmitate N=81	Oral Antipsychotics N=58
	Time from study drug discontinuation to 1st Treatment Failure within 90 days of Discontinuation		Time from study drug discontinuation to 1st Treatment Failure at any time post Discontinuation	
Event	24 (29.6%)	23 (39.7%)	34 (42.0%)	32 (55.2%)
Censored	57 (70.4%)	35 (60.3%)	47 (58.0%)	26 (44.8%)
Hazard Ratio From Cox Regression				
Treatment Group, Oral vs. Pali Palmitate	1.37		1.43	

Source: reviewer's table based on table 18 and 19 on pages 48 and 49 in Sponsor's CSR.

3.2.4.1.5 Time from Study Discontinuation to First Arrest/Incarceration

A higher proportion of subjects with an event of first arrest/incarceration within 90 days of discontinuation and at any time post discontinuation was observed in the oral antipsychotic group compared to the paliperidone palmitate injection group.

Table 7: Summary of Time from study drug discontinuation to 1st Arrest/Incarceration

Time to Event	Paliperidone Palmitate N=81	Oral Antipsychotics N=58	Paliperidone Palmitate N=81	Oral Antipsychotics N=58
	Time from study drug discontinuation to 1st Arrest/Incarceration within 90 days of Discontinuation		Time from study drug discontinuation to 1st Arrest/Incarceration at any time post Discontinuation	
Event	20 (24.7%)	17 (29.3%)	31 (38.3%)	26 (44.8%)
Censored	61 (75.3%)	41 (70.7%)	50 (61.7%)	32 (55.2%)
Hazard Ratio From Cox Regression				
Treatment Group, Oral vs. Pali Palmitate	1.21		1.29	

Source: reviewer's table based on table 20 and 21 on pages 50-52 in Sponsor's CSR.

3.2.4.1.6 Time from Study Discontinuation to First Psychiatric Hospitalization

A higher proportion of subjects with an event of first psychiatric hospitalization within 90 days of discontinuation and at any time post discontinuation was observed in the oral antipsychotic group compared to the paliperidone palmitate injection group.

Table 8: Summary of Time from study drug discontinuation to 1st Psychiatric Hospitalization

Time to Event	Paliperidone Palmitate N=81	Oral Antipsychotics N=58	Paliperidone Palmitate N=81	Oral Antipsychotics N=58
	Time from study drug discontinuation to 1st Psychiatric Hospitalization within 90 days of Discontinuation		Time from study drug discontinuation to 1st Psychiatric Hospitalization at any time post Discontinuation	
Event	2 (2.5%)	4 (6.9%)	2 (2.5%)	4 (6.9%)
Censored	79 (97.5%)	54 (93.1%)	79 (97.5%)	54 (93.1%)
Hazard Ratio From Cox Regression				
Treatment Group, Oral vs. Pali Palmitate	2.55		2.55	

Source: reviewer's table based on table 22 and 23 on pages 52-54 in Sponsor's CSR.

3.2.4.2 Reviewer's Analyses

In the Dropout Analysis Set, the observed proportion of subjects with an event of either first psychiatric hospitalization or first arrest/incarceration at any time was higher in the oral antipsychotic group (25 out of 58; 43.1%) than in the paliperidone palmitate injection group (23

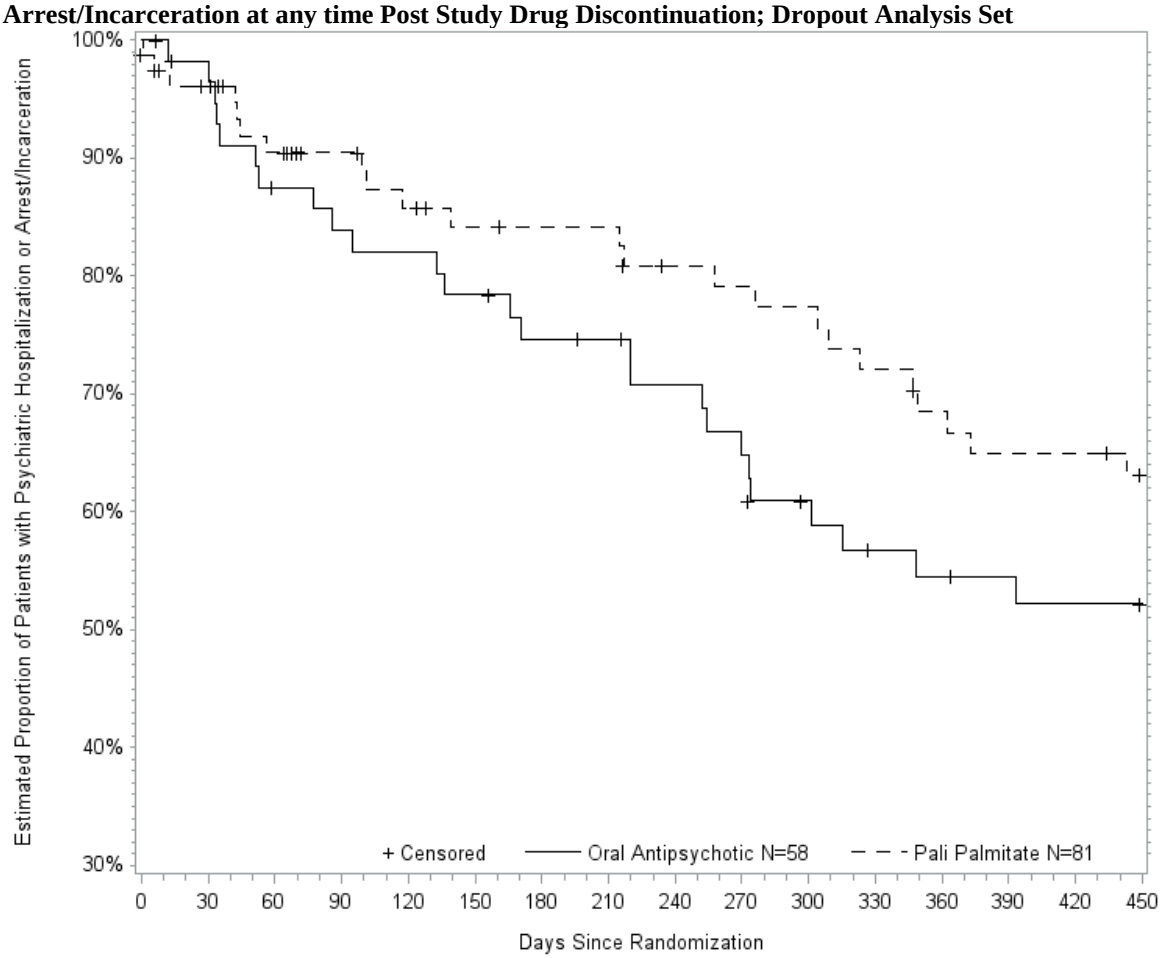
out of 81; 28.4%). The finding is supported by the Kaplan-Meier estimates of time to first event at any time post study drug discontinuation.

Table 9: Subject Psychiatric Hospitalization or Arrest/Incarceration Follow-up Status; Dropout Analysis Set

	Paliperidone Palmitate		Oral Antipsychotics	
Number of Subjects	81		58	
With event at any time post study drug discontinuation				
No	58	71.6%	33	56.9%
Yes	23	28.4%	25	43.1%

Source: reviewer's table.

Figure 6: Kaplan-Meier Estimates of Time from Randomization to 1st Psychiatric Hospitalization or Arrest/Incarceration at any time Post Study Drug Discontinuation; Dropout Analysis Set



Source: reviewer's plot.

Based on the supplemental information under this resubmission, this reviewer has updated the original dataset (eITT analysis set) with the censoring information for those 139 subjects, and rerun the primary efficacy analysis for time to first treatment failure using the updated eITT dataset. The observed proportion of subjects with an event of any treatment failure at any time was higher in the oral antipsychotic group (149 out of 218; 68.4%) than in the paliperidone

palmitate injection group (124 out of 226; 54.9%). The statistical significance was achieved by the p-value of the log-rank test at 0.0073 compared to 0.011 in their original submission. This exploratory analysis supports the robustness of the original primary analysis result.

Reviewer's note: The sponsor defined the ITT analysis set as all randomized subjects who received at least 1 dose of their randomly assigned medication. The sponsor further refined eITT (explanatory ITT) in which the analysis cutoff time was generally the last injection date +28 days for patients in the paliperidone palmitate group and the last prescription date of the randomized oral medication + the number of medication-supplied days + 1 day) for patients in the oral antipsychotic group. The eITT analysis set was used for the analyses of the primary and most secondary efficacy endpoints.

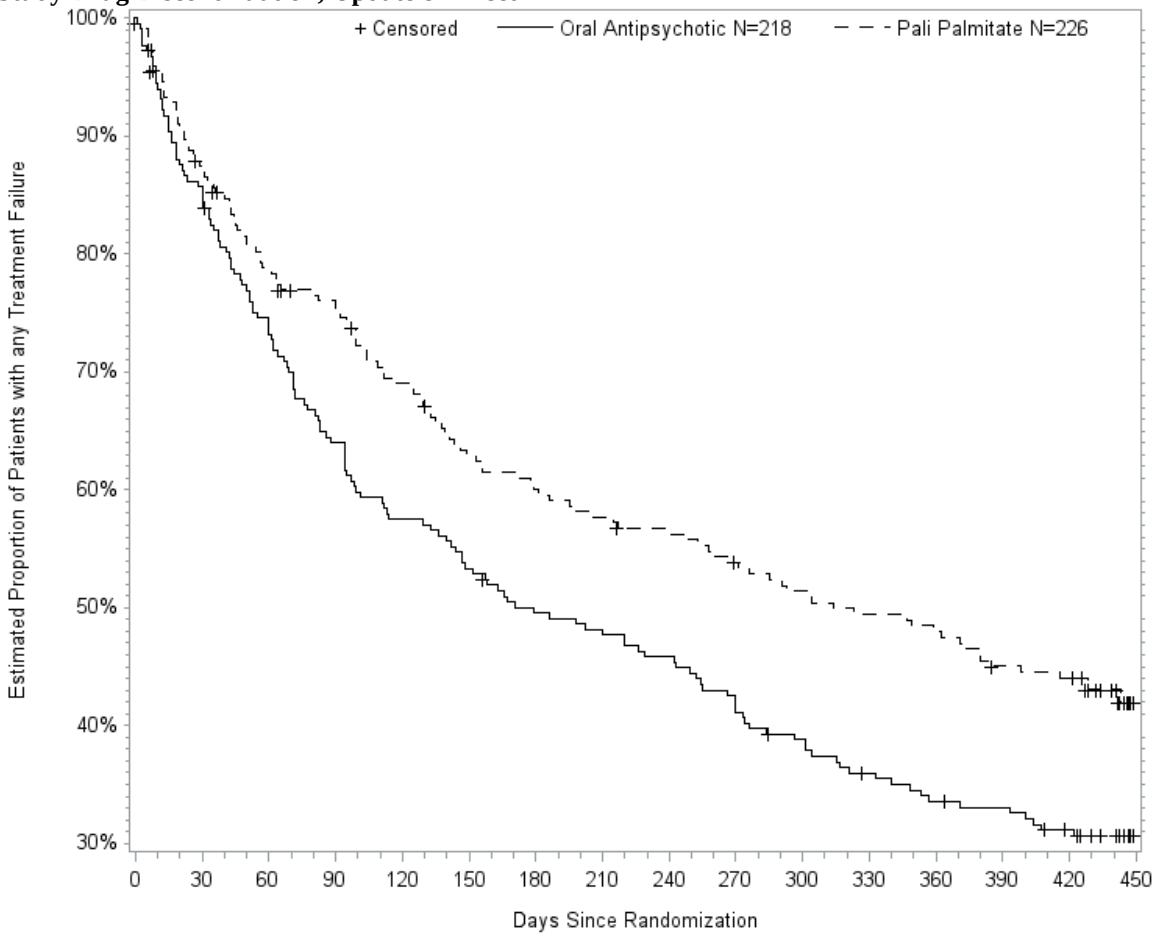
Table 10: Subject Treatment Failure Follow-up Status; Updated eITT Set

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event		
Number assessed	226	218
Event	124 (54.9%)	149 (68.3%)
Censored	102 (45.1%)	69 (31.7%)
Kaplan-Meier 25th Percentile, Days	92	55
(95% CI)	(50, 117)	(38, 71)
Kaplan-Meier Median, Days	314	179
(95% CI)	(217, 428)	(133, 254)
Kaplan-Meier 75th Percentile, Days	-	-
(95% CI)	(-, -)	(-, -)
Cumulative Probability of Event		
Month 3	0.25	0.36
(95% CI)	(0.19, 0.31)	(0.30, 0.42)
Month 6	0.4	0.5
(95% CI)	(0.33, 0.46)	(0.44, 0.57)
Month 9	0.46	0.59
(95% CI)	(0.39, 0.53)	(0.52, 0.65)
Month 12	0.52	0.66
(95% CI)	(0.45, 0.59)	(0.60, 0.73)
Month 15	0.58	0.69
(95% CI)	(0.51, 0.65)	(0.63, 0.76)
Log-Rank Test p-value	0.007	
Wilcoxon Test p-value	0.009	
Hazard Ratio From Cox Regression		
Treatment Group, Oral vs. Pali	1.38	
(95% CI)	(1.09, 1.76)	
p-value	0.008	

Source: reviewer's table.

The following Kaplan-Meier estimates of time to the first treatment failure at any time post study drug discontinuation supports a statistically significantly higher proportion of subjects with any treatment failure at any time in the oral antipsychotic group compared to the paliperidone palmitate injection group.

Figure 7: Kaplan-Meier Estimates of Time from Randomization to 1st Treatment Failure at any time Post Study Drug Discontinuation; Update eITT set



Source: reviewer's plot.

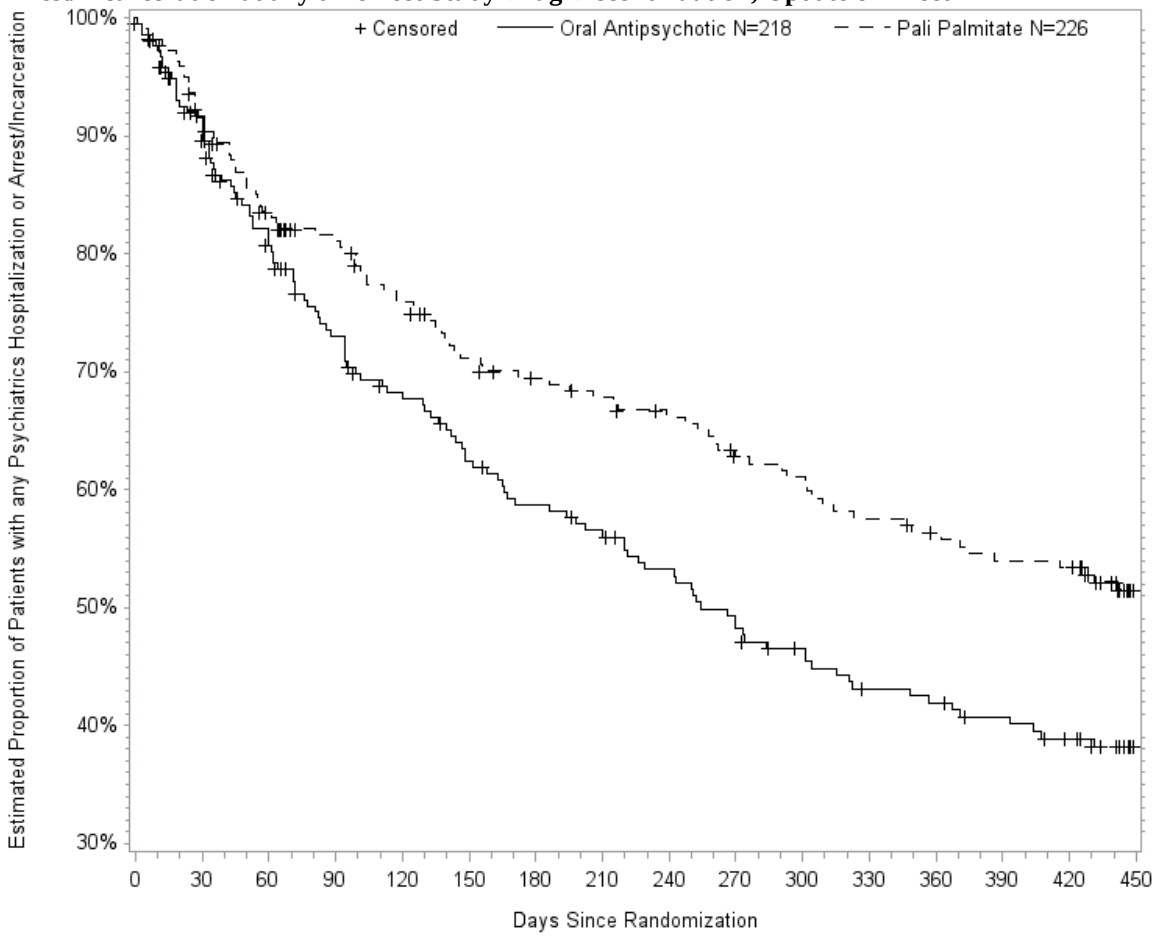
Regarding the efficacy endpoint of time to First Psychiatric Hospitalization or Arrest/Incarceration at any time post study drug discontinuation, the primary efficacy analysis result based on the updated eITT set was also statistically significant in favor of paliperidone palmitate (p-value = 0.007). And the Kaplan-Meier plot supports it graphically.

Table 11: Subject Psychiatrics Hospitalization or Arrest/Incarceration Follow-up Status; Updated eITT Set

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event		
Number assessed	226	218
Event	93 (41.2%)	118 (54.1%)
Censored	133 (58.8%)	100 (45.9%)
Kaplan-Meier 25th Percentile, Days	125	82
(95% CI)	(92, 186)	(60, 111)
Kaplan-Meier Median, Days	-	254
(95% CI)	(-, -)	(198, 348)
Kaplan-Meier 75th Percentile, Days	-	-
(95% CI)	(-, -)	(-, -)
Cumulative Probability of Event		
Month 3	0.19	0.27
(95% CI)	(0.14, 0.24)	(0.21, 0.33)
Month 6	0.3	0.41
(95% CI)	(0.24, 0.37)	(0.34, 0.48)
Month 9	0.37	0.52
(95% CI)	(0.30, 0.44)	(0.45, 0.59)
Month 12	0.44	0.58
(95% CI)	(0.37, 0.51)	(0.51, 0.65)
Month 15	0.49	0.62
(95% CI)	(0.41, 0.56)	(0.55, 0.69)
Log-Rank Test p-value	0.007	
Wilcoxon Test p-value	0.013	
Hazard Ratio From Cox Regression		
Treatment Group, Oral vs. Pali	1.45	
(95% CI)	(1.10, 1.90)	
p-value	0.007	

Source: reviewer's plot.

Figure 8: Kaplan-Meier Estimates of Time from Randomization to 1st Psychiatric Hospitalization or Arrest/Incarceration at any time Post Study Drug Discontinuation; Update eITT set



Source: reviewer's plot.

This reviewer also used the updated eITT dataset to revisit the primary efficacy analysis for the components of the primary efficacy endpoint for time to first psychiatric hospitalization and time to first arrest/incarceration.

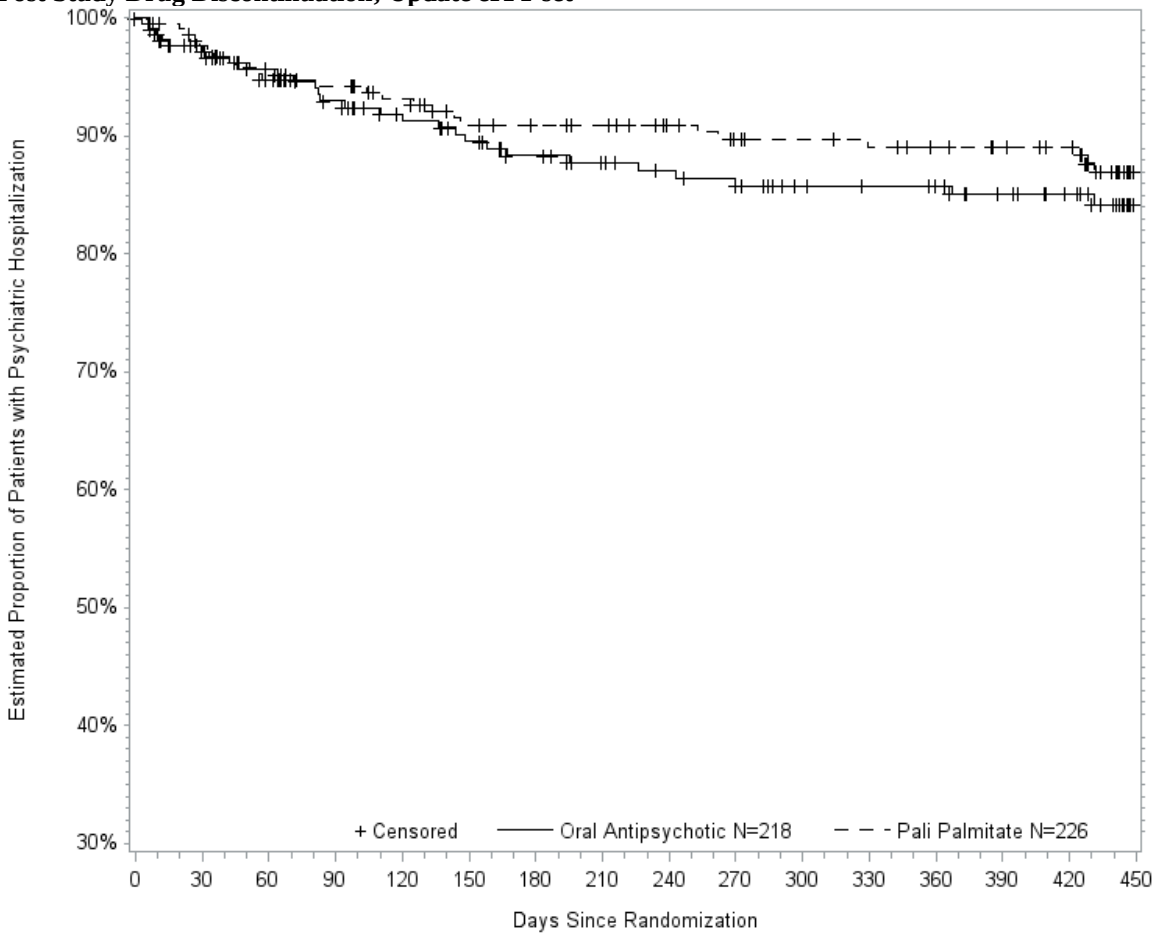
Based on the updated eITT population, the observed proportion of subjects with an event of first psychiatric hospitalization at any time appears comparable between the oral antipsychotic group (28 out of 218; 12.8%) and the paliperidone palmitate injection group (24 out of 226; 10.6%). The finding is generally supported by the Kaplan-Meier estimates of time to first event at any time post study drug discontinuation.

Table 12: Subject Psychiatric Hospitalization Follow-up Status; Updated eITT Set

Time to first psychiatric hospitalization	Paliperidone Palmitate		Oral Antipsychotics	
Number of Subjects	226		218	
With event at any time post study drug discontinuation				
No	202	89.4%	190	87.2%
Yes	24	10.6%	28	12.8%

Source: reviewer's table.

Figure 9: Kaplan-Meier Estimates of Time from Randomization to 1st Psychiatric Hospitalization at any time Post Study Drug Discontinuation; Update eITT set



Source: reviewer's plot.

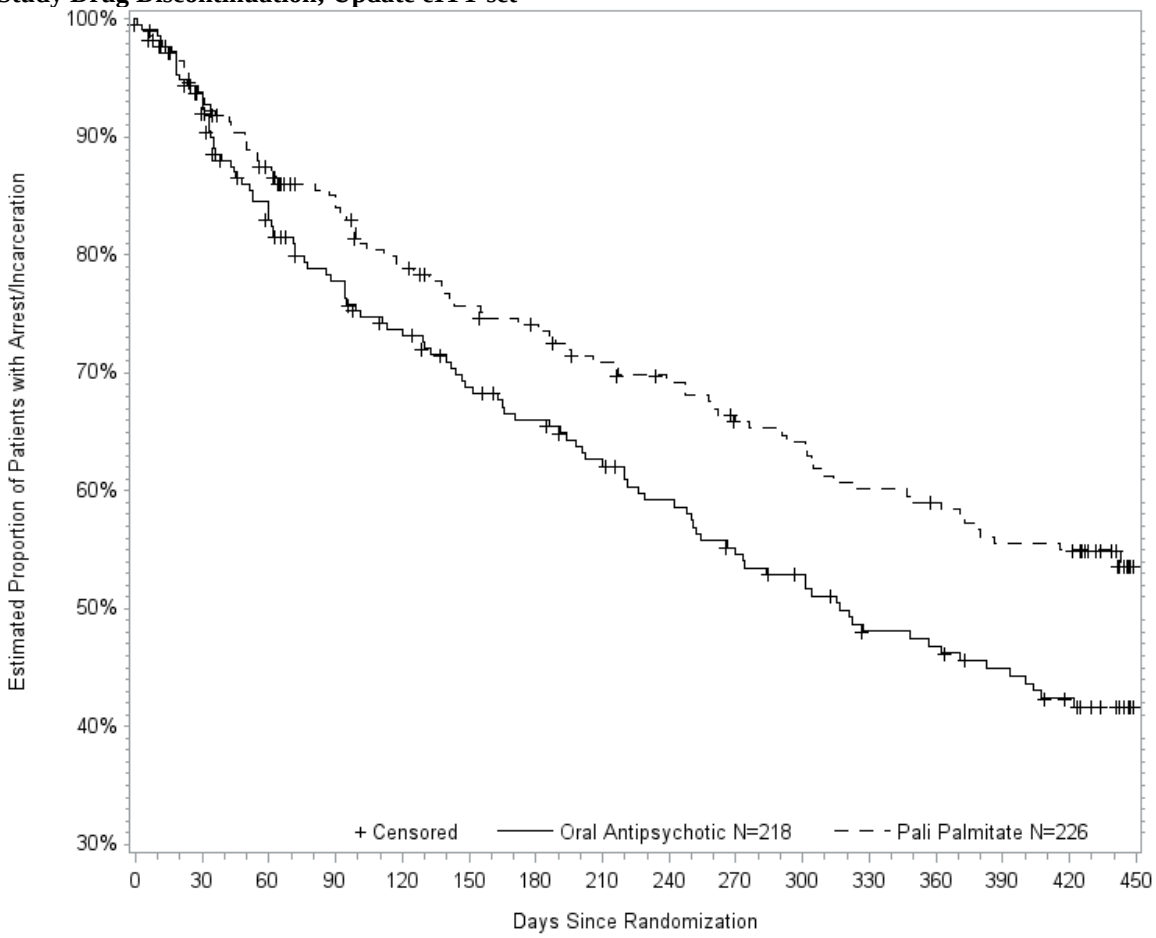
Based on the updated eITT population, the observed proportion of subjects with an event of first arrest/incarceration at any time was higher in the oral antipsychotic group (108 out of 218; 49.5%) than in the paliperidone palmitate injection group (89 out of 226; 39.8%). The finding is generally supported by the Kaplan-Meier estimates of time to first event at any time post study drug discontinuation.

Table 13: Subject Arrest/Incarceration Follow-up Status; Updated eITT Set

Time to first arrest/incarceration	Paliperidone Palmitate		Oral Antipsychotics	
Number of Subjects	226		218	
With event at any time post study drug discontinuation				
No	137	60.2%	110	50.5%
Yes	89	39.8%	108	49.5%

Source: reviewer's table.

Figure 10: Kaplan-Meier Estimates of Time from Randomization to 1st Arrest/Incarceration at any time Post Study Drug Discontinuation; Update eITT set



Source: reviewer's plot.

3.3 Evaluation of Safety

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

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

In the original submission, a total of 139 patients (31.3%) discontinued the study early without meeting the definition of a treatment failure. And in 60 patients (26.5%) in the paliperidone palmitate group and 42 patients (19.3%) in the oral antipsychotic group, the reasons for discontinuation reported in the case report forms were either "lost to follow-up" or "withdrawal by subject". Thus, there is no way to know whether or not these patients experienced treatment failure, and the relatively large differences between treatment groups undermine the interpretability of the results.

Based on previous discussions, the FDA agreed to use the failure times of the 29 dropout subjects with EMB-determined TF times outside the primary analysis window as was, and to view the result supportive of the primary efficacy result if Sponsor could make a determination whether (1) psychiatric hospitalization, (2) arrest/incarceration, and (3) suicide occurred for most or nearly all of the 110 patients and the distributions of treatment failure events were roughly balanced between the two treatment groups.

4.2 Collective Evidence

This resubmission has provided additional information to account for the reasons for discontinuation, and includes the supplemental data analyses to address FDA's concerns regarding interpretation and justification of robustness of the primary efficacy analysis in the original submission.

The aforementioned 139 subjects are analyzed as the dropout analysis set for supplemental data analyses:

Although not consistent with our original intention to look for roughly balanced distribution of treatment failures between two treatment groups, the observed proportions of subjects with an event of TF, or first arrest/incarceration, or first psychiatric hospitalization were actually numerically higher in the oral antipsychotic group than in the paliperidone palmitate injection group within 30 days, 60 days, 90 days of study drug discontinuation, and at any time post study drugs discontinuation. This is consistent with findings for the eITT analysis set in the original CSR.

Based on these post-hoc exploratory analyses, there seems no evidence that the higher rate of discontinuation in the paliperidone palmitate group compared to the oral antipsychotic group for the ITT analysis set was related to impending TF due to loss of efficacy or emerging intolerability.

4.3 Conclusions and Recommendations

In conclusion, the exploratory supplemental dropout information supports the robustness of the primary analysis and the interpretability of the positive findings in showing that treatment with paliperidone palmitate was statistically significantly superior to oral antipsychotics in delaying the time to first TF in adults with schizophrenia and a history of incarceration.

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/s/

YANG WANG
11/20/2017

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11/20/2017

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11/20/2017

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA22-264/S015
Drug Name:	INVEGA® SUSTENNA® (paliperidone palmitate) Extended-Release Injectable Suspension
Indication(s):	Schizophrenia
Applicant:	Janssen Research & Development, LLC.
Date(s):	Date of Document: July 11, 2014 PDUFA Due Date: May 11, 2015
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	PeilingYang , Ph.D., Jim Hung , Ph.D.
Medical Division:	Division of Psychiatry Products, HFD-130
Clinical Team:	Glenn Mannheim, M.D., Jing Zhang, M.D.
Project Manager:	Ann Sohn, Pharm D.
Keywords:	Paliperidone Palmitate, Schizophrenia

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

A single trial was included in this application. Based on the pre-specified primary endpoint, it appears that paliperidone palmitate was superior to treatment with an oral antipsychotic in delaying time to first treatment failure in subjects with schizophrenia who had been incarcerated, assuming that the patients who discontinued the assigned treatment or the trial would not have an event. However, 31.3% of the patients discontinued early without a treatment failure although the sponsor intended to follow up every patient throughout the study. In addition, there was a larger percent of patients who discontinued in the paliperidone palmitate group. By treating these patients as having an event, the analyses suggest that the utility of the paliperidone palmitate arm is inconclusive as compared to the oral antipsychotics arm, though it is not clear whether the patients who discontinued would have had an event, had they been completely followed up. This raises a question of whether paliperidone palmitate is worthy of approval even if it is deemed more effective. In addition, there was no trend in favor of the paliperidone palmitate arm in terms of PSP total score and in CGI-S at month 15.

1.2 Brief Overview of Clinical Studies

This supplement NDA is intended to support revisions to the product label for INVEGA® SUSTENNA® Extended-Release Suspension for intramuscular injection approved on 31 July 2009, based on findings from the trial R092670-SCH-3006 titled "A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated". The submission includes one study. A labeling revision is proposed based on the new data obtained from the study-- (b) (4) ".

1.3 Statistical Issues and Findings

Based on the pre-specified primary endpoint (time to 1st treatment failure), paliperidone palimitate demonstrated superiority to oral antipsychotic (p-value = 0.011). However, a total of 139 patients (31.3%) had an early discontinuation without a treatment failure; among those the two most common discontinuation reasons were "lost to follow up" and "patient withdrawal". All those 139 patients were censored in the primary endpoint analysis. Sensitivity analyses, which were intended to explore the impact of these early discontinuations on efficacy, did not yield the same conclusion from the primary analysis. On the other hand, it is not clear whether these sensitivity analyses by treating early discontinuations as events are justifiable.

The results of secondary endpoints measuring symptoms (change from baseline in PSP total score and in CGI-S at month 15, respectively) did not suggest a trend in favor of paliperidone palmitate. Although these analyses were confounded by competing risks and a high discontinuation rate, the results did not suggest a clear separation between treatment groups throughout the trial, not just at month 15. A question is then raised as to why there was no trend in suggesting superiority throughout the trial based on symptom endpoints while a highly statistical significance was observed in the primary endpoint.

2. INTRODUCTION

2.1 Overview

Schizophrenia is a chronic, serious mental illness that is characterized by hallucinations, delusions, and disorganized speech and behavior. Individuals with schizophrenia typically exhibit social and occupational dysfunction. The disease affects nearly 1.1% of adults in the United States. The number of incarcerated adults in America has increased significantly in recent years and a recent estimate suggests that there are nearly one million arrests annually of people with serious mental illnesses.

This supplement consisted of a trial to demonstrate the superiority of paliperidone palmitate to oral antipsychotics in schizophrenia patients who have been incarcerated.

Paliperidone palmitate (R092670) is the palmitate ester prodrug of paliperidone (9-hydroxy risperidone, R076477), a selective, monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D2) and serotonin (5 hydroxytryptamine [5-HT]) type 2A (5HT2A) antagonism of the newer, or second generation, antipsychotic drugs. Paliperidone palmitate was developed as a long acting intramuscular (IM) injectable aqueous suspension formulation for the treatment of schizophrenia and provides therapeutic plasma concentrations for weeks at a time, thereby eliminating the requirement for daily oral medication. Paliperidone palmitate also provides a slow absorption of the dose and less peak-to-trough variability in plasma concentrations, potentially reducing adverse events associated with higher peak plasma concentrations seen with oral medications. The advantages of paliperidone palmitate suggest that patients who receive paliperidone palmitate treatment may experience fewer hospitalizations, and less frequent clinical exacerbations that would necessitate a change in their antipsychotic treatment to prevent imminent hospitalizations. Improved symptom control with paliperidone palmitate treatment may lead to fewer interactions with law enforcement and resultant arrests/incarcerations, and therefore a lower overall cost of care and reduced cost burden to counties and states than those receiving standard oral medications.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\CDSESUB1\evsprod\NDA022264\0135 the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

A consistent result of the primary efficacy analysis can be generated from both raw and derived data.

3.2 Evaluation of Efficacy

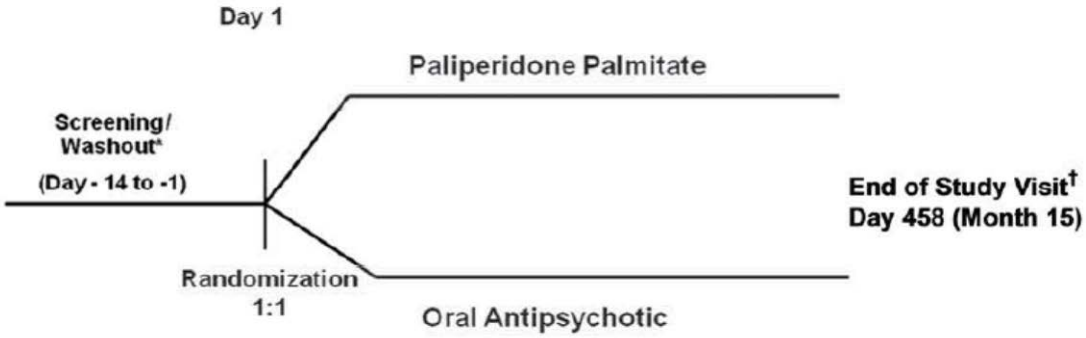
3.2.1 Primary Study Objective

The primary objective of this study was to compare the efficacy of paliperidone palmitate with oral antipsychotic treatment in delaying time to first treatment failure over 15 months, in subjects with schizophrenia who had been incarcerated.

3.2.2 Study Design

This was a 15-month, randomized, prospective, open-label, active controlled, parallel-group, multicenter study comparing paliperidone palmitate treatment with oral antipsychotic treatment in the prevention of a treatment failure in subjects with schizophrenia. The study consisted of an up-to-14-day screening/washout period and a 15-month open-label treatment period (Figure 1).

Figure 1 Overview of Study Design



During the screening/washout period, subjects without source documentation of exposure to paliperidone, paliperidone palmitate, or risperidone were required to undergo a 2-day oral tolerability test (OTT) with a daily dose of risperidone 1 mg. The OTT could be conducted at any time during the screening period, could overlap with washout of disallowed medications, and was completed before randomization.

Before randomization, for each subject who met all entry criteria, the investigator specified a set of oral antipsychotics (from 1 to 7) selected from aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone that were appropriate for the subject to receive. If the subject was randomly assigned to receive oral antipsychotic treatment, the specific oral antipsychotic was randomly chosen from the set of suitable oral antipsychotics for the subject that was prespecified by the investigator.

A Treatment Failure Event Monitoring Board (EMB) that was blinded to individual subject treatment assignment determined the occurrence and date of the first treatment failure event. The EMB determination was used for deriving the primary endpoint.

After randomization (Day 1), subjects returned to the study site on Days 8 (±4), 15 (±3) and 38 (±7) and then monthly (every 30 [±7] days) for 15 months for study visits. Subjects who discontinued their assigned study treatment or experienced a treatment failure and did not withdraw consent were encouraged to continue in the study and be followed through Month 15 of the treatment period.

3.2.3 Efficacy Measures and Analyses

1) Primary Efficacy Endpoint: Time to first treatment failure as determined by the EMB. Treatment failure was a composite endpoint that consisted of any of the events listed below:
   - Arrest /incarceration
   - Psychiatric hospitalization
   - Suicide
   - Discontinuation of antipsychotic treatment due to inadequate efficacy
   - Treatment supplementation with another antipsychotic due to inadequate efficacy
   - Discontinuation of antipsychotic treatment due to safety or tolerability
   - Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization

2) Major Secondary Efficacy Endpoints:
   - Time to first psychiatric hospitalization or first arrest/incarceration. For this analysis, patients who had a psychiatric hospitalization or arrest/incarceration were considered to have an event whether it was the first treatment failure or not.
   - Mean change from baseline in PSP total score
   - Time to first psychiatric hospitalization. For this analysis, patients who had a psychiatric hospitalization were considered to have an event whether it was the first treatment failure or not.
   - Mean change from baseline in the CGI-S score

3) Statistical Analysis Methodology
   - Analysis sets: The sponsor defined the ITT analysis set as all randomized subjects who received at least 1 dose of their randomly assigned medication. The sponsor further refined the ITT set into eITT (explanatory ITT) and pITT (pragmatic ITT) in terms of analysis time cutoff. For the eITT analysis set, the analysis cutoff time was generally the last injection date +28 days for patients in the paliperidone palmitate group and the last prescription date of the randomized oral medication + the number of medication-supplied days + 1 day) for patients in the oral antipsychotic group. On the other hand, for the pITT analysis set, the analysis cutoff time was the date of last contact regardless of medication switches/discontinuation.

     The eITT analysis set was used for the analyses of the primary and most (including the aforementioned 4 major) secondary efficacy endpoints.

     The pITT analysis set was used by the sponsor for all effectiveness analyses.

   - Analyses of primary efficacy endpoint: The distribution of time to the first treatment failure was estimated by the Kaplan-Meier method for each treatment group. The primary analysis

was the log-rank test performed on the eITT analysis set. The hazard ratio and its 95% confidence interval were explored using a Cox proportional hazards model with treatment as a fixed factor.

For the eITT analysis set, subjects who did not have an event by the designated analysis time cutoff (as defined in the preceding bullet) were censored on the cutoff date. It is to be noted that early discontinuation due to inadequate efficacy or tolerability was considered as an event per the pre-specified definition.

- Analyses of secondary efficacy endpoints:
  -Time to event efficacy endpoints: Similar methods were applied as described for the primary efficacy endpoint.

  -Change from baseline in PSP total score at the 15-month: The primary analysis was performed on the eITT analysis set using a mixed model repeated measures (MMRM) ANCOVA with terms for treatment, time, treatment-by-time interaction, and baseline PSP total score. An unstructured covariance matrix was used to model the within-subject correlations.

  -Change from baseline in CGI-S at the 15-month: Analysis analogous to that for the PSP analysis was used.

- Multiplicity: To preserve the overall type I error rate at the 2-sided 0.05 significance level, a fixed sequence approach was used to test these hypotheses starting with the primary endpoint, followed by the major secondary endpoints in the order as listed above.

Reviewer's Notes: The primary endpoint, time to treatment failure, is a composite endpoint. To avoid adverse impact from heavily dependent competing risks on interpretability of trial results, we reminded the sponsor in the IND stage that patients would need to be followed up throughout to have meaningful comparisons with respect to these major secondary endpoints. We also expressed that we would not simultaneously accept both PSP and CGI-S as key secondary endpoints even in acute-phase trials because these two endpoints measure similar domains; additionally, the open-label nature of the trial adds another potential concern of bias to these symptom evaluations regardless of whether the control is placebo or active.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

1) Patient Disposition and Study Completion/Withdrawal Information

A total of 693 patients were screened, and 450 patients were randomized to the paliperidone palmitate (n = 230) and the oral antipsychotic (n = 220) groups. The ITT analysis set included 444 subjects (226 paliperidone palmitate, 218 oral antipsychotics); the 6 subjects excluded from the ITT analysis set included 4 subjects who were randomized to paliperidone palmitate but were not treated and 2 subjects (both randomized to oral antipsychotics) at site 001054 who were excluded due to audit findings.

A total of 181 patients completed the 15-month visit (Visit 18), 41.2% of subjects in the paliperidone palmitate group and 40.4% of subjects in the oral antipsychotics group. There were 263 subjects who discontinued from the study early; among those, nearly half (124 subjects; 47.1%) had already reached the primary endpoint (Table 1). The most frequently reported reasons for those early discontinuations without an event in the paliperidone palmitate and the oral antipsychotics groups were lost to follow-up (15.0%, 11.9%), withdrawal by subject (11.5%, 7.3%), and other (6.2%, 5.5%), respectively.

Table 1 Patient Disposition, All Randomized Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects Screened			693
Number of Screen Failures			243
Number of Subjects Randomized	230	220	450
Number of Subjects in the ITT Analysis Set [a]	226	218	444
Number of Subjects Completed Study	93 (41.2%)	88 (40.4%)	181 (40.8%)
With event [b]	38 (16.8%)	45 (20.6%)	83 (18.7%)
Without event [b]	55 (24.3%)	43 (19.7%)	98 (22.1%)
Number of Subjects Discontinued Study Early			
Total	133 (58.8%)	130 (59.6%)	263 (59.2%)
Adverse Event	5 (2.2%)	4 (1.8%)	9 (2.0%)
Death	1 (0.4%)	0	1 (0.2%)
Lack of Efficacy	0	0	0
Lost to Follow-Up	53 (23.5%)	55 (25.2%)	108 (24.3%)
Withdrawal by Subject	37 (16.4%)	27 (12.4%)	64 (14.4%)
Noncompliance with Study Drug	0	3 (1.4%)	3 (0.7%)
Physician Decision	5 (2.2%)	4 (1.8%)	9 (2.0%)
Protocol Violation	0	1 (0.5%)	1 (0.2%)
Other [c]	32 (14.2%)	36 (16.5%)	68 (15.3%)
With event [b]	52 (23.0%)	72 (33.0%)	124 (27.9%)
Adverse Event	4 (1.8%)	4 (1.8%)	8 (1.8%)
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-Up	19 (8.4%)	29 (13.3%)	48 (10.8%)
Withdrawal by Subject	11 (4.9%)	11 (5.0%)	22 (5.0%)
Noncompliance with Study Drug	0	2 (0.9%)	2 (0.5%)
Physician Decision	0	2 (0.9%)	2 (0.5%)
Protocol Violation	0	0	0
Other [c]	18 (8.0%)	24 (11.0%)	42 (9.5%)
Without event [b]	81 (35.8%)	58 (26.6%)	139 (31.3%)
Adverse Event	1 (0.4%)	0	1 (0.2%)
Death	1 (0.4%)	0	1 (0.2%)
Lack of Efficacy	0	0	0
Lost to Follow-Up	34 (15.0%)	26 (11.9%)	60 (13.5%)
Withdrawal by Subject	26 (11.5%)	16 (7.3%)	42 (9.5%)
Noncompliance with Study Drug	0	1 (0.5%)	1 (0.2%)
Physician Decision	5 (2.2%)	2 (0.9%)	7 (1.6%)
Protocol Violation	0	1 (0.5%)	1 (0.2%)
Other [c]	14 (6.2%)	12 (5.5%)	26 (5.9%)

[a] ITT subjects are those that were randomized and treated.
[b] Event refers to the EMB-determined treatment failure event – the primary study endpoint.
[c] Verbatim reasons for "other" included custody (incarcerated, jail,) for 40 subjects (18 paliperidone palmitate, 22 oral antipsychotics) and subject relocation for 8 subjects (4 paliperidone palmitate, 4 oral antipsychotics).
Four subjects randomized to Paliperidone Palmitate were not treated; 2 subjects randomized to Oral Treatment from site 001054 were excluded from ITT analysis set due to audit findings.
Note: All percentages are based on the ITT population.

(Source: Sponsor's Table 4, confirmed by the reviewer's analysis)

2) Patient Demographic and Baseline Characteristics

The demographic and baseline characteristics were similar in both treatment arms. Mean age was 38 years, majority were males, black or African American. Mean time since release from the last incarceration was 42 days (Table 2).

Table 2 Patient Demographic and Baseline characteristics, eITT Population

	Paliperidone Palmitate	Oral Antipsychotics	Total
Number of Subjects	226	218	444
Age (years)			
N	226	218	444
Mean (SD)	37.7 (10.57)	38.6 (10.36)	38.1 (10.47)
Median	39.0	40.0	40.0
Range	(18; 61)	(19; 61)	(18; 61)
18-25	39 (17.3%)	32 (14.7%)	71 (16.0%)
26-50	161 (71.2%)	161 (73.9%)	322 (72.5%)
51-60	25 (11.1%)	24 (11.0%)	49 (11.0%)
>60	1 (0.4%)	1 (0.5%)	2 (0.5%)
Gender			
N	226	218	444
Male	193 (85.4%)	190 (87.2%)	383 (86.3%)
Female	33 (14.6%)	28 (12.8%)	61 (13.7%)
Race			
N	226	217	443
White	73 (32.3%)	74 (34.1%)	147 (33.2%)
American Indian or Alaska Native	2 (0.9%)	3 (1.4%)	5 (1.1%)
Black or African American	145 (64.2%)	130 (59.9%)	275 (62.1%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	1 (0.5%)	2 (0.5%)
Asian	2 (0.9%)	1 (0.5%)	3 (0.7%)
Other	1 (0.4%)	6 (2.8%)	7 (1.6%)
Multiple	2 (0.9%)	2 (0.9%)	4 (0.9%)
Ethnicity			
N	226	218	444
Hispanic or Latino	31 (13.7%)	36 (16.5%)	67 (15.1%)
Not Hispanic or Latino	185 (81.9%)	176 (80.7%)	361 (81.3%)
Unknown	2 (0.9%)	1 (0.5%)	3 (0.7%)
Not Reported	8 (3.5%)	5 (2.3%)	13 (2.9%)
Time Since Release from the Last Incarceration (days)			
N	226	217	443
Mean (SD)	38.9 (50.29)	45.7 (53.04)	42.2 (51.71)
Median	28.0	35.0	31.0
Range	(1; 575)	(1; 446)	(1; 575)

(Source: The sponsor's Table 5, confirmed by the reviewer's analysis)

3.2.5 Sponsor's Primary Efficacy Results

1) Composite primary endpoint

Time to first treatment failure was statistically significantly longer in the group with paliperidone palmitate compared to the group with an oral antipsychotic (p-value = 0.011). The exploratory Cox regression analysis resulted in a hazard ratio (paliparidone palmitate to oral antipsychotic) of 0.700 with a 95% CI of (0.532, 0.922) for the eITT analysis set. The analysis performed on the pITT analysis set was also statistically significant with a p-value of 0.010 and a hazard ratio of 0.717 with a 95% CI of (0.555, 0.925) (Tables 3 & 4, Figures 2 & 3).

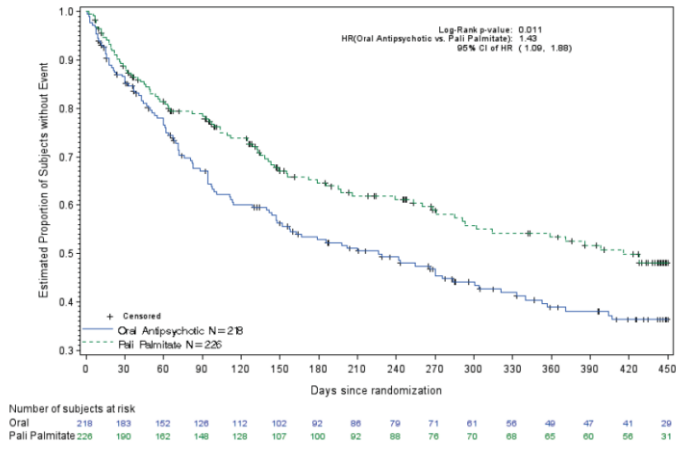
Table 3 Analysis Results of Time to First Treatment Failure - per EMB Determination; eITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event[a]		
Number assessed	226	218
Event	90 (39.8%)	117 (53.7%)
Censored	136 (60.2%)	101 (46.3%)
Kaplan-Meier 25th Percentile, Days	109	62
(95% CI)	(63, 143)	(47, 82)
Kaplan-Meier Median, Days	416	226
(95% CI)	(285, -)	(147, 304)
Kaplan-Meier 75th Percentile, Days	-	-
(95% CI)	(-, -)	(-, -)
Cumulative Probability of Event[a]		
Month 3	0.22	0.33
(95% CI)	(0.16, 0.27)	(0.26, 0.39)
Month 6	0.35	0.47
(95% CI)	(0.29, 0.42)	(0.40, 0.54)
Month 9	0.41	0.55
(95% CI)	(0.34, 0.48)	(0.47, 0.62)
Month 12	0.47	0.61
(95% CI)	(0.39, 0.54)	(0.54, 0.69)
Month 15	0.52	0.64
(95% CI)	(0.44, 0.60)	(0.56, 0.71)
Log-Rank Test p-value[b]	0.011	
Wilcoxon Test p-value[b]	0.014	
Hazard Ratio From Cox Regression		
Treatment Group, Oral vs. Pali Palmitate	1.43	
(95% CI)	(1.09, 1.88)	
p-value	0.011	

[a] Quartiles and cumulative probabilities are based on Kaplan-Meier estimates.
[b] P-values are for testing difference between paliperidone palmitate and oral antipsychotic treatment.

(Source: Sponsor's Table 16, confirmed by the reviewer's analysis)

Figure 2 Kaplan-Meier Estimates of Time to First Treatment Failure Per EMB Determination; eITT Analysis Set



(Source: The sponsor's Figure 4, confirmed by the reviewer's analysis)

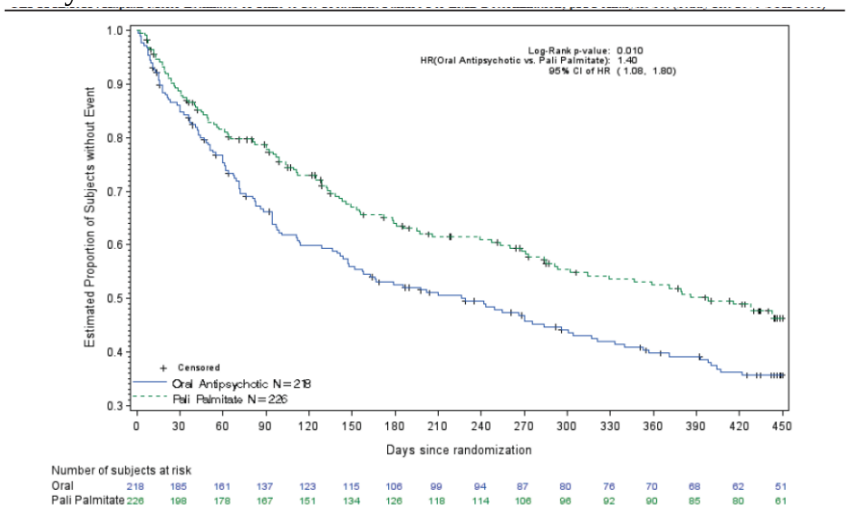
Table 4 Exploratory Analysis Results of Time to First Treatment Failure - per EMB Determination; pITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event[a]		
Number assessed	226	218
Event	108 (47.8%)	131 (60.1%)
Censored	118 (52.2%)	87 (39.9%)
Kaplan-Meier 25th Percentile, Days	104	61
(95% CI)	(63, 138)	(43, 76)
Kaplan-Meier Median, Days	398	229
(95% CI)	(285, -)	(147, 304)
Kaplan-Meier 75th Percentile, Days	-	-
(95% CI)	(-, -)	(-, -)
Cumulative Probability of Event[a]		
Month 3	0.22	0.34
(95% CI)	(0.17, 0.28)	(0.27, 0.40)
Month 6	0.36	0.47
(95% CI)	(0.29, 0.42)	(0.41, 0.54)
Month 9	0.41	0.54
(95% CI)	(0.35, 0.48)	(0.47, 0.61)
Month 12	0.48	0.60
(95% CI)	(0.41, 0.54)	(0.53, 0.67)
Month 15	0.54	0.64
(95% CI)	(0.47, 0.61)	(0.58, 0.71)
Log-Rank Test p-value[b]	0.010	
Wilcoxon Test p-value[b]	0.008	
Hazard Ratio From Cox Regression		
Treatment Group, Oral vs. Pali Palmitate	1.40	
(95% CI)	(1.08, 1.80)	
p-value	0.010	

[a] Quartiles and cumulative probabilities are based on Kaplan-Meier estimates.
[b] P-values are for testing difference between paliperidone palmitate and oral antipsychotic treatment.

(Source: Sponsor's Table TEFTFKM01P, confirmed by the reviewer's analysis)

Figure 3 Kaplan-Meier Estimates of Time to First Treatment Failure per EMB Determination; pITT Analysis Set



(Source: The sponsor's Figure GEFTFKM01P, confirmed by the reviewer's analysis)

2) Components of the primary endpoint

All component events occurred more frequently in subjects treated with oral antipsychotics than in subjects treated with paliperidone palmitate, except for discontinuation due to safety or tolerability in both eITT and pITT analysis sets (Tables 5 & 6). The most prevalent component was arrest/incarceration (48 in the paliperidone palmitate group vs. 64 in the oral antipsychotic group based on the eITT analysis set).

Table 5 Frequency Distribution of Component Events of First Treatment Failure, Per EMB Determination; eITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Total
First treatment failure			
Number of Subjects	226	218	444
Any Event	90 (39.8%)	117 (53.7%)	207 (46.6%)
Arrest/incarceration	48 (21.2%)	64 (29.4%)	112 (25.2%)
Discontinuation of antipsychotic treatment due to inadequate efficacy	1 (0.4%)	9 (4.1%)	10 (2.3%)
Suicide	0	0	0
Discontinuation of antipsychotic treatment due to safety or tolerability	15 (6.6%)	8 (3.7%)	23 (5.2%)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	7 (1.6%)
Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	44 (9.9%)
Treatment supplementation with another antipsychotic due to inadequate efficacy	5 (2.2%)	6 (2.8%)	11 (2.5%)

(Source: Sponsor's Table 17, confirmed by the reviewer's analysis)

Table 6 Frequency Distribution of Component Events of First Treatment Failure, Per EMB Determination; pITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Total
First treatment failure			
Number of Subjects	226	218	444
Any Event	108 (47.8%)	131 (60.1%)	239 (53.8%)
Arrest/incarceration	58 (25.7%)	70 (32.1%)	128 (28.8%)
Discontinuation of antipsychotic treatment due to inadequate efficacy	1 (0.4%)	11 (5.0%)	12 (2.7%)
Suicide	0	0	0
Discontinuation of antipsychotic treatment due to safety or tolerability	21 (9.3%)	9 (4.1%)	30 (6.8%)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	7 (1.6%)
Psychiatric hospitalization	20 (8.8%)	30 (13.8%)	50 (11.3%)
Treatment supplementation with another antipsychotic due to inadequate efficacy	5 (2.2%)	7 (3.2%)	12 (2.7%)

(Source: The sponsor's Figure TEFTKTP01P, confirmed by the reviewer's analysis)

3) Time to individual components

Analyses of time to individual components were explored, which also suggested that the statistically significant finding in the composite primary endpoint was mainly driven by the

arrest/incarceration component (Table 7). However, these analyses should be considered exploratory. Refer to section 3.2.5 for reviewer's comments.

Table 7 Analyses of Time to Component Events of Treatment Failure, eITT

Time to Event	Paliperidone Palmitate (N=226)	Oral Antipsychotics (N=218)	HR (95% CI)
Time to Arrest/Incarceration	64 (28.3%)	87 (39.9%)	0.67 (0.49, 0.93)
Time to Psychiatric Hospitalization	22 (9.7%)	25 (11.5%)	0.84 (0.47, 1.49)
Time to Increased Psychiatric Services	4 (1.8%)	7 (3.2%)	0.55 (0.16, 1.88)
Time to Treatment Discontinuation Due to Inadequate Efficacy	2 (0.9%)	15 (6.9%)	0.129 (0.03, 0.57)
Time to Treatment Supplementation	7 (7.1%)	6 (6.0%)	1.104 (0.37, 3.28)
Time to Discontinuation Due to Safety or tolerability	16 (6.6%)	13 (3.8%)	1.183 (0.57, 2.46)
Time to 1st Suicide	0	0	--

(Source: The reviewer's analysis)

3.2.6 Sponsor's Secondary Efficacy Results

1) 1st secondary endpoint--time to First Psychiatric Hospitalization or Arrest/Incarceration
The result was also statistically significant in favor of paliperidone palmitate (p-value = 0.019) based on the primary analysis set (eITT), with a hazard ratio (95% CI) from the exploratory Cox regression analysis of 0.7 (0.519, 0.945) (Table 8). Based on the pITT analysis set, the result nearly reached a statistical significance (p-value =0.056) with a hazard ratio (95% CI) of 0.768 (0.585, 1.009) (Table 9).

Table 8 Time to First Psychiatric Hospitalization or Arrest/Incarceration, eITT

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event[a]		
Number assessed	226	218
Event	76 (33.6%)	98 (45.0%)
Censored	150 (66.4%)	120 (55.0%)
Kaplan-Meier 25th Percentile (95% CI), Days	139 (99, 206)	88 (62, 120)
Kaplan-Meier Median (95% CI), Days	NE	274 (202, 407)
Kaplan-Meier 75th Percentile, Days	NE	NE
Cumulative Probability of Event[a] (95% CI)		
Month 3	0.18 (0.12, 0.23)	0.26 (0.19, 0.32)
Month 6	0.30 (0.23, 0.36)	0.40 (0.32, 0.47)
Month 9	0.37 (0.30, 0.45)	0.49 (0.42, 0.57)
Month 12	0.43 (0.35, 0.51)	0.55 (0.47, 0.63)
Month 15	0.47 (0.39, 0.56)	0.60 (0.52, 0.68)
Log-Rank Test p-value[b]	0.019	
Hazard Ratio (95% CI) From Cox Regression, Oral vs. Pali Palmitate	1.43 (1.06, 1.93)	

NE = not estimable.
[a] Quartiles and cumulative probabilities are based on Kaplan-Meier estimates.
[b] P-values are for testing difference between paliperidone palmitate and oral antipsychotic treatment.

(Source: Sponsor's Table 19, confirmed by the reviewer's analysis)

Table 9 Time to First Psychiatric Hospitalization or Arrest/Incarceration, pITT

	Paliperidone Palmitate	Oral Antipsychotics
Time to Event[a]		
Number assessed	226	218
Event	97 (42.9%)	112 (51.4%)
Censored	129 (57.1%)	106 (48.6%)
Kaplan-Meier 25th Percentile, Days	138	86
(95% CI)	(99, 195)	(61, 120)
Kaplan-Meier Median, Days	457	317
(95% CI)	(347, -)	(221, 431)
Kaplan-Meier 75th Percentile, Days	-	-
(95% CI)	(-, -)	(-, -)
Cumulative Probability of Event[a]		
Month 3	0.18	0.26
(95% CI)	(0.13, 0.23)	(0.20, 0.31)
Month 6	0.29	0.39
(95% CI)	(0.23, 0.35)	(0.32, 0.46)
Month 9	0.37	0.47
(95% CI)	(0.31, 0.44)	(0.40, 0.54)
Month 12	0.43	0.52
(95% CI)	(0.36, 0.50)	(0.45, 0.59)
Month 15	0.49	0.57
(95% CI)	(0.42, 0.56)	(0.50, 0.64)
Log-Rank Test p-value[b]	0.057	
Wilcoxon Test p-value[b]	0.034	
Hazard Ratio From Cox Regression		
Treatment Group, Oral vs. Pali Palmitate	1.30	
(95% CI)	(0.99, 1.71)	
p-value	0.057	

[a] Quartiles and cumulative probabilities are based on Kaplan-Meier estimates.
[b] P-values are for testing difference between paliperidone palmitate and oral antipsychotic treatment.

(Source: Sponsor's Table TEFHAKM01P, confirmed by the reviewer's analysis)

2) 2nd secondary endpoint--mean change from baseline in PSP total score to month 15

There was no statistically significant difference between treatment groups (p-value= 0.689 for eITT) (Tables 10). There was also no trend favoring paliperidone palmitate during the entire course of the trial (Figure 4).

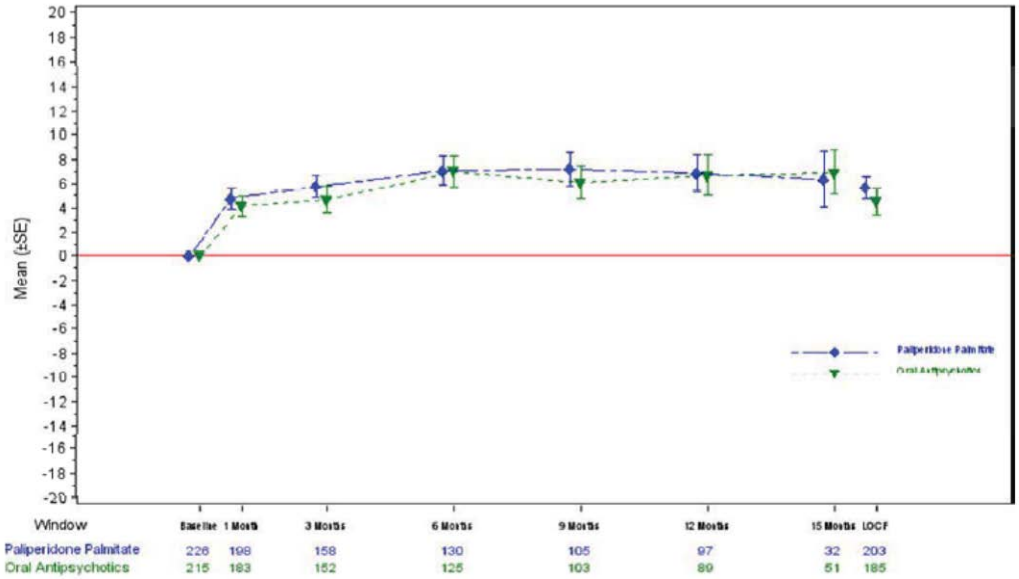
Table 10 Mixed Model Repeated Measures Results for PSP Total Score: Overall Treatment Effect; eITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Difference
PSP Total Score			
Overall Treatment Effect			
LS Mean	60.33	59.94	0.39
SE	0.690	0.690	0.976
95% CI	(58.98;61.69)	(58.58;61.30)	(-1.53;2.31)
p-value [a]	<.0001	<.0001	0.6891
LS Mean - Change from Baseline	5.75	5.36	0.39
SE	0.690	0.690	0.976
95% CI	(4.40;7.11)	(4.00;6.72)	(-1.53;2.31)
p-value [a]	<.0001	<.0001	0.6891

[a] p-value based on repeated measures model that includes baseline value, treatment, time, and treatment by time interaction. An unstructured variance-covariance matrix was used to model the correlations among repeated measures from individual subject.

(Source: Sponsor's Table 20, confirmed by the reviewer's analysis)

Figure 4 PSP Total Score: LS Mean ±SE Change from Baseline Over Time; eITT Analysis Set



(Source: sponsor's Figure 7 and confirmed by the reviewer's analysis)

3) 3rd secondary endpoint-- Time to psychiatric hospitalization

Based on the eITT analysis set, subjects who had a psychiatric hospitalization prior to their eITT analysis cutoff dates were considered to have an event. There was no statistically significant finding in favor of paliperidone palmitate (p-value =0.551) (Table 7).

4) 4th secondary endpoint--Mean change from baseline in CGI-S to month 15

There was no statistically significant difference between treatment groups at month 15 (Table 11), the observed differences between treatment groups at each visit were also very small (Figure 5).

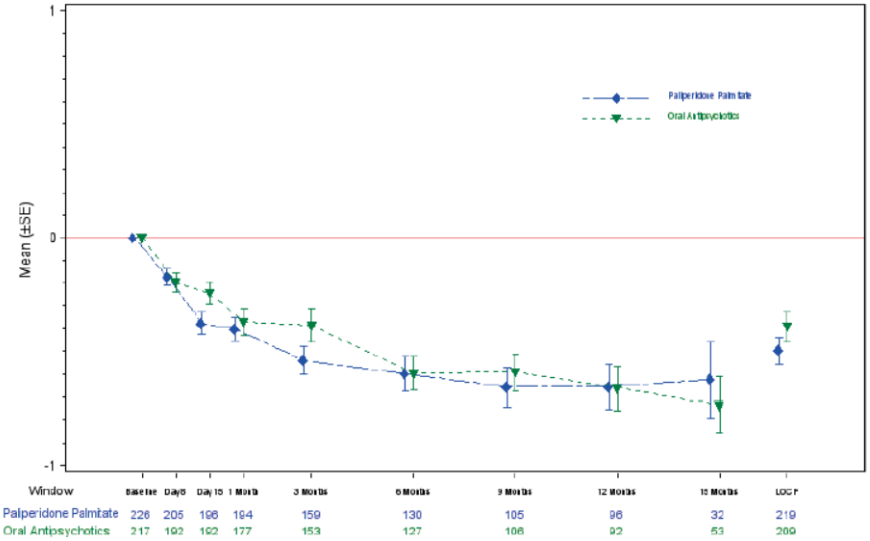
Table 11 Mixed Model Repeated Measures Results for CGI-S: Overall Treatment Effect; eITT Analysis Set

	Paliperidone Palmitate	Oral Antipsychotics	Difference
Clinical Global Impression of Severity			
Overall Treatment Effect			
LS Mean	3.37	3.42	-0.06
SE	0.038	0.037	0.053
95% CI	(3.29;3.44)	(3.35;3.50)	(-0.16;0.05)
p-value [a]	<.0001	<.0001	0.2962
LS Mean - Change from Baseline	-0.48	-0.43	-0.06
SE	0.038	0.037	0.053
95% CI	(-0.56;-0.41)	(-0.50;-0.36)	(-0.16;0.05)
p-value [a]	<.0001	<.0001	0.2962

[a] p-value based on repeated measures model that includes baseline value, treatment, time, and treatment by time interaction. An unstructured variance-covariance matrix was used to model the correlations among repeated measures from individual subject.
CGI-S Score: 1 - Normal, not at all ill, 2 - Borderline Mentally ill, 3 - Mildly ill, 4 - Moderately ill, 5 - Markedly ill, 6 - Severely ill, 7 - Among the most extremely ill subjects.

(Source: Sponsor's Table 21 and verified by the reviewer)

Figure 5 CGI-S Total Score: LS Mean ±SE Change from Baseline Over Time; eITT Analysis Set



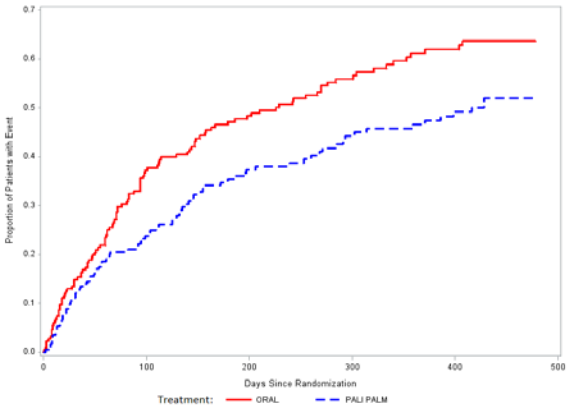
(Source: Sponsor's Figure 9 and verified by the reviewer)

3.2.7 Reviewer's Results:

1) Primary endpoint:

- A CDF (cumulative distribution function) plot based on Kaplan-Meier estimation method for the primary endpoint was presented below (Figure 6):

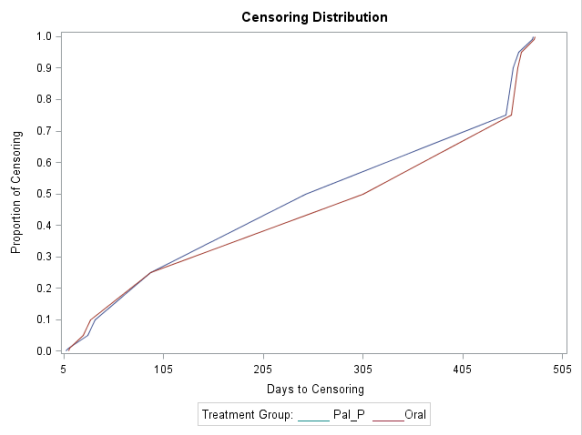
Figure 6 Cumulative Proportion of Patients with Event



(Source: The reviewer's analysis)

- Censoring distribution: A total of 237 patients were censored in the primary analysis of time to 1st treatment failure. Based on the graphical distributions of time to censoring (Figure 7), the paliperidone palmitate curve generally stays on top of the other one, suggesting slightly shorter time to censoring for subjects in the paliperidone palmitate group. Refer to "Sensitivity Analyses – B" below for the impact of censored subjects on efficacy.

Figure 7 Censoring Distribution



(Source: The reviewer's analysis)

- Sensitivity analyses:

A. Two patients at site 001054 ([(b) (6)] and [(b) (6)]), both randomized to oral antipsychotics, were excluded from the sponsor's analyses due to critical findings from a site audit. These two patients had a treatment failure. If these two subjects were included in the analysis, the result was almost the same as that with these two patients excluded (Table 12).

Table 12 Analysis of Time to First Treatment Failure (including two patients who were excluded from sponsor's analyses due to critical audit findings)

Time to Event	PaliperidonePalmitate	Oral Antipsychotics
Number assessed	226	220
Event	90	119
Censored	136	101
Kaplan-Meier Median, Days (95% CI)	416 (285, -)	210 (147, 301)
Log-Rank Test P-value	0.008	
HR (95% CI)	0.691 (0.526, 0.909)	

(Source: The reviewer's analysis)

B. A total of 139 patients discontinued early without a treatment failure. Above all, there were more patients who discontinued the assigned treatment or the study in the paliperidone palmitate group (35.8% vs. 26.6% for the paliperidone palmitate group and oral antipsychotics group, respectively). This may substantially undermine the interpretation of the efficacy result since it is unknown how many of these patients would have been treatment failures. This will, at least, raise an issue with the utility of the paliperidone palmitate arm compared to the oral antipsychotics arm. To address this issue, this reviewer considered two methods for handling these patients:

- Treat all these 139 patients as having an event.

- Treat patients who discontinued because of "lost to follow-up" or "patient withdrawal" as having an event. This would add a total of 102 events.

The analyses above show that there was no statistically significant difference in delaying time to treatment failure between treatment groups (p=0.2805, p=0.1885) (Tables 13 & 14).

Table 13 Sensitivity Analysis of Time to First Treatment Failure (by treating all 139 early discontinuations as an event)

Time to Event	Paliperidone Palmitate	Oral Antipsychotics
Number assessed	226	218
Event	171	175
Censored	55	43
Kaplan-Meier Median, Days (95% CI)	143 (124, 190)	134 (94, 164)
Log-Rank Test P-value	0.2805	
HR (95% CI)	0.891 (0.721, 1.100)	

(Source: The reviewer's analysis)

Table 14 Sensitivity Analysis of Time to First Treatment Failure (by treating 102 early discontinuations for reason of lost to follow-up or patient withdrawal as an event)

Time to Event	Paliperidone Palmitate	Oral Antipsychotics
Number assessed	226	218
Event	150	159
Censored	76	59
Kaplan-Meier Median, Days (95% CI)	268 (185, 386)	179 (129, 243)
Log-Rank Test P-value	0.1885	
HR (95% CI)	0.861 (0.689, 1.077)	

(Source: The reviewer's analysis)

The two tables suggest that the utility of the paliperidone palmitate arm is inconclusive as compared to the oral antipsychotics arm. This raises a question of whether the paliperidone palmitate arm is worthy of approval if it is deemed more effective.

2) Secondary endpoints**:**

Because a large proportion of patients discontinued early before reaching a treatment failure, the competing risks could potentially confound the analyses of these secondary endpoints whether based on the eITT or pITT analysis set. Hence, these results should be considered exploratory.

3.2.8 Conclusions

The trial seemed to demonstrate superiority of paliperidone palmitate based on the pre-specified primary endpoint. However, the additional analyses described above suggest that the utility of the

paliperidone palmitate arm is inconclusive as compared to the oral antipsychotics arm. This raises a question of whether paliperidone palmitate is worthy of approval if it is deemed more effective. The secondary endpoints also showed no clear trend of favoring paliperidone palmitate in endpoints that measure symptoms (PSP total score and CGI-S).

3.3 Evaluation of Safety

Please refer to Dr. Mannheim's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Exploratory subgroup analyses of time to first treatment failure were performed on age, gender, and race. The numerical results generally trended in favor of paliperidone palmitate except in very small subgroups such as patients >50 years old, female (Table 15). The study was conducted in the US only, so no subgroup analysis was performed by geographic region.

Table 15 Subgroup Analysis of Time to First Treatment Failure

Variable	Paliperidone Palmitate		Oral Antipsychotics		HR (95% CI)
	N	# of Event (%)	N	# of Event (%)	
Age (year)					
18-25	39	16 (41.0)	32	18 (56.3)	0.65 (0.33, 1.27)
26-50	161	62 (38.5)	161	91 (56.5)	0.63 (0.46, 0.87)
>50	26	12 (46.2)	25	8 (32.0)	1.67 (0.68, 4.11)
Sex					
Female	33	13 (39.4)	28	11 (39.3)	1.54 (0.69, 3.47)
Male	193	77 (39.9)	190	106 (55.8)	0.64 (0.48, 0.86)
Race					
White	73	37 (50.7)	74	39 (52.7)	0.82 (0.52, 1.28)
Black	145	52 (35.9)	130	68 (52.3)	0.72 (0.50, 1.03)
Others	8	1 (12.5)	14	10 (71.4)	0.12 (0.02, 0.93)

(Source: The reviewer's analysis)

4.2 Other Special/Subgroup Populations

Exploratory subgroup analyses of time to first treatment failure were performed on length of illness, baseline CGI-S, baseline PSP, BMI and substance abuse. The numerical results trended in favor of paliperidone palmitate (Table 16).

Table 16 Subgroup Analysis of Time to First Treatment Failure in Other Special Populations

Variable	Paliperidone Palmitate		Oral Antipsychotics		HR (95% CI)
	N	# of Event (%)	N	# of Event (%)	
Substance Use					
Yes	208	88 (42.3)	202	113 (55.9)	0.72 (0.54, 0.95)
No	18	2 (11.1)	16	4 (25.0)	0.46 (0.08, 2.50)
Length of Illness					
<=5	42	14 (33.3)	35	19 (54.3)	0.59 (0.30, 1.18)
>5	184	76 (41.3)	183	98 (53.6)	0.74 (0.55, 0.99)
Baseline CGI					
<=4	190	74 (38.9)	185	97 (52.4)	0.72 (0.53, 0.97)
>4	36	16 (44.4)	32	19 (59.4)	0.69 (0.35, 1.34)
Baseline PST Total Score					
<=30	11	4 (36.4)	6	4 (66.7)	0.24 (0.06, 0.89)
30-70	198	82 (41.4)	188	98 (52.1)	0.79 (0.58, 1.07)
>70	17	4 (23.5)	21	13 (61.9)	0.28 (0.09, 0.89)
BMI					
<=25	83	32 (38.6)	71	38 (53.5)	0.64 (0.40, 1.02)
>25 < 30	76	35 (46.1)	87	46 (52.9)	0.82 (0.53, 1.27)
>30	66	22 (33.3)	60	33 (55.0)	0.64 (0.37, 1.10)

(Source: The reviewer's analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A total of 139 patients (31.3%) had an early discontinuation without a treatment failure; among those the two most common discontinuation reasons were "lost to follow up" and "patient withdrawal". Based on the pre-specified primary endpoint (time to 1st treatment failure) censoring all these 139 patients at the time of discontinuation, paliperidone palimitate seemed to demonstrate superiority to oral antipsychotic (p-value = 0.011). However, there was a larger percent of patients who discontinued the assigned treatment or the trial in the Paliperidone Palmitate group. This raises an issue on the utility of the Paliperidone Palmitate arm compared to the oral antipsychotics arm. By treating the patients who discontinued as having an event, the analyses suggest that the utility of the Paliperidone Palmitate arm is inconclusive as compared to the oral antipsychotics arm. This raises a question of whether the Paliperidone Palmitate arm is worthy of approval even if it is deemed more effective.

The results of secondary endpoints measuring symptoms (change from baseline in PSP total score and in CGI-S at month 15, respectively) did not really suggest a trend in favor of paliperidone palmitate. Although these analyses were also confounded by competing risks and a high discontinuation rate, the results did not suggest a clear (or meaningful) separation between treatment groups throughout the trial, not just at month 15. A question is then raised as to why there was no clear trend in suggesting superiority throughout the trial based on symptom endpoints while a highly statistical significance was observed in the primary endpoint.

5.2 Conclusions and Recommendations

A single trial was included in this application. Based on the pre-specified primary endpoint, it appears that paliperidone palmitate was superior to treatment with an oral antipsychotic in delaying time to first treatment failure in subjects with schizophrenia who had been incarcerated, assuming that the patients who discontinued would not have an event. However, 31.3% of the patients discontinued early although the sponsor intended to follow up every patient throughout the study. In addition, there was a larger percent of patients who discontinued in the paliperidone palmitate group. By treating these patients as having an event, the analyses suggest that the utility of the paliperidone palmitate arm is inconclusive as compared to the oral antipsychotics arm, though it is not clear whether the patients who discontinued would have had an event, had they been completely followed up. This raises a question of whether paliperidone palmitate is worthy of approval even if it is deemed more effective. In addition, there was no trend in favor of the paliperidone palmitate arm in terms of PSP total score and in CGI-S at month 15.

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/s/

QUQUAN LIU
03/31/2015

PEILING YANG
03/31/2015
I concur with the review.

HSIEN MING J HUNG
03/31/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Drug Name/NDA: Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg (NDA 022264)
Sponsor: Janssen Pharmaceuticals, Inc.

Supplements:

022264 Invega Sustenna	S-015	7/11/14, and RS on 6/20/2017	PA	Revisions to the Section 14 of product label based on findings from study R092670-SCH-3006	Pending
	S-023	8/30/16	PA	Alignment with Invega Trinza USPI and inclusion of long term hyperprolactinemia data into USPI	AP letter dated 6/15/2017
	S-027	11/17/17	PA	PLLR ConversionLLR conversion	Pending

BACKGROUND

- The last approved labeling, for comparison purposes, was labeling supplement S-023 which was approved on 6/15/2017.
- This review will only encompass pending prior approval supplement S-015, which was resubmitted on 6/20/2017. S-027, submitted as a PA supplement, is still under review.
- S-015 is a comparative efficacy supplement which proposes revisions to the product label based on findings from study R092670-SCH-3006 titled "A Fifteen-Month, Prospective, Randomized, Active- Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated."
- Sponsor originally submitted this supplement on 7/11/2014, and received a CR action on 5/11/2015.
- A Class II resubmission was submitted on 6/20/217.

REVIEW

022264/S-015
Reviewed by Team:
Clinical Review by Daniel Lee, MD (dated 12/18/2017)
Biometric Review by Yang Wang, PhD (dated 11/20/2017)
OPDP Review by Christine Bradshaw, (dated 11/22/2017)

This supplement proposes the following changes to the PI for Invega Sustenna:

{See appended electronic signature page}

Shin-Ye Sandy Chang, PharmD
Regulatory Project Manager

{See appended electronic signature page}

Paul David, RPh
Chief, Project Management Staff

Enclosures: 1) Annotated Labeling denoting differences between last approved labeling and final, agreed upon, labeling, and 2) labeling e-mail agreement from the Sponsor

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/s/

SHIN-YE CHANG
12/20/2017

PAUL A DAVID
12/20/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **November 22, 2017**

To: Shin-Ye Sandy Chang, Regulatory Project Manager
Division of Psychiatry Products (DPP)

CC: Kim Updegraff, ADL, DPP

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, Team Leader, OPDP

Subject: **NDA 022264/S-15**
OPDP labeling comments for INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for Intramuscular use (Invega Sustenna)

In response to DPP's consult request dated August 7, 2017, OPDP has reviewed the draft product labeling (PI) and Medication Guide for Invega Sustenna. This efficacy supplement (S-15) provides for revisions to the Clinical Studies section of the PI.

OPDP's comments on the draft PI and Medication Guide are based on the version of the PI provided by Sandy Chang via email on November 3, 2017 and updated by Kim Updegraff on November 21, 2017, and are provided below.

If you have any questions, please feel free to contact me by phone at 301-796-6796 or by email at Christine.Bradshaw@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials.

Thank you!

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/s/

CHRISTINE J BRADSHAW
11/22/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **April 23, 2015**

To: Ann Sohn, PharmD
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 022264 S-015**
INVEGA SUSTENNA (paliperidone palmitate) Extended-Release Injectable Suspension

---

OPDP acknowledges receipt of the September 19, 2014, consult request from DPP for proposed product labeling (PI) for Invega Sustenna. OPDP notes that DPP indicated on April 23, 2015, that final labeling negotiations will not be initiated during the current review cycle because a Complete Response letter will be issued. Therefore, OPDP will not provide comments on the proposed PI during this review cycle.

OPDP requests that DPP submit a new consult request during a subsequent review cycle to provide comments regarding labeling for this application.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

Thank you!

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/s/

SUSANNAH O'DONNELL
04/23/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 3, 2015

TO: Ann Sohn, Regulatory Project Manager
Glenn Mannheim, M.D., Medical Officer
Jing Zhang, M.D., Team Leader
Division of Psychiatry Products

FROM John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 22264 S-15

APPLICANT: Janssen Research and Development, LLC

DRUG: Paliperidone Palmitate (Invega Sustenna®) Extended Release Injection

NME: No

INDICATION: Treatment of schizophrenia, delay time to treatment failure in previously incarcerated patients

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: September 19, 2014

INSPECTION SUMMARY GOAL DATE: March 3, 2015

REGULATORY ACTION GOAL DATE: May 11, 2015

PDUFA DUE DATE: May 11, 2015

I. BACKGROUND

Invega Sustenna® (paliperidone palmitate) was originally approved in 2009 for the treatment of schizophrenia. In this supplement S-15 to NDA 022264, Janssen Research and Development, LLC (**Janssen**) proposes to update the product label to include the results of a long-term study conducted in incarcerated subjects with schizophrenia.

Schizophrenia affects 0.5 to 1% of the United States (**US**) population. The risk for schizophrenia appears to be consistent across diverse geographic, ethnic, cultural, and socioeconomic groups and also across gender, but with onset about 10 years earlier in men (late teens to early twenties) than in women. Schizophrenia is characterized by fundamental and characteristic distortions of thinking and perception and by inappropriate or blunted affect. The diagnosis requires the presence of two or more characteristic symptoms for at least six months (hallucinations, delusions, severely disorganized speech or behavior, severe blunting of emotions) along with evidence of social and/or occupational dysfunction. As a life-long disorder, the clinical outcome varies from reasonable recovery to total incapacitation.

Medications are usually effective for schizophrenia symptoms, both positive (hallucinations, delusions, paranoia, and agitation) and negative (blunted affect, lack of motivation, social withdrawal). Relative to conventional agents (haloperidol), second-generation agents (paliperidone) have less extrapyramidal effects. Gaps as brief as ten days pose increased risks of hospitalization and suicide (80% at five years). Longer-acting agents appear to reduce relapse rates (from 40% to 25% at one year). Paliperidone is a monoaminergic antagonist that exhibits the characteristic dopamine and serotonin antagonism of second-generation agents. The oral paliperidone extended release formulation was approved for schizophrenia in 2006 (initial treatment) and in 2007 (maintenance treatment). Paliperidone palmitate (**PP**) is a long-acting formulation of paliperidone for intramuscular (**IM**) injection (low water solubility and slow absorption).

The single study supporting this NDA supplement (Study R092670-SCH-3006) was audited at good clinical practice (**GCP**) inspections of three study sites selected based on large subject enrollment. This study is briefly described below, with emphasis on study features relevant to inspectional findings.

Study R092670-SCH-3006

Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated (PRIDE)

This 15-month, randomized, open-label, active-controlled study was conducted between 2010 and 2013 in 450 subjects at 56 US study sites. The primary study objective was to evaluate the efficacy of PP relative to oral agents (**OA**) in delaying treatment failure in previously incarcerated subjects with schizophrenia, currently on parole or probation after incarceration. Treatment failure was defined as any of the following:

- Any arrest by an officer of the law, or any re-incarceration
- Suicide, psychiatric hospitalization, or special care to prevent imminent psychiatric hospitalization
- Discontinuation of treatment due to inadequate safety, tolerability, or efficacy
- Treatment supplementation with another agent due to inadequate efficacy.

Subject Selection:

- Adults (age 18 to 65 years) with diagnosis of schizophrenia per Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (**DSM-IV**)
- Study diagnosis confirmed by Mini International Neuropsychiatric Interview, Version 6.0 (**MINI-6**); current treatment for schizophrenia with more than one oral antipsychotic agent

- Documented involuntary detainment by an officer of the law (legal custody) at least twice, at least once leading to incarceration within 24 months and released from most recent custody within 90 days

Treatment Groups and Regimen

- Subjects were randomized in equal ratio to PP or OA. For OA, one agent was randomly assigned from a list of one to seven OAs deemed appropriate for that subject by the clinical investigator (**CI**):
  - Aripiprazole
  - Haloperidol
  - Olanzapine
  - Paliperidone
  - Perphenazine
  - Quetiapine
  - Risperidone.
- For PP, injections were administered at study visits at Day 8 (Visit 1, 234 mg), Day 15 (Visit 2, 156 mg), and Day 38 (Visit 4), then monthly for the next 13 months (Visits 5-17, flexible dosing, 78 to 234 mg beginning on Day 38, CI discretion).
- The CI documented the reason for not selecting any of the seven OAs. The CI selected the dose appropriate for the subject and provided a voucher for filling the prescription at a local pharmacy. OA treatment was initiated on Day 1 (preference for monotherapy, dose adjustment at any time).

Major Endpoints and Analyses

- Primary efficacy: Time from randomization to treatment failure, as adjudicated by a blinded Treatment Failure Event Monitoring Board (**EMB**); Kaplan-Meier analysis and log-rank test
- Time to first psychiatric hospitalization, arrest, or incarceration; safety monitoring by AEs, laboratory testing, physical examinations, and safety questionnaires
- Safety questionnaires: InterSePT Scale for Suicidal Thinking-Plus (**ISST-Plus**), Extrapyramidal Symptom Rating Scale, Abbreviated (**ESRS-A**), and Sexual Side Effects Questionnaire (**SSEQ**)
- Study evaluations at weekly study visits for one month (Visits 1-4, Days 8-38), then at monthly study visits for 15 months (Visits 5-18)

Sponsor Report of Major Findings

- Rates of study completion were similar for PP and OA (about 40%), as were the reasons for early discontinuation (lost to follow-up 23-25%, withdrawal by subject 12-16%).
- Proportions of subjects with treatment compliance > 80% were: 95% for PP by injection records, 79% for OA by prescriptions, and 24% for OA by prescription refill records.
- Primary endpoint: Relative to OA, PP was superior in delaying treatment failure ($p = 0.011$, median times of 416 and 226 days).
- Major secondary endpoints: Relative to OA, PP was superior also in reducing the proportion of subject with failure events (40% PP, 54% OA), and in delaying psychiatric hospitalization or arrest or re-incarceration ($p = 0.019$).
- One PP subject died due to sudden death of unknown cause. Subject proportions of AEs rates were:
  - Serious AE (SAE): PP 19% and OA 24%
  - AE leading to therapy discontinuation: PP 12% and OA 9%
  - Extrapyramidal AE: PP 26% and OA 20%
  - Prolactin-related AE: PP 25% and OA 5%

II. INSPECTIONS

The following three sites in Study R092670SCH3006 were selected for GCP inspection based on large subject enrollment. No special concerns about study conduct were identified by NDA review.

Clinical Investigator		Site and Enrollment	Inspection Outcome
1	Jesse M. Carr, M.D. 230 N. Maryland Avenue 207 Glendale, CA	Site 019 23 subjects	November 4 – 5, 2014 NAI
2	Paul W. Murphy, M.D. 1100 North St. Francis, Suite 300 Wichita, KS	Site 007 26 subjects	October 8 – 15, 2014 Pending, preliminary NAI
3	Mary L. Stedman, M.D. 3212 Cove Bend Drive Tampa, FL	Site 016 30 subjects	November 19 – 26, 2014 Pending, preliminary NAI

NAI = no action indicated (no significant deficiencies); Pending = preliminary communication with field investigator

1. Jesse M. Carr, M.D.

a. What was inspected:

- Records review: institutional review board (**IRB**) oversight and sponsor monitoring, clinical investigator (**CI**) financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study R092670SCH3006, Site 019: 33 subjects were screened, 23 were enrolled, and 19 completed the study. Study completion rate was higher than might be expected, given the subject selection criteria (schizophrenia and multiple previous incarcerations). Case records were reviewed for all enrolled subjects, including detailed review for 18 subjects.

Evidence of biased study conduct was not observed, including no evidence of non-voluntary enrollment (coercion) or CI conflicts of financial interest.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, AE monitoring and reporting, and drug accountability. Source records appeared complete. IRB oversight and sponsor monitoring appeared acceptable. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

2. Paul W. Murphy, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study R092670SCH3006, Site 007: 38 subjects were screened, 26 were enrolled, and 12 completed the study. As might be expected given the subject selection criteria (schizophrenia and multiple previous incarcerations), 14 subjects were lost to follow up. Case records were reviewed for 15 enrolled subjects, including detailed review for 10 subjects.

A review of the pharmacy records (15 subjects; eight OA, seven PP) indicated inadequate OA treatment compliance (below 80%) for all OA subjects. Evidence of biased study conduct was not observed, including no evidence of non-voluntary enrollment (coercion) or CI conflicts of financial interest.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, AE monitoring and reporting, and drug accountability. Source records appeared complete. IRB oversight and sponsor monitoring appeared acceptable. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The observations noted above are based on preliminary communication with the field investigator.

3. Mary L. Stedman, M.D

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study R092670SCH3006, Site 016: 36 subjects were screened, 30 were enrolled, and 9 completed the study. As might be expected given the subject selection criteria (schizophrenia and multiple previous incarcerations), 21 subjects were lost to follow up. Case records were reviewed for all enrolled subjects, including detailed review for 15 subjects.

A review of pharmacy records suggested adequate treatment for all subjects. Evidence of biased study conduct was not observed, including no evidence of non-voluntary enrollment (coercion) or CI conflicts of financial interest.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, AE monitoring and reporting, and drug accountability.

Source records appeared complete. IRB oversight and sponsor monitoring appeared acceptable. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The observations noted above are based on preliminary communication with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Janssen submitted this NDA 22264 S-015 to update the product label of Invega Sustenna® to include the results of a long-term, randomized, open-label, active-controlled efficacy study (PRIDE, Study R092670-SCH-3006) conducted at 56 US study sites in 450 incarcerated subjects with schizophrenia. This study was audited at GCP inspections of three study sites selected based on large subject enrollment. At the three inspections combined, records for all (79) enrolled subjects (18%) were reviewed, including detailed review for 33 subjects (7%).

At all three study sites, no significant deficiencies were observed and a Form FDA 483 was not issued. Minor deficiency observations were verbally discussed. The study conduct at all inspected study sites appeared adequate, including IRB oversight and sponsor monitoring of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the three inspected study sites appear reliable as reported in the NDA.

Note: For Sites 007 (Murphy) and 016 (Stedman), the establishment inspection report (**EIR**) has not been received from the field office and the final inspection outcome remains pending. The observations noted above are based on preliminary communication with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division if new findings of clinical or regulatory significance are identified at receipt and review of the EIR.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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/s/

JONG HOON LEE
03/02/2015

JANICE K POHLMAN
03/03/2015

KASSA AYALEW
03/03/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022264Orig1s015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: September 19, 2014

To: Ni Aye, Khin, M.D., DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D.,M.P.H., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Thompson, M.D. Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Glenn Mannheim/MO/DPP
Jing Zhang Medical TL

From: Ann Sohn, Regulatory Health Project Manager/DPP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22264/S-015
IND#: 67356
Applicant/ Applicant contact information (to include phone/email):
Janssen Research & Development LLC
Beth Geter-Douglass Tel: 609-730-4409 (W) (b) (6) (C)
Email: bgeterdo@its.jnj.com
Drug Proprietary Name: Invega Sustenna
Generic Drug Name: paliperidone palmitate
NME or Original BLA (Yes/No/Not Applicable*): No
Application Submission Date: 7/11/14
Review Priority (Standard or Priority or Not Applicable*): standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): delay time to treatment failure in schizophrenia in comparison to oral antipsychotics in incarcerated

PDUFA:
Action Goal Date: 5/11/15
Inspection Summary Goal Date: 03/03/15

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site # 001019 Carr, Jesse M., M.D. 230 N. Maryland Avenue #207 Glendale, CA 91206 USA	R092670SCH3006	23	Comparison with oral antipsychotics delaying time to treatment failure in schizophrenia
Site # 001007 Murphy, Paul W., M.D. 1100 North St. Francis Suite 300 Wichita, KS 67214 USA	R092670SCH3006	26	Comparison with oral antipsychotics delaying time to treatment failure in schizophrenia
Site # 001016 Stedman, Mary L., M.D. 3212 Cove Bend Drive Tampa, FL 33613 USA	R092670SCH3006	30	Comparison with oral antipsychotics delaying time to treatment failure in schizophrenia

III. Site Selection/Rationale

Summarize the reason for requesting OSI/DGCPC consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection. For example:

Rationale for OSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for OSI's thoughts on things to consider in your decision making process*

This submission consists of single Study Protocol No.: R092670SCH3006, entitled: A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated. Subjects were enrolled from 56 sites (55 in the United States and 1 in Puerto Rico). Study took place from 05/05/2010 to 12/09/2013, with datalock on 01/15/2014. The primary objective of this study was to compare the efficacy of paliperidone palmitate with one of 7 oral antipsychotics (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone) in delaying time to first treatment failure over 15 months, in subjects with schizophrenia who had been incarcerated. Treatment failure was defined as any of the following events: arrest/incarceration; psychiatric hospitalization; suicide; discontinuation of antipsychotic treatment due to inadequate efficacy; treatment supplementation with another antipsychotic due to inadequate efficacy; discontinuation of antipsychotic treatment due to safety or tolerability; or increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization. No PK blood tests were done to assess subject compliance. Study population primarily consisted of poor, non-Caucasians, who were paroled (36 %), on probation (60%), without insurance or real support. Given the study population, it is essential to determine that study subjects on oral antipsychotics actually received study drug, that enrollment was voluntary, that no coercion of going back to jail was used, if they were admitted from the criminal justice, and that none of the investigators had any, non-declared financial relations.

Rational for Site Selection: The three larger sites were selected by Dr. Liu (Statistician). Site 001019 had only one event in the oral antipsychotic treatment group. Information on treatment effect probably couldn't provide much help in selection of sites because of big variations by site in treatment effects due to small sample sizes. The drop-out by site wasn't provided in the submission and this information will be requested in the 74-day letter.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
__X__ Significant primary efficacy results pertinent to decision-making
__X__ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
__X__ Other (specify): See above

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
__X__ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*

One (b) (6), Site No: (b) (6) (b) (6)has filed FDA Form 3455 indicating that he has received consulting fees a $ 50, 000 from Ortho-McNeil Janssen Scientific Affairs, LLC.

Should you require any additional information, please contact Ann Sohn, Regulatory Health Project Manager/DPP at *301-796-2232 or Glenn Mannheim, MD, Medical Officer* at 301-796-1117.

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/s/

ANN J SOHN
09/19/2014

MEMORANDUM OF MEETING
IND 67356 Invega Sustenna (paliperidone palmitate injection)
Type C Face to Face Meeting
Janssen Research & Development, L.L.C.
May 24, 2012

Participants –

FDA

Thomas Laughren, M.D.	Director, Division of Psychiatry Products
Mitchell Mathis, M.D.	Deputy Director, Division of Psychiatry Products
Robert Levin, M.D.	Clinical Reviewer, Team Lead
Christina Burkhart M.D.	Clinical Reviewer
Ni Khin, M.D.	Clinical Team
Yeh-Fong Chen, Ph.D.	Statistical Reviewer
Susannah Hubert	OPDP Reviewer
Jessica Cleck Derenick	OPDP Reviewer
Ann Sohn, Pharm.D.	Regulatory Project Manager

Sponsor

Larry Alphs, M.D., Ph.D.	Therapeutic Area Lead, Medical Affairs
Peter Briscoe, M.D.	Compound Development Team Leader
Jacqueline Brown, R.Ph.	US Regulatory Affairs
Lindsay Cobbs, R.Ph.	FDA Liaison
Peter Dorson, Pharm.D.	Principal Scientific Affairs Liaison
H. Lynn Starr, M.D.	Clinical Leader, Medical Affairs
Lian Mao, Ph.D.	Biostatistics Medical Affairs
Isaac Nuamah, Ph.D.	Biostatistics Leader
Dottie Sokolowski	Regulatory Compliance Lead
James Tan, Ph.D.	Global Regulatory Affairs Leader

Background:

Janssen Research & Development has requested a Type C Meeting to discuss the adequacy of study R092670-SCH-3006 titled "A Fifteen-Month, Prospective, Randomized, Active-Controlled, Open-Label, Flexible-Dose Study of Paliperidone Palmitate Compared with Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults with Schizophrenia Who Have Been Incarcerated" to support revisions to the USPI.

Study R092670-SCH-3006 is a 15-month, randomized, prospective, open-label, active controlled, parallel-group, multicenter (50 U.S. sites) study comparing paliperidone palmitate treatment with oral antipsychotic treatment in the prevention of treatment failure in subjects with schizophrenia. Subjects will be males and females, 18 to 65 years of age, with a diagnosis of schizophrenia and a history of being taken into custody at least twice in the previous 2 years with the last release from custody within 90 days.

The study will have an up-to-14-day screening phase and a 15-month open-label treatment phase. Subjects will be randomly assigned in 1:1 ratio to treatment with either paliperidone palmitate or one of 7 specific oral antipsychotics (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone). Each subject who is randomly assigned to receive oral antipsychotic treatment will have his or her antipsychotic randomly selected (with equal probability) from the subset of oral antipsychotics that the investigator judges suitable for the particular subject.

Subjects randomly assigned to treatment with paliperidone palmitate will begin with two injections given one week apart (on Day 1: 234 mg by IM deltoid injection and on Day 8: 156 mg IM). Subsequently, subjects will receive flexibly-dosed monthly maintenance injections within the range of 78 mg to 234 mg.

The primary efficacy endpoint will be the time from randomization to the occurrence of a treatment failure. Treatment failure is defined as any of the following:

- Arrest/incarceration
- Psychiatric hospitalization
- Suicide
- Discontinuation of antipsychotic treatment due to inadequate efficacy
- Treatment supplementation of a subject in the Invega Sustenna group with another antipsychotic due to inadequate efficacy as determined by the study physician (exception: following Day 15, subjects can receive supplemental oral paliperidone until the dose of paliperidone palmitate can be increased at the next injection day)
- Discontinuation of antipsychotic treatment due to safety or tolerability
- Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization

The principal investigator and a blinded Event Monitoring Board will adjudicate treatment failure.

The sponsor's primary hypothesis is that treatment with paliperidone palmitate will be superior to oral antipsychotics in delaying the time to treatment failure in subjects diagnosed with schizophrenia who have been incarcerated. Given positive results from study R092670-SCH-3006, the sponsor is requesting that (b) (4) a description of the study be included in the Clinical Studies section of the USPI.

The sponsor's proposed (b) (4):

(b) (4)

Questions:

Study Design
Question 1

Does the Division agree that the overall design of ongoing study R092670-SCH-3006 is adequate to establish that paliperidone palmitate, compared with oral antipsychotic treatment, will delay the time to the occurrence of protocol-defined treatment failure in subjects diagnosed with schizophrenia?

Preliminary Comments:

In principle, we do not object to a study of this design, since it has the potential to produce useful results to clinicians. Assuming the study were to produce positive results, we would be willing to discuss how the information might be characterized in labeling. (b) (4) [redacted] (b) (4) [redacted] *Exactly what details to provide would be a matter for review.*

Given certain novel features of this study, you should be aware that we would almost certainly take this issue to an Advisory Committee to obtain further expert opinion on how to interpret the results. (b) (4) [redacted] *when in fact, the results might more reasonably be interpreted as showing an advantage for a depot antipsychotic compared to an oral antipsychotic for this particularly troublesome group of patients.*

Discussion at Meeting: *There was no further discussion*

Question 2

In particular, can the FDA confirm the adequacy of the following aspects of the study?

a) Steps taken to maintain the rigor of this open-label trial which reflects a pragmatic, real-life study design
b) Use of the widely prescribed oral antipsychotic treatments as comparators: aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone
c) Patient population – defined as individuals who have been diagnosed with schizophrenia and who have been recently (within 90 days before the first day of screening) released from custody (custody defined as documented involuntary detainment by an officer of the law; incarceration is defined as involuntary confinement by an officer of the law; incarceration is a subcategory of custody)
d) Total number of subjects – a total of approximately 442 subjects will be randomly assigned (1:1 ratio) to treatment with either paliperidone palmitate or oral antipsychotics

e) No stabilization phase is incorporated to allow examination of maintenance of effect of paliperidone palmitate in comparison with oral antipsychotics to reflect real world circumstances

Preliminary Comments:

Generally, we would like to discuss one particular aspect of the study design: We would like to better understand your plan for patients randomized to the oral antipsychotic group to further randomize among the subset of oral antipsychotics that the investigator has judged as being suitable for that particular subject. This seems needlessly complicated. We would recommend that these patients be given an oral antipsychotic that the investigator feels is most appropriate for that patient, i.e., "treatment as usual" before randomization. Because this is a large, multicenter trial, we would predict that prescribing patterns will differ among investigators and that most oral antipsychotics will be represented in the final analysis.

Discussion at Meeting:

The sponsor discussed the rationale for the equipoise-stratified randomization scheme for the oral antipsychotic treatment group. The sponsor stated that the randomization process would add scientific rigor to the study. The Division agreed that the equipoise-stratified randomization for the oral antipsychotic treatment group would be acceptable; however, the treatment-as-usual approach might better represent the real-world approach in clinical practice.

The investigator and the subject would jointly decide on de-selection of any of the 7 possible antipsychotics used in the study. It would be permissible to have the choice limited to one antipsychotic. No reason for de-selection would be rejected. The investigator must articulate clearly the reason for de-selection of a particular antipsychotic. The sponsor and the Division acknowledged that there may be many reasons for de-selection of a particular oral antipsychotic (e.g., the patient's previous experience and expectations about treatment, the investigator's prescribing practices and experience with various treatments, regional prescribing practices, etc.).

Primary Endpoint

Question 3

Does the FDA agree with the following?

a) The proposed primary endpoint of treatment failure defined as any of the following:
    1) Arrest/incarceration
    2) Psychiatric hospitalization
    3) Suicide
    4) Discontinuation of antipsychotic treatment due to inadequate efficacy
    5) Treatment supplementation with another antipsychotic due to inadequate efficacy

6) Discontinuation of antipsychotic treatment due to safety or tolerability
7) Increase in the level of psychiatric services to prevent imminent psychiatric hospitalization

b) A blinded adjudication board determination of treatment failure

Preliminary Comments:

We do not object to your proposed definition of treatment failure and the use of a blinded adjudication board.

Discussion at Meeting:

The sponsor acknowledged that it could be complicated to determine whether particular events represent treatment failures. There will be ambiguous cases, even though the criteria for the primary endpoint are relatively hard endpoints. In the initial study design, the proposed primary endpoint of treatment failure was to be determined jointly by the blinded adjudication board and the investigator. However, it is quite possible that the adjudication board and the investigator will not agree on the interpretation of a specific case. Therefore, the primary endpoint will be the adjudication of the first treatment failure by the blinded board. The investigator's judgment about the first treatment failure will be the key secondary, sensitivity analysis.

The blinded EMB will not examine the data until the 15-month study period is completed. The sponsor stated that there will be ambiguous cases and that it will be important for the members of the EMB to articulate their adjudications clearly and consistently. The members of the EMB will also be required to declare if they have become unblinded on any level. The sponsor will prospectively discuss the adjudication process in detail with the investigators and adjudication board. The Division agreed that the first treatment failure as adjudicated by a blinded EMB is an acceptable primary endpoint.

Indication and Labeling

Question 4

Does the FDA agree that, given positive results from R092670-SCH-3006?

(b) (4)

b) A description of the study can be included in the CLINICAL TRIALS section of the USPI?

Preliminary Comments:

We would not object to characterizing the results of the study in Clinical Studies, [redacted] (b) (4) *. (see response to Question #1).*

Discussion at Meeting:

The sponsor asked how the Division would characterize the active comparator antipsychotics in labeling, if the study is positive. For example, would the active control be described as "oral antipsychotics," or would they be described more specifically as the individual antipsychotics? The Division will have to consider this carefully, and the decision will be based on a review of the study results. One of the complexities is that these could be considered comparative claims. The Division would seek advice from an advisory committee on how to describe the study results in labeling.

Statistical Analysis

Question 5

As it is our intent that study R092670-SCH-3006 will support a statement about the efficacy of Invega Sustenna compared to oral antipsychotics, are the following planned statistical analyses adequate for interpretation of the study results?

The primary null hypothesis is that there is no difference in the distributions of time to treatment failure between the treatment groups in subjects with schizophrenia. The primary hypothesis will be tested using a log-rank test based on the explanatory intent-to-treat analysis set. The cumulative distribution function of time to treatment failure will be estimated by the Kaplan-Meier method. An estimate of the hazard ratio and its 95% confidence interval will be determined using a Cox proportional hazards model with treatment as the covariate.

Preliminary Comments:

The proposed analysis method should be acceptable. To further assess the robustness of the efficacy findings, you should propose alternative censoring schemes for sensitivity analyses.

Discussion at Meeting:

The sponsor indicated that they would submit the statistical analysis plan approximately three months before the completion of the trial. We asked whether they are interested in analyzing the subcomponents for the proposed composite primary endpoint. We noted that to have meaningful results for those analyses, patients should be followed after their first event. They informed us that they do plan to follow patients for all 15 months. Thus, they should be able to analyze data for each subcomponent. However, it would be a substantial effort if all patients' events need to be adjudicated.

Conclusions:

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Janssen Research & Development, L.L.C. is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

Ann Sohn, Pharm.D.
Regulatory Project Manager

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/s/

THOMAS P LAUGHREN
06/06/2012