Janssen Research & Development

Statistical Analysis Plan

Comparison of Single-arm, Open-label Extension Study of Paliperidone Palmitate 6-Month Formulation with Paliperidone Palmitate 1-Month and 3-Month Formulations Using Real World Data (IBM Medicaid Multistate Database)

Protocol R092670SCH4067; Phase 4

R092670 (paliperidone palmitate)

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1. INTRODUCTION

Schizophrenia is a severe and chronic behavioral health disorder with debilitating long-term outcomes associated with cognitive and functional impairment. The prevalence rate of schizophrenia is estimated to be approximately 1% worldwide (Lehman 2010). Patients with schizophrenia experience multiple relapses throughout the course of their illness and this comes at a cost to the patient and society. During these episodes, patients can lose a significant number of workdays to the illness and in the event of severe symptoms, will require substantial healthcare resources.

Treatment adherence and reducing treatment discontinuation are therefore key factors in minimizing recurrent relapses.

Paliperidone palmitate (Invega®, Janssen Pharmaceuticals) is a long acting injectable (LAI) atypical antipsychotic approved by the US Food and Drug Administration for treatment of schizophrenia. The 1-month paliperidone palmitate extended-release injectable suspension (PP1M injectable formulation, Invega® Sustenna) was approved by the FDA for the acute and maintenance treatment of schizophrenia in adults in July 2009, and for the treatment of schizoaffective disorder in November 2014. A 3-month paliperidone palmitate extended-release injectable suspension was approved by the FDA in May 2015 for preventing relapse among patients with schizophrenia (PP3M injectable formulation, Invega® Trinza).

Invega® Hafyera®, a 6-month paliperidone palmitate extended-release injectable suspension (LAI) also known as PP6M, is the latest in this series of LAIs that includes the PP1M, and PP3M, approved in 2021. Real-world data has shown that PP1M and PP3M are superior to oral antipsychotics in delaying the time to relapse or treatment failure (Alphs 2015; Segarra 2021)[3], and PP6M is expected to further improve these outcomes. To evaluate this hypothesis, an External Comparator Arm (ECA) study will be conducted to compare relapse rates among PP6M (R092670PSY3016) patients separately against PP1M and PP3M patients in IBM® Medicaid Multistate® Database (IBM MDCD). The patients from the IBM MDCD comparator cohorts will be selected and matched closely with those patients from the open-label study (R092670PSY3016).

1.1. Objectives and Endpoints

The primary objective of this study is to compare effectiveness of PP6M (R092670PSY3016) versus PP3M and PP1M (IBM MDCD) in delaying time to first relapse.

The overall primary hypothesis to be tested in this study is that 24 months treatment with PP6M is superior to 24 months' treatment with PP3M or PP1M in delaying time to first relapse in subjects with schizophrenia disorder. The primary effectiveness null hypothesis is that there is no difference in the distribution of time to first relapse among 3 treatment groups.

The primary endpoint for the study is the delay/prevention of relapse. A relapse event represented one or a combination of following events as listed in the open-label study for PP6M:

- Psychiatric hospitalization for schizophrenia (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms);
- Emergency Department/Room/Ward visit due to a worsening of the subject's symptoms of schizophrenia, but a psychiatric hospitalization does not occur;
- The subject inflicts deliberate self-injury or exhibits violent behavior resulting in suicide, clinically significant injury to him/herself or another person, or significant property damage;
- The subject has suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment.

A relapse event will be recorded on the first date during study period that a subject meets at least one of the above criteria in Real-world data (RWD, IBM MDCD) for PP1M and PP3M.

The secondary objectives included examination of reasons for relapse and to characterize schizophrenia patients on paliperidone palmitate therapies.

1.2. Study Design

Schematic display of Study Design is shown in Figure 1. Medication exposure, data collection period, baseline period and study start (index) date determination are explained in details below.

1.2.1. Medication Exposure

Two dosing schemes will be considered: Moderate-dose and High-dose. PP6M, PP3M, and PP1M patients will be assigned into one of these 2 drug dose categories based on their PP injection dose at study entry. Details regarding patient categorization in moderate and higher doses are presented in Table 1.

Table 1: Conversion Between Doses and Injection Volumes for the 1-, 3-, and 6-Month Paliperidone Palmitate Products

Dose	F013 Formulation			F015 Formulation					
	PP1M Dose			PP3M Dose[a]			PP6M Dose[b]		
	mg eq.	mg	Volume	mg eq.	mg	Volume	mg eq.	mg	Volume
N/A	25 mg eq.	39 mg	0.25 mL	…	…	…	…	…	…
	50 mg eq.	78 mg	0.50 mL	175 mg eq.	273 mg	0.875 mL	…	…	…
	75 mg eq.	117 mg	0.75 mL	263 mg eq.	410 mg	1.315 mL	…	…	…
Moderate dose[c]	100 mg eq.	156 mg	1.00 mL	350 mg eq.	546 mg	1.750 mL	700 mg eq.	1092 mg	3.50 mL
High dose[c]	150 mg eq.	234 mg	1.50 mL	525 mg eq.	819 mg	2.625 mL	1000 mg eq.	1560 mg	5.00 mL

[a] PP3M dose = 3.5x the patient's previous PP1M dose

[b] PP6M dose = 7x the patient's previous PP1M dose or approximately 2x the previous PP3M dose

[c] Doses shown in bold italics represents the PP3M and PP6M doses evaluated during Double-blind Phase of Study R092670PSY3015

Key: N/A = Not applicable; PP1M=paliperidone palmitate 1-month product; PP3M=paliperidone palmitate 3-month product; PP6M=paliperidone palmitate 6-month product

1.2.2. Data Collection Period

PP6M cohort patients included in PSY3016-ECA study will be same as PSY3016 Open Label Extension (OLE) study. PP6M cohort consists of patients that are transitioned from Clinical Trial PSY3015 and already met the PSY3016-ECA study inclusion/exclusion criteria adapted from Clinical Trial PSY3015 (see 1.3 Inclusion/Exclusions). In addition to inclusion/exclusion criteria, these PP6M patients also met the "no relapse" requirement during 12-month double-blind phase in PSY3015 to be eligible for PSY3016 OLE study.

PP3M and PP1M cohorts will be extracted from the IBM MDCD RWD insurance claims database and will include patients that meet inclusion/exclusion criteria adapted from Study PSY3015. Patients with PP3M and PP1M injection dates starting from 2017 will be included in this PSY3016-ECA study to minimize biases are associated with differences in calendar times. PSY3016-ECA study period will be from 2017 until the end of available data (last patient out is listed as 06/2021).

1.2.3. Baseline Period and Study Start (Index) Dates

Baseline period and study start-date (Index date) for the PP6M, PP3M, and PP1M cohorts will be determined as described below.

- **Baseline Period:** Baseline period for PP3M and PP1M cohorts will be a period between index PP injection date and up to 12-month prior to this date. All RWD (PP3M and PP1M) patients must have continuous medical and prescription coverage based on their insurance enrollment records during this period. For PP6M cohort, baseline period will be listed as 12-month double blinded PSY3015 study period and inclusion and exclusion criteria will be applied at PSY3015 study screening.
- **Index date (PP6M):** Index date for the PP6M cohort will be the start date of the open-label extension (OLE) phase in PSY3016 study. PP6M cohort includes patients with Moderate/High dose PP6M injections in PSY3016 OLE phase and are relapse free and PP adherent during their 12-month double blinded PSY3015 study period.
- **Index date (PP3M) :** Among the schizophrenia patients with both PP3M and PP1M injections in IBM MDCD, PP3M patients will be evaluated first for the index date determination. In PP3M cohort, patients receiving Moderate/High dose PP3M injections (see Table 1) starting from January 1st, 2017, will be identified first and their PP3M injections will be evaluated for inclusion/exclusion criteria (see Section 1.3 Inclusion/ Exclusion). In addition to their pre-index/baseline inclusion/exclusion criteria listed below, a PP3M patient will also meet the stability criteria. PP3M patients must be on PP1M/PP3M injections and adherent to their medication for at least 6-month prior to their index PP3M injection date. Based on the stability requirement, the last two doses of PP1M, or 1 dose of PP3M needs to be same, and/or equivalent. Days between injections will be evaluated backwards starting from index date of PP3M. Up to 45 days of gap between injections will be allowed to consider these patients adherent. If a patient had two or more eligible PP3M injection dates, inclusion/exclusion criteria will be applied for each PP3M injection date and the first eligible PP3M injection date will be used for selection purposes. While calculating number of stable days during baseline period, except for injectable Risperidone, oral and/or injectable antipsychotic drugs other than LAI paliperidone palmitate (see Appendix for the list of all antipsychotic drugs) will not be

allowed during stabilization period. If this condition is violated during baseline period, PP3M patient will not be considered as stable up to this time point and any PP1M/PP3M injections prior to this violation will not be counted towards 6-month stability period and considered ineligible. Duration of stable period will then be calculated based on the difference between index PP3M injection date and the earliest eligible PP injection date during baseline period. These PP3M patients must have at least 12-month pre- and post-index continuous enrollment records and have at least 2 PP3M injection on or after index date. Once all potential PP3M injection dates are evaluated for eligibility, the first PP3M injection date that meets all eligibility criteria will be selected in case patient have multiple potential entry dates. Eligible PP3M patients will be considered as "final" PP3M cohort. This patient cohort will be removed from the IBM MDCD PP1M pool.

- **Index date (PP1M) :** After removing eligible PP3M patients from PP1M patient pool, remaining PP1M patients will be evaluated first for their index date determination. In PP1M cohort, patients receiving Moderate/High dose of PP1M injections (see Table 1) starting from January 1st, 2017, will be identified and their PP1M injection dates will be evaluated for inclusion/exclusion. Similar to PP3M, PP1M injection dates starting from January 2017 will be considered as "potential" index dates and will be evaluated up to 12-month before this date (baseline period) for inclusion/exclusion criteria and up to 6-month for stability. PP1M patients may not have PP3M injections during baseline period. For PP1M cohort, except for injectable Risperidone, other injectable antipsychotic drugs (see Appendix for the list of antipsychotic drugs) will not be allowed between PP1M index date and 6-month stabilization period. If this condition is violated, earlier PP1M injections prior to this event will be ineligible and will not be counted towards stability period and number of days and duration of stabilization period will be calculated based on the first eligible PP1M injection date during baseline period and PP1M index date. Up to 45 days of gap between injections will be allowed to consider these patients' adherence. Patients with PP1M injections will be included in the study if these index dates meet both 6-month stability and 12-month baseline inclusion/exclusion. If a patient had more than 1 eligible PP1M injection dates, the first eligible PP1M injection date will be used. These PP1M patients also required to have at least 12-month pre- and post-index continuous enrollment records and must have at least 5 PP1M injections on or after index date. Once all potential index dates are evaluated for PP1M patients, the first index date that meets all eligibility criteria will be selected in case patient have multiple potential entry dates.

1.3. Inclusion/Exclusion

1.3.1. PP6M Cohort

All PP6M cohort patients from PSY3016 OLE will be eligible for this study.

1.3.2. PP3M and PP1M Cohorts

Patients from PP3M and PP1M cohorts will be selected from the IBM MDCD data source. First, PP3M cohort patients will be evaluated for inclusion based on the study start date and baseline period as described above. The inclusion/exclusion criteria adapted from double-blind PSY3015 study will be applied to identify eligible patients. Once eligible PP3M patients are identified, they

will be removed from the PP1M pool, and the remaining patients will be evaluated for their eligibility based on their study start and baseline period inclusion/exclusion criteria for PP1M cohort.

Applicable Inclusion/Exclusion criteria in IBM MDCD based on Clinical Protocol R092670PSY3016 are listed below:

Inclusion Criteria

- PSY3016 OLE study and IBM MDCD patients must have medium/high dose paliperidone palmitate injections
- Age ≥ 18 at index PP injection
- Schizophrenia diagnosis at or prior to PP index date
- At least 12 months continuous medical and prescription (Rx) enrollment records before and after index PP injection dates for PP3M and PP1M cohorts. Enrollment records with "medical insurance only" or indicating dual eligibility (ie. Medicaid and Medicare) will not be considered as "continuous" enrollment period since some of the medical and/or prescription claims might be captured by Medicare and may not appear in Medicaid.
- PP3M and PP1M patient cohorts must have at least 6-month stable period as described in section "Baseline Period and Study Start (Index) Dates" and PP3M cohort patients must have at least 2 PP3M injections and PP1M patients must have at least 5 PP1M injections during study period.

Exclusion Criteria

- Relapse record during the 12-month baseline period including
  - Mental health related inpatient hospitalization,
  - Emergency room visits due to Schizophrenia,
  - Self-injury or Violent/Aggressive behavior results in suicide, or
  - Suicidal or Homicidal ideation,
- Patients with injectable antipsychotic Rx administration other than long acting injectable paliperidone palmitate within 6-month pre-index date for PP3M or PP1M injections except for injectable Risperidone,
- Patients with "Autism" prior to index date,
- Patients with "Dementia" prior to index date,
- Patients with "Manic episode" or "Bipolar disorder" prior to index date,
- BMI >40 (Morbidly obese patients) and/or patients with abnormal weight loss /underweight diagnosis during baseline period
- Female patients with pregnancy / delivery records during baseline or study period (1 January 2016, forward)

- Patients with following severe chronic conditions
- Diabetes (DM patients with complications and/or DM patients on Insulin)
- Heart conditions (Patients with Prolonged QT Syndrome, Arrythmia, Sick sinus
- syndrome, Complete atrioventricular block / Congestive heart failure, or
- Polymorphic ventricular tachycardia)
    - Chronic renal diseases (Hepatic insufficiency etc.)
    - Thyroid diseases
    - Chronic liver diseases
    - Hematologic diseases
    - Coagulation disorders
- Patients with cancer (By Diagnosis and Antineoplastic and/or Chemotherapy Rx)
- Clozapine use within 2 months index date for PP injection
- Inducers of proteins involved in the metabolism of paliperidone
- Systemic antifungals
- Dopamine agonists

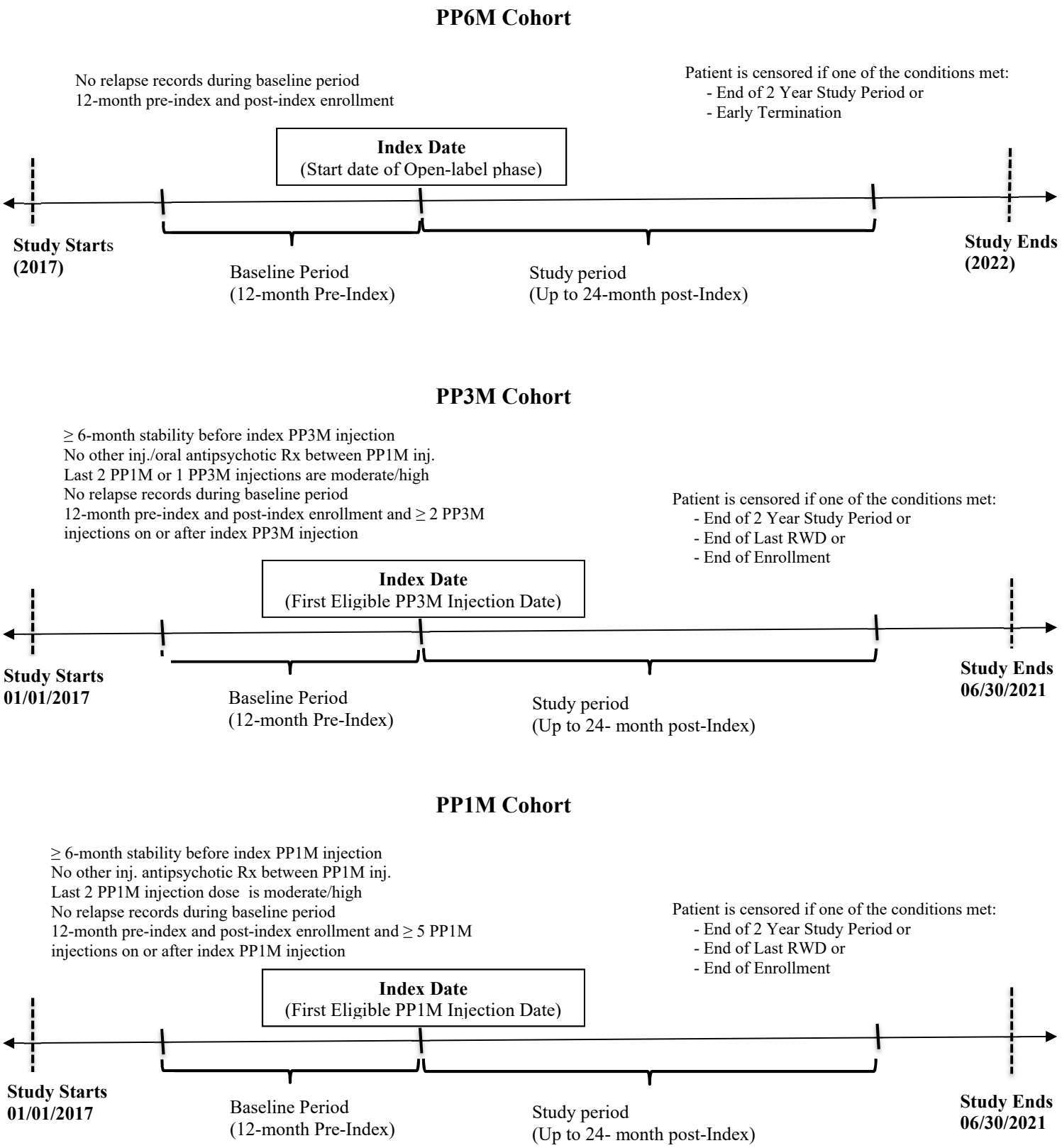
ICD-9-CM, ICD-10-CM, CPT, and Rx codes will be applied to inclusion/exclusion criteria adapted from double-blind PSY3015 study. These codes are listed in Appendix 3 through Appendix 7.

To ensure that data follow-up periods between the PP6M and PP1M/PP3M (RWD) pairs will be comparable, the RWD cohort study periods will be censored so that the maximum study period duration for real-world endpoint evaluation will be same as the maximum study period duration in the open label clinical trial, which is 24-months. Clinicians and their patients may want to know the potential effect on relapse when patients fully adhering to the treatment, ie, the extent of the pharmacological effect. Likewise, it is useful to estimate differences in relapse rates in a population that might not have been fully adherent due to various reasons, including adverse events and treatment discontinuation, ie, an average population effect. Treatment policy types of estimand strategy provides a population-level effect of the tested therapy, which may be of primary interest to policy makers. There is a need for greater transparency and alignment in how external control arm patient cohort selection maps to PSY3016 to minimize measurement error in terms of adherence to medications post index date. PP3M cohort will include those patients with at least 2 injections of PP3M and PP1M cohort will include those patients with at least 5 injections of PP1M after the corresponding index dates.

Time to relapse for all 3 cohorts will be derived as the first occurrence of any of the events listed in the Relapse Criteria. If a patient relapses, days to relapse will be calculated based on the difference between the event date minus the index date +1. Patients who do not experience a relapse will be censored. The time of censoring will be calculated as earliest of the following conditions minus the index date +1.:

- Patient reaches maximum study period (2-year)
- Early termination (PP6M only)
- End of RWD availability prior to 2-year study period (RWD cohorts only),
- Patient leaving the insurance plan (RWD cohorts only).

Figure 1: Schematic Display of Study Design



2. STATISTICAL HYPOTHESIS

The primary effectiveness endpoint for this study will be the time to first relapse event. The overall primary hypothesis to be tested in this study will be that 24 months' treatment with PP6M is superior to 24 months' PP1M or PP3M treatments in delaying time to first relapse in subjects with schizophrenia disorder. The primary null hypothesis is that there is no difference in distribution of time to first relapse among PP6M and PP3M or PP1M.

3. POPULATIONS (ANALYSIS SET) FOR ANALYSIS

The full analysis set will include all patients who received PP6M during PSY3016 open-label extension study population. Analysis set will also include PP6M matched patients that were in PP3M and PP1M cohorts and corresponds to "ITT" population in PSY3016 open-label extension study and from IBM MDCD.

3.1. PP6M Population

PP6M population will include all PSY3016 Open-label extension (OLE) study patient population.

3.2. PP3M and PP1M (ECA) Populations

External PP3M and PP1M comparison groups will resemble the open-label extension study population with respect to key inclusion/exclusion criteria and baseline demographic and disease characteristics. Important covariates to be considered for selection of external cohorts include:

- Covariates that mimic the inclusion/exclusion criteria for the PSY3016 trial (please see Appendix 3, 7, 8, and 9) in the external comparator group
- Covariates that will be utilized to minimize selection bias (i.e., to build the propensity score model)

Patients will be selected from IBM MDCD database will be aligned to PP6M trial cohort with respect to study eligibility (inclusion/exclusion) criteria. These external cohort of patients will be selected based on baseline demographic and disease characteristics to ensure comparability of treatment groups and carry out propensity score matching with open label PP6M cohort patients.

The open-label extension study analysis dataset had "Planned Treatment for Period 01 (TRT01P)" and "Planned Treatment for Period 01 (N) (TRT01PN)" variables set to "PP6M" and "1" respectively. These 2 variables will be added to IBM MDCD analysis datasets and set to "PP3M" and "2" for PP3M cohort and "PP1M" and "3" for PP1M cohort respectively. PP6M patients will be matched with PP1M and PP3M patients. To identify these 3 "matched" patients, "Matched ID" variables for PP6M, PP3M, and PP1M cohorts will be included in analysis datasets.

3.3. Propensity Score Matching

Propensity Scoring matching will be performed in the following order:

PP3M-PP1M: All eligible PP3M and PP1M patients from IBM MDCD database will be included in the matching process. First, 2 RWD cohorts will be combined into a single dataset and then TRT01PN variable will be used as exposure indicator to determine whether the patient came from PP3M cohort (TRT01PN =2) or PP1M (TRT01PN =3) in SAS PSMATCH procedure. Baseline demographic and disease characteristics including index drug dose (moderate/higher dose), age categories (18-25, 26-50, 51-65, and >65), gender, race, and other treatment related factors including presence of baseline depressive disorder, Charlson Comorbidity Index Score, and Elixhauser Comorbidity Index Score will be included in matching process. Propensity scores will be calculated using the following factors; Exact match categories (Index drug dose, Age category, gender) and Others (Race, Presence of baseline depressive disorder, Charlson Comorbidity Index Score, and Elixhauser Comorbidity Index Score). Charlson Comorbidity and Elixhauser Comorbidity Index Scores will be calculated using medical coding algorithm described by Quan et al. (Quan 2005). Patients will be matched at 1:1 ratio using the nearest neighbor matching algorithm with a caliper of 0.2 SD without replacement such that index drug dose, age category, and gender will be an exact match[5,6]. Once these patients are matched, their patient IDs and Match IDs will be saved. This data set will be the base for PP6M related matching process.

PP6M-PP3M: All PP6M cohort patients and PP3M cohort patients that previously matched with eligible PP1M cohort patients from IBM MDCD database will be matched. First, PP6M and PP3M cohorts will be combined into a single dataset. This dataset will contain variables for baseline characteristics including index drug dose (moderate/higher-dose), patient demographics (age categories [18-25, 26-50, 51-65, and > 65] and gender), and an exposure indicator of whether the patient came from PP6M cohort (TRT01PN=1) or PP3M (TRT01PN=2). Propensity scores will be calculated using the following factors: Exact match categories (PP dose, gender) and age categories. Factors are chosen based on previous clinical findings that supported their relevance. Patients will be matched at 1:1 ratio using the nearest neighbor matching algorithm with a caliper of 0.2 SD without replacement such that index PP3M dose, and gender will be an exact match (Austin 2021; Chesnaye 2021). Once these patients are matched, their patient IDs and Match IDs will be saved.

PP6M-PP1M: All PP6M cohort patients and PP1M cohort patients that previously matched with eligible PP3M cohort patients from IBM MDCD database will be paired using PP3M Match IDs that are created during PP6M-PP3M matching process. First, PP3M patients that matched with PP6M cohort will be identified and using their PP6M-PP3M and PP3M-PP1M Match IDs, PP1M patients will be mapped with PP6M patients.

Common support (ie, comparable distribution of scores between the groups) will be determined based on PP6M PS distribution. PP3M and PP1M patients will be considered for matching only when their PS score are within the common support.

The quality of matching will be assessed using the absolute standardized mean difference (SMD) for each baseline factor. Standardized differences in covariate means before and after matching will be computed and compared. The absolute standardized differences between cohorts $<0.10^{7}$ considered to be a good match

Overall attrition summary will be listed for PP3M and PP1M to show size of database for IBM MDCD.

Once the PS matching is completed, patient demographics (age, age category, gender [from ADaM "adsl" and RWD "enrollment" tables]), Rx (Total duration of exposure and exposure categories, mean and mode dose, and last dose from ADaM "adex/adexsum" and RWD "drug claims" tables), disposition (Completed and censored ["Discontinued/Withdrawn" patients from ADaM "addisp", and Enrollment discontinuation due to RWD study period limitation or lack of individual's insurance enrollment]), and time to event (relapse information from ADaM "adtte" and RWD "medical claims" tables) records from matched samples will be combined to create proper analyses data sets including time to event analysis dataset.

Baseline demographic characteristics will be summarized with descriptive statistics for the PP6M, PP3M and PP1M cohorts before and after matching.

Study Outcomes

The outcomes of the single-arm open-label PP6M clinical trial (time to first relapse and individual time to relapse components) will be reproduced in the ECA. Pairwise comparisons will be carried out. The reasons for Relapse will be summarized. Time to event endpoints of interest included:

- Time to 1st Psychiatric hospitalization.
- Time to 1st Emergency room visit due to Schizophrenia
- Time to 1st Deliberate self-injury, violent/Aggressive behavior potentially results in suicide
- Time to 1st Suicidal or Homicidal ideation

If any of the relapse conditions are within seven-day period, then they will be considered as part of a single relapse episode. Any subsequent relapse record that is greater than seven days after previous relapse will be considered as a new relapse event. Number of relapses during 24-month study period will also be summarized.

4. STATISTICAL ANALYSES

4.1. Inferential Analysis

Comparative effective analyses will be carried out for time to first relapse among the matched groups. Kaplan-Meier survival curves will be used to assess time to first relapse in three matched cohorts. Hazard ratio and 95% CI will be used to describe reduction in risk of relapses. The overall Type I error rate for testing PP6M vs PP3M and PP6N vs PP1M will be controlled at the 2-sided 0.05 significance level using a Holm's step-down procedure. In Holm's procedure, p-values from

analyses of PP6M vs PP3M and PP1M will be ordered from lowest to highest. Let $p(1) < p(2)$ to be ordered p-values corresponding null hypotheses H(1) and H(2). In Step 1, if $p(1) < 0.05/2$ then corresponding null hypothesis will be rejected and testing will move to the second step; otherwise, none of the hypotheses will be rejected and we will stop testing. In Step 2, p(2) will be tested at 0.05 level.

Kaplan-Meier survival analysis will be conducted to estimate time to relapse. The median time to first relapse will be reported for all matched cohorts. Due to paired nature of the data, the dependence between paired survival time will be taken into consideration when performing survival analysis. Therefore, stratified log-rank test will be conducted to assess the equality of survival curves in matched samples[5]. Treatment differences will be compared using a log-rank test. The cumulative distribution function of the time to treatment failure will be estimated by the Kaplan-Meier method. The 95% CIs for the median treatment failure rates, as well as the failure rates at 6 months, 12 months, 18 months, and at 24 months will be provided. The reasons for relapses will be summarized.

4.1.1. Cox Regression

In the matched samples, a Cox model will be used to regress time to first relapse on treatment status, with a robust variance estimator used to account for the clustering within matched sets (Austin 2021). Hazard ratio and 95% CI will be used to describe reduction in risk of relapses.

4.2. Sensitivity Analysis

To assess robustness of our results, sensitivity analysis will be performed using propensity score matching at 1:2 ratio using the nearest neighbor matching algorithm with a caliper set at 0.2 SD and without replacement such that index drug dose, age category, and sex will be in exact match (Austin 2021; Chesnaye 2021).

4.2.1. Assessment of the Covariate Balance

Baseline characteristics in the RWD (PP1M and PP3M) and trial (PP6M) cohorts will be assessed for balance both before and after propensity score matching. Standardized mean difference of <10% will be considered negligible imbalance between groups (Chesnaye 2021). If the standardized differences remain too large after matching, the propensity score model will be revisited. Besides having similar means, continuous variables will be examined to ascertain that the distribution and variance are similar between groups.

4.2.2. Assessment of Primary Endpoints

Unadjusted hazard ratios will be calculated using Cox proportional hazard model to regress time to first relapse, with a variance estimator used to account for the clustering within matched sets (Austin 2015). The data will be assessed for meeting the proportional hazards assumption and the global p-value will be reported. Unadjusted hazards ratios will be reported for PP3M vs. PP1M, PP6M vs PP3M, PP6M vs PP1M.

5. LIMITATIONS

This study is subject to the following limitations:

- Unlike randomized controlled trials, ECAs derived from RWD cannot control for unmeasured or unknown confounders; they are restricted to known confounders that are available in both the trial data and the claims database. RWDs also reflect real-world patterns of care and vary in data quality and completeness. As with any Real-world database, where data are collected for clinical care and insurance claims, misclassification and incomplete or delayed data entry might have been inherent in the used databases. In some cases, the relevant information recorded in the trial may not be collected in the RWD, such as with lab values and mental health related scales.
- Not all inclusion and exclusion criteria from R092670PSY3016 study could be applied to the IBM MDCD patients.
- All clinical trial outcomes could not be wholly reproduced in the ECA due to a lack of similar outcomes in the claims database.
- The generalizability of findings from this study will be for the US Medicaid eligible population and this warrants further analysis on Commercial, and Medicare insured populations.

6. REFERENCES

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7. SUPPORTING DOCUMENTATION

Appendix 1 List of Abbreviations

ANOVA	analysis of variance
ANCOVA	analysis of covariance
ECA	external Control Arm
LAI	long-acting injectables
PP	paliperidone palmitate
PP1M	paliperidone palmitate 1-month injectable formula
PP3M	paliperidone palmitate 3-month injectable formula
PP6M	paliperidone palmitate 6-month injectable formula
RWD	Real World Data
RWE	Real World Evidence
SAP	Statistical Analysis Plan
SD	standard deviation

Appendix 2 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Initial release

Appendix 3: Mental Health-related Diagnosis Codes for Inclusion, Exclusions

Criteria	Code type	Codes
Schizophrenia Dx	ICD-9-CM	295.70-295.75, 295.80-295.85, 295.90-295.95, 297, 297.0-297.3, 297.8-297.9
	ICD-10-CM	F20, F250, F251, F258, F259
Manic episode / Bipolar disorder	ICD-9-CM	296.0, 296.00-296.06, 296.1, 296.10-296.16, 296.4, 296.40-296.46, 296.5, 296.50-296.56, 296.6, 296.60-296.66, 2967, 296.8, 296.80-296.81, 296.89
	ICD-10-CM	F30, F31
Dementia	ICD-9-CM	046.0, 046.1, 046.11, 046.19, 094.1, 290, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.2, 290.20, 29021, 290.3, 290.4, 290.40, 290.41, 290.42, 290.43, 290.8, 290.9, 291.1, 291.2, 292.82, 294, 294.1, 294.10, 294.11, 294.2, 294.20, 294.21, 294.8, 294.9, 310, 310.2, 330, 330.1, 330.2, 330.3, 330.8, 330.9, 331, 331.1, 331.11, 331.19, 331.2, 331.3, 331.4, 331.5, 331.7, 331.8, 331.82, 333.4, 780.93, 797
	ICD-10-CM	F01, F02, F03
Autism	ICD-9-CM	299.9
	ICD-10-CM	Z9183, F840
Depressive disorder	ICD-9-CM	296.2, 296.20, 296.21, 296.22, 296.23, 296.24, 296.3, 296.30, 296.31, 296.32, 296.33, 296.34, 300.4, 300.40, 309.0, 309.00, 309.1, 309.10, 311, 311.0, 311.00
	ICD-10-CM	F32, F33, F34

Appendix 4: Relapse Definition in RWD by Diagnosis Codes

Criteria	Code type	Codes
Suicidal Ideation	ICD-9-CM	V62.84
	ICD-10-CM	R45.851
Homicidal Ideation	ICD-9-CM	V62.85
	ICD-10-CM	R45.850
Deliberate Self-injury, Violent Behavior	ICD-9-CM	312, 312.89, 312.10
	ICD-10-CM	F03.91, F91.8, R45.5, R45.6
Violent behavior resulting in suicide *	ICD-9-CM	E950 - E958
	ICD-10-CM	T1491, X71, X72, X73, X74, X75, X76, X77, X78, X79, X80, X81, X82, X83, T36, T37, T38, T39, T40, T41, T42, T43, T44, T45, T46, T47, T48, T49, T50, T51, T52, T53, T54, T55, T56, T57, T58, T59, T60, T61, T62, T63, T64, T65, T66, T67, T68, T69, T70, T71

* Only "initial encounter" diagnosis codes will be included

Appendix 5: Listing of Antipsychotic Medications

Typical			
Chlorpromazine	Zuclopenthixol	Periciazine	Pipamperone
Thioridazine	Prochlorperazine	Chlorprothixene	Piperacetazine
Loxapine	Pimozide	Benperidol	Pipotiazine
Molindone	Lenperone	Clopenthixol	Promazine
Perphenazine	Chlorpromazine	Cyamemazine	Spiperone
Thiothixene	Thioridazine	Dixyrazine	Sulforidazine
Trifluoperazine	Loxapine	Fluspirilene	Thiopropazate
Haloperidol	Oxyprotepine	Levomepromazine	Thioproperazine
Fluphenazine	Penfluridol	Periciazine	
Droperidol	Perazine	Oxypertine	
Atypical			
Amisulpride	Paliperidone	Sulpiride	Nemonapride
Aripiprazole	Paliperidone Palmitate	Ziprasidone	Reserpine
Asenapine	Perospirone	Zotepine	Sultopride
Blonanserin	Quetiapine	Amoxapine	Tiapride
Clotiapine	Remoxipride	Amisulpride	Veralipride
Clozapine	Risperidone	Brexpiprazole	Sertindole
Iloperidone	Amisulpride	Cariprazine	Sulpiride
Lurasidone	Aripiprazole	Carpipramine	Ziprasidone
Mosapramine	Asenapine	Clocapramine	Zotepine
Olanzapine	Blonanserin	Clorotepine	
Olanzapine/Fluoxetine	Sertindole	Melperone	

Appendix 6: List of Antipsychotics by CPT and HCPCS Drug Codes

CPT-4

80159 - Clozapine
80173 - Haloperidol

HCPCS

C9125 - Risperidone inj
C9255 - Injection, paliperidone palmitate, 1 mg
C9497 - Loxapine, inhalation powder, 10 mg
J0400 - Injection, aripiprazole, intramuscular, 0.25 mg
J0401 - Injection, aripiprazole, extended release, 1 mg
J0780 - Injection, prochlorperazine, up to 10 mg
J1630 - Injection, haloperidol, up to 5 mg
J1631 - Injection, haloperidol decanoate, per 50 mg
J1790 - Injection, droperidol, up to 5 mg
J1810 - Injection, droperidol and fentanyl citrate, up to 2 ml ampule
J2358 - Injection, olanzapine, long-acting, 1 mg
J2426 - Injection, paliperidone palmitate extended release, 1 mg
J2680 - Injection, fluphenazine decanoate, up to 25 mg
J2794 - Injection, risperidone, long acting, 0.5 mg
J2950 - Injection, promazine hcl, up to 25 mg
J3230 - Injection, chlorpromazine hcl, up to 50 mg
J3280 - Injection, thiethylperazine maleate, up to 10 mg
J3310 - Injection, perphenazine, up to 5 mg
J3400 - Injection, trifluprомazine hcl, up to 20 mg
J3486 - Injection, ziprasidone mesylate, 10 mg
Q0161 - Chlorpromazine hydrochloride, 5 mg, oral
Q0164 - Prochlorperazine maleate, 5 mg, oral
Q0165 - Prochlorperazine maleate, 10 mg, oral
Q0171 - Chlorpromazine hydrochloride, 10 mg
Q0172 - Chlorpromazine hydrochloride, 25 mg
Q0174 - Thiethylperazine maleate, 10 mg, oral
Q0175 - Perphenazine, 4 mg, oral
Q0176 - Perphenazine, 8mg, oral
S0136 - Clozapine, 25 mg
S0163 - Risperidone inj
S0166 - Injection, olanzapine, 2.5 mg
S0183 - Prochlorperazine maleate, oral, 5mg

Appendix 7: List of Mental Health Related Medical and Data Specific Codes

Code Type	Description
ICD-9-CM	230 - 319 Mental, Behavioral and Neurodevelopmental Disorders
ICD-10-CM	F01 - F99 Mental, Behavioral and Neurodevelopmental Disorders
MS DRG	876 - 887 Mental Diseases & Disorders
CPT-4	90785 - Interactive complexity add-on (for psychotherapy codes) 90791 - Psychiatric/psychological diagnostic interview without medical services (intake interview) 90792 - Psychiatric diagnostic interview (for prescribers / medical services) 90832 - Individual psychotherapy, 30 minutes 90833 - Use add-on code for Individual psychotherapy, 30 minutes with the patient and/or family member (time range 16-37 minutes), when performed with an evaluation and management service. 90834 - Individual psychotherapy, 45 minutes 90836 - When performed with an evaluation & management service 90837 - Individual psychotherapy, 60 minutes 90838 - When performed with an evaluation & management service 90839 - Psychotherapy for crisis, first 60 minutes 90840 - Add-On service code - describes billing an additional 30 minutes of crisis therapy services rendered after the first 90 minutes of treatment. 90845 - Psychoanalysis 90847 - Family psychotherapy (conjoint psychotherapy) (with patient present), 50 minutes 90849 - Multiple-family group psychotherapy 90853 - Group psychotherapy 90875 - Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 30 minutes 90876 - 45 minutes 96101 - Psychological testing, interpretation and reporting per hour by a psychologist (per hour) 96102 - Psychological testing per hour by a technician (per hour) 96103 - Psychological testing by a computer, including time for the psychologist's interpretation and reporting (per hour) 96105 - Assessment of Aphasia 96111 - Developmental Testing, Extended 96116 - Neurobehavioral Status Exam (per hour) 96118 - Neuropsychological testing, interpretation and reporting by a psychologist (per hour) 96119 - Neuropsychological testing per hour by a technician 96120 - Neuropsychological testing by a computer, including time for the psychologist's interpretation and reporting 96150 - Health & Behavioral Assessment – Initial (each 15 mins) 96151 - Reassessment (each 15 mins)

Code Type	Description
	96152 - Health & Behavior Intervention – Individual (each 15 mins)
	96153 - Health & Behavior Intervention – Group (each 15 mins)
	96154 - Health & Behavior Intervention – Family with Patient (each 15 mins)
	96155 - Health & Behavior Intervention – Family without Patient (each 15 mins)
Standard services	
	Psychiatric and/or Substance Abuse
Revenue codes	
	0114 - Private medical or general-psychiatric
	0513 - Clinic-psychiatric
	0900 - Psychiatric/psychological treatments-general class
	0901 - Psychiatric/psychological treatments-electroshock treat
	0902 - Psychiatric/psychological treatments-milieu therapy
	0903 - Psychiatric/psychological treatments-play therapy
	0904 - Psychiatric/psychological treatments-activity therapy
	0909 - Psychiatric/psychological treatments-other
	0910 - Psychiatric/psychological services-general classification
	0911 - Psychiatric/psychological svcs-rehabilitation
	0912 - Psychiatric/psychological svcs-day care or less intense
	0913 - Psychiatric/psychological svcs-night care or intense
	0914 - Psychiatric/psychological svcs-individual therapy
	0915 - Psychiatric/psychological svcs-group therapy
	0916 - Psychiatric/psychological svcs-family therapy
	0917 - Psychiatric/psychological svcs-biofeedback
	0918 - Psychiatric/psychological svcs-testing
	0919 - Psychiatric/psychological svcs-other
	0961 - Professional fees-psychiatric
	1001 - BH R & B Residential - Psych
Standard place	
	Inpatient Psychiatric Facility
	Psych Facility Partial Hosp
	Community Mental Health Center
	Intermed Care/Mental Retarded
	Residential Subst Abuse Facil
	Psych Residential Treatmnt Ctr
	Non-resident Subst Abuse Facil

Code Type	Description
Standard provider	
	Mental Health/Chemical Dep NEC
	Mental Health Facilities
	Chemical Depend Treatment Ctr
	Mental Hlth/Chem Dep Day Care
Procedure groups	
	Psychotherapy, individual
	Psychotherapy, family
	Psychotherapy, group
	Psych advice
	Other psychiatric services

Appendix 8: List of Chronic Conditions Included in Exclusion List and Their ICD-9-CM/ICD-10-CM/Rx Listings

Criteria	Code type	Codes
Congestive heart failure, arrythmia	ICD-9-CM	410, 412, 428, 4254, 4255, 425.7, 425.8, 425.9, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 426.0, 426.7, 426.9, 427.0, 427.1, 427.2, 427.3, 427.4, 427.6, 427.8, 427.9, 785.0, V45.0, V53.3, 426.13, 426.10, 426.12, 996.01, 996.04
	ICD-10-CM	I21, I22, I252, I43, I495, I50, I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, I442, P290, I47, I48, I49, I441, I442, I443, I456, I459, R000, R001, R008, T821, Z450, Z950
Sick sinus syndrome, Complete atrioventricular block	ICD-9-CM	427.81, 426.0
	ICD-10-CM	I495, I442
Ventricular tachycardia	ICD-9-CM	427.1
	ICD-10-CM	I472
Prolonged QT Syndrome	ICD-9-CM	426.82
	ICD-10-CM	I45.81
	Rx	Type IA antiarrhythmics (Quinidine,Procainamide,Disopyramide), Type IC antiarrhythmics (Flecainide, Encainide), Class III antiarrhythmics (Sotalol, Amiodarone), Antipsychotics (Chlorpromazine, Haloperidol, Droperidol, Quetiapine, Olanzapine, Amisulpride, Thioridazine), Tricyclic antidepressants (Amitriptyline, Doxepin, Imipramine, Nortriptyline, Desipramine), Other antidepressants (Mianserin, Citalopram, Escitalopram, Venlafaxine, Bupropion, Moclobemide), Antihistamines (Diphenhydramine, Astemizole, Loratidine, Terfanadine), Other Rx (Chloroquine, Hydroxychloroquine, Quinine), Macrolides (Erythromycin, Clarithromycin)
Patients with DM with complications and/or on Insulin	ICD-9-CM	250.4, 250.5, 250.6, 250.7, 250.8, 250.9
	ICD-10-CM	E102, E103, E104, E105, E106, E107, E108, E112, E113, E114, E115, E116, E117, E118, E122, E123, E124, E125, E126, E127, E128, E132, E133, E134, E135, E136, E137, E138, E142, E143, E144, E145, E146, E147, E148
	Rx	Insulin
Renal diseases	ICD-9-CM	582, 585, 586, V56, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 588.0, V42.0, V45.1, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, V56,
	ICD-10-CM	I120, I131, N18, N19, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N250, Z490, Z491, Z492, Z940, Z992
Thyroid diseases	ICD-9-CM	239.7;240.0-240.9;241.0-241.9;242.00-242.91;243;244.0-244.9;245.0-245.9;246.0-246.9
	ICD-10-CM	E00, E01, E02, E03, E04, E05, E06, E07, E89.0
Chronic liver diseases	ICD-9-CM	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8, 570, 571, 070.6, 070.9, 456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8, 573.3, 573.4, 573.8, 573.9, V42.7, 0702.2, 070.23, 070.32, 070.33, 070.44, 070.54
	ICD-10-CM	B18, I85, K70, K72, K73, K74, I864, I982, K711, K765, K766, K767, I864, I982, K713, K714, K715, K717, K760, K762, K763, K764, K768, K769, Z944
Patients with Cancer	ICD-9-CM	140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 174, 175, 176, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 200, 201, 202, 203, 204, 205, 206, 207, 208, 196, 197, 198, 199
	ICD-10-CM	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C85, C88, C90-C97
	Rx	Antineoplastic and Chemotherapy Drugs
Coagulation disorders	ICD-9-CM	286, 287.1, 287.3, 287.4, 287.5
	ICD-10-CM	D65, D66, D67, D68, D69
Hematologic disease	ICD-9-CM	280-285, 288-289
	ICD-10-CM	D55, D56, D57, D60, D61

Appendix 9: List of Other Criteria Included in Inclusion/Exclusion List and Their ICD-9-CM/ICD-10-CM/Rx Listings

Criteria	Code type	Codes
Pregnancy / Delivery records during baseline	ICD-9-CM	640-677, 760-763, V22-V24, V27-V28, V30-V39
	ICD-10-CM	Oxx, Oxxx, Oxxxx, Oxxxxx, Z33-Z39, P00-P03, Z3201, Z34, Z36, Z37, Z38, Z39, Z3A
	CPT	59000-59899
Patients with >=40 and/or < 18 BMI	ICD-9-CM	278.01, 278.03, 783.21, 783.22, V85.41-V85.45
	ICD-10-CM	E6601, E662, R634, R636, Z684, Z6841-Z6845
Clozapine use within 2 months index PP injection	Rx	Clozapine, Clozaril, Fazaclo, Versacloz
	HCPCS	S0136
Inducers of protein involved in paliperidone metabolism	Rx	Rifampicin, Carbamazepine, Oxcarbazepine, Barbiturates, Phenytoin, Troglitazone
Systemic antifungals	Rx	Ketoconazole, Itraconazole, Fluconazole, Fosfluconazole, Voriconazole, Posaconazole, Isavuconazole, Griseofulvin, Terbinafine
Dopamine agonists	Rx	Ropinirole, Pramipexole, Pergolide, Cabergoline, Lisuride, Amantadine etc..