Global Epidemiology, Janssen Research & Development, LLC*

Non-interventional Postauthorization Safety Study - Protocol

Stroke risk among users of typical vs. atypical antipsychotics stratified by broad age group, a post-authorization safety study

Protocol PCSESP001292 (CR108624)

Haldol Haloperidol

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EU PAS Register Number: Study Not Registered

Status:	Approved Draft		
Protocol version:	1.3	**Version date:**	30 April 2019
Prepared by:	Janssen Research & Development		
EDMS number:			

Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

1. PASS INFORMATION

Title:	**Stroke risk among users of typical vs. atypical antipsychotics stratified by broad age group, a post-authorization safety study**
Protocol version:	1.3
Date of last version of the protocol:	N/A
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Active substance (INN common name):	Haloperidol
Pharmaco-therapeutic group (ATC Code):	N05AD01
Medicinal product(s):	Haloperidol
Product reference:	N/A
Procedure number:	N/A
Name of Marketing Authorization Holder(s)	Janssen Research and Development, LLC
Joint PASS	No
Research question and objectives	The primary objective of this study is to extend the recent FDA Sentinel tabulations regarding stroke risk among new users of typical and atypical antipsychotics to patients aged 65 and older regardless of dementia status. 1. To compare the risk of stroke in each of the target cohorts {patients aged 65 and older who are newly exposed to 1) typical antipsychotics or, 2) haloperidol} versus the comparator cohort {patients aged 65 and older who are newly exposed to atypical antipsychotics} This study objective is intended to answer the following research questions: • Is haloperidol associated with an increased risk of stroke among patients 65 and older compared to atypical antipsychotics that is detectable in healthcare databases? • Are typical antipsychotics associated with an increased risk of stroke among patients 65 and older compared to atypical antipsychotics that is detectable in healthcare databases?
Country(-ies) of study	United States
Author	Daniel Fife, DFife@its.jnj.com

2. MARKETING AUTHORIZATION HOLDER(S)

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Qualified Person Pharmacovigilance:	
Name:	N/A (Study not registered in EU-PAS)
Signature:	
Date:	

3. RESPONSIBLE PARTIES

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LIST OF IN-TEXT TABLES AND FIGURES

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AMENDMENTS AND UPDATES

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and will follow the review and approval process in accordance with local regulations.

Amendment number	Date	Page	Brief summary
1	10 June, 2019		Truncate analysis at 30 September, 2015, as was done in the Sentinal analysis. This avoids the need to include experience coded after the transition to ICD-10. Tabulate as a graph, the incidence of stroke by calendar year and 10 year age group to assess whether there's evidence of a substantial change in stroke incidence diagnosis after the change to ICD-10

4. ABSTRACT

Protocol Title: Stroke risk among users of typical vs. atypical antipsychotics stratified by broad age group, a post-authorization safety study (1.3, 30 April 2019)

Sponsor's Responsible Medical Officer: Daniel Fife, MD, Janssen Pharmaceutial Research and Development

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale

The FDA in the past has denied a request to include stroke risk as part of the black box warning for haloperidol and haloperidol decanoate, even though it is included on the company core data sheet (CCDS). Tabulations on antipsychotics and stroke from the Sentinel Data found no increased risk with haloperidol or typical antipsychotics relative to atypical antipsychotics, and this was a prominent part of the FDA's rationale for denying the request. However, these tabulations were done in patients aged < 65 years who did not have a dementia diagnosis. The primary objective of this study is to extend the recent FDA Sentinel tabulations regarding stroke risk among new users of typical and atypical antipsychotics to patients aged 65 and older regardless of dementia status. A secondary objective is to replicate the findings from the recent FDA Sentinel tabulations regarding stroke risk among new users of typical and atypical antipsychotics. To achieve these objectives, we will conduct 6 population-level effect estimation studies using three different propensity scoring methods: unadjusted, logistic regression model replicating the covariates chosen by Sentinel, and a large-scale regularized regression model using a LASSO logistic regression technique.

Research Question and Objectives

Primary Objective

The primary objective of this study is to extend the recent FDA Sentinel tabulations regarding stroke risk among new users of typical and atypical antipsychotics to patients aged 65 and older regardless of dementia status.

1. To compare the risk of stroke in each of the target cohorts {patients aged 65 and older who are newly exposed to 1) typical antipsychotics, 2) haloperidol} versus the comparator cohort {patients aged 65 and older who are newly exposed to atypical antipsychotics}

This study objective is intended to answer the following research questions:

- Is haloperidol associated with an increased risk of stroke among patients 65 and older compared to atypical antipsychotics that is detectable in healthcare databases?
- Are typical antipsychotics associated with an increased risk of stroke among patients 65 and older compared to atypical antipsychotics that is detectable in healthcare databases?

Secondary Objective(s)

The secondary objectives of this study are:

1. To replicate the findings from the recent FDA Sentinel tabulations regarding stroke risk among new users of typical and atypical antipsychotics by comparing: the risk of stroke in each of the

target cohorts {patients aged 18-64 without a recent dementia diagnosis who are newly exposed to 1) typical antipsychotics, 2) haloperidol} versus the comparator cohort {patients aged 18-64 without a recent dementia diagnosis who are newly exposed to atypical antipsychotics}

This study objective is intended to answer the following research questions:

- Is haloperidol associated with an increased risk of stroke among patients aged 18-64 without a recent dementia diagnosis that is detectable in healthcare databases?
- Are typical antipsychotics associated with an increased risk of stroke among patients aged 18-64 without a recent dementia diagnosis that is detectable in healthcare databases?

2. To compare the risk of stroke in each of the target cohorts {patients aged 18-64 who are newly exposed to 1) typical antipsychotics, 2) haloperidol} versus the comparator cohort {patients aged 18-64 who are newly exposed to atypical antipsychotics}

The above study objective is intended to provide a suitable comparator to the patients aged 65 and older who are described in the Primary objective, which does not exclude for dementia.

Study Design

This is a retrospective, non-interventional, study that will be done from two US health care databases (see section 8.4 below).

Setting and Patient Population

This is a retrospective non-interventional, study that will be done from two US health care databases (see section 8.4 below for further information).

Variables

Evaluation of Safety

See Section 10 below.

Data Sources

See sections 8.3 and 8.4 below

Study Size

See section 8.5 below.

Data Analysis

See section 8.7 below.

Milestones

See MILESTONES (section 5) below.

DATA COLLECTION SCHEDULE

N/A

5. MILESTONES

Milestone:	Planned Date:
Start of data collection	04-February-2019
End of data collection	15-March-2019
Examination of diagnostics and completion of protocol	26-April-2019
Registration with ClinicalTrials.gov submitted	15-May-2019
Completion of tabulations	01-June-2019
Completion of CSR	28-June-2019
Draft publication	15-July-2019

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

CCAE	IBM MarketScan® Commercial Database IBM MarketScan® Commercial Database
CCDS	Company Core Data Sheet
CRF	Case Report Form
CDT	Clinical Development Team
eDC	electronic data capture
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MDCR	IBM MarketScan® Medicare Supplemental Database
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)

Definition of Term(s)

Study	The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed
Retrospective non-interventional study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.
Post Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

6. BACKGROUND AND RATIONALE

For the past 15 years, there has been disagreement about whether antipsychotic medications cause strokes and, if so, whether there are differences with regard to stroke risk between typical and atypical antipsychotics or between haloperidol and atypical antipsychotics, and whether there is an interaction with age or indication. The Company Core Data Sheet (CCDS) for haloperidol and haloperidol decanoate describes an increased risk of stroke with haloperidol. In contrast, the US package insert carries a black box warning for mortality in elderly patients with dementia-related psychosis, but it does not mention stroke. The relevant sections of these two documents read:

CCDS: "In randomized, placebo-controlled clinical trials in the dementia population, there was an approximately 3-fold increased risk of cerebrovascular adverse events with some atypical antipsychotics. Observational studies comparing the stroke rate in elderly patients exposed to any antipsychotic to the stroke rate in those not exposed to such medicinal products reported an approximately 1.6- to 1.8-fold increased stroke rate among exposed patients. This increase may be higher with all butyrophenones, including haloperidol. The

mechanism for this increased risk is not known. An increased risk cannot be excluded for other patient populations. TRADENAME must be used with caution in patients with risk factors for stroke."

US package insert (black box 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. 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. HALDOL Injection is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS)."

Over the past few years, all major health authorities except the FDA have accepted language similar to that in the CCDS. In contrast, in 2018 the FDA refused permission to include such language in the US package insert. This refusal was based in part on a company literature review that produced conflicting outcomes as only two studies were found, one on the association between haloperidol and stroke and one on the association of butyrophenones and stroke. Both studies showed an association of stroke with drug exposure, however, the haloperidol study was conducted in a middle-aged schizophrenic population whose exposer is much greater than the elderly dementia population.

The FDA's refusal was also based on tabulations the FDAQ recently did on typical and atypical antipsychotics and stroke based on the Sentinel data. Those tabulations found that, in patients aged 18 to 64 who did not have a recent diagnosis of dementia, the crude stroke incidence was higher for those among new users of typical antipsychotics than among new users of atypical antipsychotics [45K vs 805K new users, hazard ratio (HR) 1.75, 95% CI (1.17, 2.63)] but, after 1:1 propensity score (PS) matching using a 0.05 caliper on the propensity score scale, this difference disappeared [45K vs 45K new users, hazard ratio 0.87, 95% CI (0.54, 1.41)]. In a similar comparison for haloperidol vs. atypical antipsychotics, the HR was not statistically significant in the crude analysis [13K vs 801K new users, HR 1.80, 95% CI (0.93, 3,48)] or in analysis done after PS matching [13K vs 13K new users, HR 1.31 (0.54, 3.21)]. The FDA asserted that "This, along with our previous strong suspicions of confounding in observational studies comparing mortality in elderly users of typical antipsychotics to users of atypical antipsychotics makes it likely that the observed differences in stroke among the elderly are also due to confounding. It cannot be concluded that haloperidol or other typical antipsychotics increase the risk of stroke to a greater degree than atypical antipsychotics."

The CDT is preparing a response to further pursue with FDA the possibility of including a stroke warning in the US package insert similar to the stroke warning in the SMPC. As part

of that response, the CDT has requested that we challenge the FDA's contention that the findings from their study of people aged 18 to 64, and without dementia, are applicable to the population aged >= 65 years, among whom dementia is a common indication for the use of antipsychotic medications. Specifically, they requested that we try to replicate the main findings from Sentinel tabulations and, if that was successful, we do similar tabulations on patients aged >= 65 years to see whether, after PS matching, the risk of stroke in new users of haloperidol or typical antipsychotics is the same as the risk of stroke in new users of atypical antipsychotics, as was hypothesized by FDA.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective

The primary objective of this study is to extend the recent FDA Sentinel tabulations regarding stroke risk among new users of typical and atypical antipsychotics to patients aged 65 and older regardless of dementia status.

1. To compare the risk of stroke in each of the target cohorts {patients aged 65 and older who are newly exposed to 1) typical antipsychotics, 2) haloperidol} versus the comparator cohort {patients aged 65 and older who are newly exposed to atypical antipsychotics}

This study objective is intended to answer the following research questions:

- Is haloperidol associated with an increased risk of stroke among patients 65 and older compared to atypical antipsychotics that is detectable in healthcare databases?
- Are typical antipsychotics associated with an increased risk of stroke among patients 65 and older compared to atypical antipsychotics that is detectable in healthcare databases?

Secondary Objective(s)

The secondary objectives of this study are:

2. To replicate the findings from the recent FDA Sentinel tabulations regarding stroke risk among new users of typical and atypical antipsychotics by comparing: the risk of stroke in each of the target cohorts {patients aged 18-64 without a recent dementia diagnosis who are newly exposed to 1) typical antipsychotics, 2) haloperidol} versus the comparator cohort {patients aged 18-64 without a recent dementia diagnosis who are newly exposed to atypical antipsychotics}

   This study objective is intended to demonstrate that the present study provides a reasonable replication of a recent tabulation from FDA that the Agency offered as a reasonnot to include language about strok risk in the Haldol label.

3. To compare the risk of stroke in each of the target cohorts {patients aged 18-64 who are newly exposed to 1) typical antipsychotics, 2) haloperidol} versus the comparator cohort {patients aged 18-64 who are newly exposed to atypical antipsychotics}

This study objective is intended to answer the following research questions that will provide a more suitable comparator for #1 above than does #2 above (because neither #1 above nor this comparison excludes for dementia):

- Is haloperidol associated with an increased risk of stroke among patients aged 18-64 without a recent dementia diagnosis that is detectable in healthcare databases?
- Are typical antipsychotics associated with an increased risk of stroke among patients aged 18-64 without a recent dementia diagnosis that is detectable in healthcare databases?

8. RESEARCH METHODS

8.1. Study Design

8.1.1. Overview of Study Design

This study will involve population-level effect estimation using a retrospective, observational, comparative cohort design. We define ‘retrospective’ to mean the study will be conducted using data already collected prior to the start of the study. We define ‘observational’ to mean there is no intervention or treatment assignment imposed by the study. We define 'cohort' to mean a set of patients satisfying one or more inclusion criteria for a duration of time. We define ‘comparative cohort design’ to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time period after cohort entry (1). The study will be conducted in two administrative claims databases in the US, as described in section 8.4. The specific exposure cohorts are described in section 8.2.2. The time-at-risk definitions are described in section 8.2.1. the statistical analysis plan for population-level effect estimation is described in section 8.7.3.

8.1.2. Rationale for Study Design Elements

A retrospective analysis of health care data is the most practical way to study the large number subjects required to estimate the risk ratios of interest. In such a study, a cohort design with matching on a propensity score generated by regularized logistic regression is the most practical way to minimize confounding.

8.2. Setting and Patient Population

8.2.1. Study Setting and Duration

The retrospective data collection period will document data available from 01-January-2002 through 31-December-2017 (the study end date).

After seeing the resuls of these analyses, we implemented two post-hoc analyses:

1. Repeat the analyses, including the diagnostics, with the study end date re-defined as 30 September, 2015 and thus avoid the need to include data that was coded after the change from ICD-9 to ICD-10, and

2. Tabulate as a graph, the incidence of stroke by calendar year and 10 year age group to assess whether there's evidence of a substantial change in stroke incidence diagnosis after the change to ICD-10

The present study cover all but the first year of the date range used in the Sentinel study whose query was from 1 January 2001 to 30 September 2015 but whose data availability dates varied by source with start dates from 1/1/2000 to 1/1/2012 and whose end dates varied from 9/30/15 through 10/31/15 (4).

The primary time-at-risk will be defined as the 'on treatment with censoring at switch' period, defined as the time from 1 day after exposure cohort start date (based on the date of first exposure to the cohort-defining drug(s)) to 0 days from exposure cohort end date, where exposure cohort end date was defined as the persistent period of exposure, allowing for 30 day gap between successive exposures until the 30 days after the final exposure record, representing the date the subject expected to finish the supply of the last drug dispensing per the prescription information with an additional 30-day surveillance window. If two cohorts are being compared, a patient's time-at-risk in either cohort ends if he receives a drug that would qualify him for the other. For all analyses, a qualifying person from an exposure cohort will contribute time-at-risk from
the time-at-risk start date until leaving the cohort.

Exit criteria for the exposure cohorts:
Patients leave the exposure cohorts with the first of

- Reaching the study end date
- Reaching the end of primary time at risk for the (first) exposure episode (see "primary time at risk" above)
- Having the outcome of interest (stroke as a principal hospital discharge diagnosis)
- Receiving a dispensing of the comparator drug
- Reaching the end of the observation period for the database the patient is in

The overall study population could be considered as patients who entered any of the target cohorts or comparator cohorts. Patients who qualify for the target cohorts and then subsequently receive a drug associated with the comparator cohorts will contribute time-at-risk to the target cohort until they are censored by receiving the drug associated with the comparator cohort, at which time they will no longer contribute time-at-risk. Patients who qualify for the comparator cohort and then subsequently receive a drug associated with the target cohort will contribute time-at-risk to the comparator cohort until they are censored by receiving the drug associated with the target cohort, at which time they will no longer contribute time-at-risk. In other words, for any pairwise comparison if a patient met the new user definition for both target and comparator therapies at a different time during the study, this patient would be eligible only for the cohort they entered first and would contribute time-at-risk to that cohort alone.

8.2.2. Selection Criteria

8.2.2.1. Study Populations

1. New users of typical antipsychotics aged 18 to 64 years without a recent dementia diagnosis
2. New users of haloperidol aged 18 to 64 years without a recent dementia diagnosis
3. New users of typical antipsychotics aged >= 65 years
4. New users of haloperidol aged >= 65 years
5. New users of typical antipsychotics aged 18 to 64 years
6. New users of haloperidol aged 18 to 64 years
7. New users of atypical antipsychotics aged 18-64 years without a recent dementia diagnosis
8. New users of atypical antipsychotics aged >= 65 years
9. New users of atypical antipsychotics aged 18-64 years

Cohorts 1-6 are Target (T) cohorts. Cohorts 7 – 9 are Comparator (C) cohorts.
Each cohort has an index cohort entry event of an initial drug exposure and satisfies the following inclusion criteria:

- First exposure to the particular drug(s) in the past 183 days (index date)
- Had at least 183 days of continuous observation time prior to index
- Exactly 0 condition occurrences of 'Cancer' any time in the 183 days before or on the index date
- Exactly 0 condition occurrences of 'Stroke' any time in the 183 days before or on the index date
- Exactly 0 exposures to any other typical or atypical antipsychotics any time in the 183 days before or on the index date

Each cohort labelled 'without a recent dementia diagnosis' additionally satisfies the following inclusion criteria:

- Exactly 0 condition occurrences of 'Dementia' any time in the 183 days before or on the index date

Throughout the document, when a drug class is referenced, the specific ingredients that are included in the drug class are as follows:

- Typical antipsychotics:
  - Haloperidol
  - Loxapine
  - Thioridazine
  - Molindone
  - Thiothixene
  - Fluphenazine
  - Trifluoperazine
  - Perphenazine
  - Chlorpromazine
- Atypical antipsychotics:
  - Aripriprazole
  - Asenapine
  - Brexpiprazole

- Cariprazine
- Clozapine
- Iloperidone
- Lurasidone
- Paliperidone
- Ziprasidone
- Risperidone
- Quetiapine
- Olanzapine

For all exposure cohorts, we derive 'drug eras' as periods of persistent exposure to a particular active ingredient. 'Drug eras' are derived from verbatim drug exposure records, including outpatient pharmacy dispensing claims records. From an outpatient pharmacy dispensing claims record, we define the drug exposure start date = dispensing date and define the exposure end date = dispensing date + days supply. 'Drug eras' consolidate drug exposure records of a particular ingredient for a given patient by combining together records where the drug exposure end date of one record is within a 'persistence window' of the drug exposure start date of a subsequent record. A 'persistence window' of 30 days means that a person will be assumed to be persistently exposed to a drug so long as two successive dispensings have no more than a 30-day gap between the end date of the first and the start date of the second. A 'surveillance window' was appended to the end date of each period of persistent exposure. A 'surveillance window' of 30 days means that a person who completed a drug regimen will continue to be followed for 30 days after the last exposure end date. As an example, if a person had an initial prescription dispensing for haloperidol on 1Jan2015, which came with 30 days supply, and a second prescription for haloperidol on 15Feb2015, also with 30 days supply, the data would be processed as follows: the first exposure record would be assigned start date = 1Jan2015 and end date = 31Jan2015 (1Jan2015 + 30d). The second exposure record would be assigned start date = 15Feb2015, end date = 17Mar2015 (15Feb2015+30d). Because the two exposures were less than 30 days apart (15Feb2015 – 31Jan2015 = 16 days), these two exposure records would be consolidated into one drug era record, with start date = 1Jan2015 and end date = 17Mar2015. With an additional 'surveillance window' of 30 days, this drug era record would be expanded to have start date = 1Jan2015 and end date = 17Apr2015 (17Mar2015 + 30d). The drug era logic used here does not account for stockpiling if subsequent prescriptions overlap in time, nor does it account for dose tailoring, since the period of exposure is defined at the ingredient level.

Each patient may be counted only once in any comparison. A patient who initially qualifies for one cohort in a comparison and later qualifies for the other will be placed in the cohort for which he or she first qualifies, as a replication of was done in the Sentinel study. Patients who are eligible for a cohort with haloperidol as the exposure and are also eligible for a cohort with typical antipsychotics as the exposure (because they start haloperidol and another typical antipsychotic on the same day) will be put in the typical antipsychotic cohort and not the haloperidol cohort. Patients who are eligible for both a T cohort and a C cohort (because on the index date the patient starts haloperidol or another typical antipsychotic and also starts an atypical antipsychotic) will be excluded.

The human-readable textual description of each cohort definition is listed below, and the listing of concepts and associated source codes for each concept-set in italics is provided in Annex 1. The complete specification for each cohort definition, including human-readable textual description, listing of all included concepts and associated source codes, and computer executable SQL, has been generated using the OHDSI open-source analytics tool (5), ATLAS. The hyperlinks below are available internally within JNJ; In the following cohort definitions, please note that when referring to exposure, the "event" is the initial exposure and is not based in any way on the occurrence of outcome events.

8173. [Epi 581] T1. New users of typical antipsychotics age 18-64 without a recent dementia diagnosis

Initial Event Cohort

People having any of the following:

- a drug exposure of *[Epi 581] Typical Antipsychotics*
    - with age between 18 and 64 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics*
  where event starts between 183 days Before and 1 days Before index start date

- and exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date

- and exactly 0 occurrences of a drug exposure of Any Drug
    - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: No stroke 183 days prior

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*
  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*
  where event starts between 183 days Before and 1 days Before index start date

Inclusion Criteria #3: No dementia 183 days prior

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Dementia*
  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**
End Date Strategy
Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *[Epi 581] Typical Antipsychotics*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of *[Epi 581] Atypical Antipsychotics*

Cohort Collapse Strategy:
- Collapse cohort by era with a gap size of 0 days.

8174. [Epi 581] T2. New users of haloperidol age 18-64 without a recent dementia diagnosis

Initial Event Cohort
People having any of the following:
- a drug exposure of *Haloperidol*
    - with age between 18 and 64 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:
- exactly 0 occurrences of a drug exposure of Haloperidol
  where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics excl. Haloperidol*
  where event starts between 183 days Before and 0 days After index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of Any Drug
    - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Inclusion Rules
Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:
- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*
  where event starts between 183 days Before and 1 days Before index start date

Inclusion Criteria #3: No dementia 183 days prior

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Dementia*
  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of Haloperidol

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:

Exit Cohort based on the following:

- a drug exposure of [Epi 581] Atypical Antipsychotics

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

8163. [Epi 581] T3. New users of typical antipsychotics age 65 years and older

Initial Event Cohort

People having any of the following:

- a drug exposure of *[Epi 581] Typical Antipsychotics*
  - with age >= 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics*
  where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of Any Drug
  - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Inclusion Rules
Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*

  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**
End Date Strategy
Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *[Epi 581] Typical Antipsychotics*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *[Epi 581] Atypical Antipsychotics*

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

8172. [Epi 581] T4. New users of haloperidol age 65 years and older

Initial Event Cohort
People having any of the following:

- a drug exposure of *Haloperidol*
  - with age >= 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *Haloperidol*
  where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics excl. Haloperidol*
  where event starts between 183 days Before and 0 days After index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of Any Drug
  - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Inclusion Rules
Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*

  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**
End Date Strategy
Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *Haloperidol*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *[Epi 581] Atypical Antipsychotics*

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

8571. [Epi 581] T5. New users of typical antipsychotics age 18-64

Initial Event Cohort
People having any of the following:

- a drug exposure of *[Epi 581] Typical Antipsychotics*
    - with age between 18 and 64 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics*
  where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of Any Drug
    - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Inclusion Rules
Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*

  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**
End Date Strategy
Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *[Epi 581] Typical Antipsychotics*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of *[Epi 581] Atypical Antipsychotics*

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

8572. [Epi 581] T6. New users of haloperidol aged 18 to 64 years

Initial Event Cohort
People having any of the following:

- a drug exposure of *Haloperidol*
    - with age between 18 and 64 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *Haloperidol*
  where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics excl. Haloperidol*
  where event starts between 183 days Before and 0 days After index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of Any Drug
    - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Inclusion Rules
Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*

where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**
End Date Strategy
Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *Haloperidol*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *[Epi 581] Atypical Antipsychotics*

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

8176. [Epi 581] C1. New users of atypical antipsychotics age 18-64 without a recent dementia diagnosis

Initial Event Cohort
People having any of the following:

- a drug exposure of *[Epi 581] Atypical Antipsychotics*
    - with age between 18 and 64 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics* where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics* where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of Any Drug
    - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Inclusion Rules
Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*

  where event starts between 183 days Before and 1 days Before index start date

Inclusion Criteria #3: No dementia 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Dementia*

  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**
End Date Strategy
Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *[Epi 581] Atypical Antipsychotics*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of *[Epi 581] Typical Antipsychotics*

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

8175. [Epi 581] C2. New users of atypical antipsychotics aged 65 years and older

Initial Event Cohort
People having any of the following:

- a drug exposure of *[Epi 581] Atypical Antipsychotics*
  - with age >= 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Typical and atypical antipsychotics HCPCS codes*
  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**
Inclusion Rules
Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*

  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**
End Date Strategy
Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *[Epi 581] Atypical Antipsychotics*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of *[Epi 581] Typical Antipsychotics*

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

8573. [Epi 581] C3. New users of atypical antipsychotics age 18-64

Initial Event Cohort

People having any of the following:

- a drug exposure of *[Epi 581] Atypical Antipsychotics*
    - with age between 18 and 64 (inclusive)

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *[Epi 581] Atypical Antipsychotics*
  where event starts between 183 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of *[Epi 581] Typical Antipsychotics*
  where event starts between 183 days Before and 0 days Before index start date
- and exactly 0 occurrences of a drug exposure of Any Drug
    - Drug Source Concept is *[Epi 581] Typical and atypical antipsychotics HCPCS codes*

  where event starts between all days Before and all days After index start date

Limit cohort of initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: No stroke 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Stroke*

  where event starts between 183 days Before and 0 days Before index start date

Inclusion Criteria #2: No cancer 183 days prior
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *[Epi 581] Cancer*

  where event starts between 183 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *[Epi 581] Atypical Antipsychotics*

- allowing 30 days between exposures
- adding 30 days after exposure end

Censoring Events:

Exit Cohort based on the following:

- a drug exposure of *[Epi 581] Typical Antipsychotics*

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

Target Cohorts

Six of the exposure cohorts described in section 8.2.2.1 will be used as target cohorts (T):

T1. New users of typical antipsychotics aged 18 to 64 years without a recent dementia diagnosis
T2. New users of haloperidol aged 18 to 64 years without a recent dementia diagnosis
T3. New users of typical antipsychotics aged >= 65 years
T4. New users of haloperidol aged >= 65 years
T5. New users of typical antipsychotics aged 18 to 64 years
T6. New users of haloperidol aged 18 to 64 years

Comparator Cohorts

Three of the exposure cohorts described in section 8.2.2.1 will be used as comparator cohorts (C):

C1. New users of atypical antipsychotics aged 18-64 years without a recent dementia diagnosis
C2. New users of atypical antipsychotics aged >= 65 years
C3. New users of atypical antipsychotics aged 18-64 years

In total, 6 target cohorts (T)-comparator cohort (C) comparisons will be made for population-level effect estimation:

1. **T1**: New users of typical antipsychotics aged 18-64 without a recent dementia diagnosis vs. **C1**: New users of atypical antipsychotics aged 18-64 without a recent dementia diagnosis
2. **T2**: New users of haloperidol aged 18 to 64 years without a recent dementia diagnosis vs. **C1**: New users of atypical antipsychotics aged 18-64 years without a recent dementia diagnosis
3. **T3**: New users of typical antipsychotics aged >= 65 years vs. **C2**: New users of atypical antipsychotics aged >= 65 years
4. **T4**: New users of haloperidol aged >= 65 years vs. **C2**: New users of atypical antipsychotics aged >= 65 years
5. **T5:** New users of typical antipsychotics aged 18 to 64 years vs. **C3** New users of atypical antipsychotics aged 18-64 years
6. **T6:** New users of haloperidol aged 18 to 64 years vs. **C3** New users of atypical antipsychotics aged 18-64 years

Note that #1 and #2 were the main comparisons in the Sentinel report, #3 and #4 are our repetition of that approach in the population aged >= 65 (regardless of dementia status), as

evidence for or against including a warning in our label, #5 and #6 are intended to provide appropriate analogues to #3 and #4 in the broader context of ascertaining whether, across age groups, typical antipsychotics or haloperidol are associated with greater stroke risk than are atypical antipsychotics.

8.3. Variables

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. Two different propensity score models will be fit: a regularized logistic regression as described by Suchard(8) and a logistic regression fitted using the same variables as in the Sentinel report.

The baseline covariates used to replicate the Sentinel report's propensity score were the following observed between 183d and 1d prior to cohort index:

- Age group (5-year bands)
- Index year
- Gender
- Charlson Index - Romano adaptation, using conditions all time on or prior to cohort index
- Health service utilization
- Drug utilization
- Acute myocardial infarction
- Diabetes
- Heart failure
- Hypercholesterolemia
- Hypertension
- Kidney failure (acute or chronic)
- Obesity
- Transient ischemic attack
- Atrial fibrillation or atrial flutter
- Peripheral vascular disease
- Anxiety
- Bipolar disorder
- Depression
- Posttraumatic stress disorder
- Schizophrenia/psychotic disorder
- Substance abuse
- Use of angiotensin-converting -enzyme inhibitors
- Use of antiarrhythmics
- Use of beta blockers
- Use of statins
- Use of oral anticoagulants
- Use of non-oral anticoagulants
- Use of angiotensin receptor blockers

- Use of antiplatelets
- Use of diuretics

The baseline covariates used to fit the large-scale regularized regression model will be:

- Demographics
  - Gender
  - Age group (5-year bands)
  - Index year
  - Index month
- Condition occurrence record for the concept or any its descendants observed during 183d on or prior to cohort index
- Condition occurrence record for the concept or any its descendants observed during 30d on or prior to cohort index
- Drug exposure record for the concept or any its descendants observed during 183d on or prior to cohort index
- Drug exposure record for the concept or any its descendants observed during 30d on or prior to cohort index
- Procedure occurrence record for the concept or any its descendants observed during 183d on or prior to cohort index
- Procedure occurrence record for the concept or any its descendants observed during 30d on or prior to cohort index
- Measurement record for the verbatim concept observed during 183d on or prior to cohort index
- Measurement record for the verbatim concept observed during 30d on or prior to cohort index
- Charlson Index - Romano adaptation, using conditions all time on or prior to cohort index
- Diabetes Complications Severity Index
- $CHADS_2$ score
- CHA_2DS_2-VASc score
- Number of distinct conditions observed in 183d on or prior to cohort index (defined as unique SNOMED condition concepts)
- Number of distinct conditions observed in 30d on or prior to cohort index (defined as unique SNOMED condition concepts)
- Number of distinct drugs observed in 183d on or prior to cohort index (defined as unique RxNorm ingredient concepts)
- Number of distinct drugs observed in 30d on or prior to cohort index (defined as unique RxNorm ingredient concepts)
- Number of distinct procedures observed in 183d on or prior to cohort index (defined as unique CPT4/HCPCS/ICD9P/ICD10P concepts)
- Number of distinct procedures observed in 30d on or prior to cohort index (defined as unique CPT4/HCPCS/ICD9P/ICD10P concepts)
- Number of distinct observations observed in 183d on or prior to cohort index
- Number of distinct observations observed in 30d on or prior to cohort index
- Number of distinct measurements observed in 183d on or prior to cohort index (defined as unique LOINC concepts)
- Number of distinct measurements observed in 30d on or prior to cohort index (defined as unique LOINC concepts)

- Number of visits observed in 183d on or prior to cohort index
- Number of visits observed in 30d on or prior to cohort index
- Number of inpatient visits observed in 183d on or prior to cohort index
- Number of inpatient visits observed in 30d on or prior to cohort index
- Number of ER visits observed in 183d on or prior to cohort index
- Number of ER visits observed in 30d on or prior to cohort index

Specific drug exposure concepts that define the target and comparator cohorts will be excluded from the propensity score model fitting but will be used for clinical characterization. No missing data imputation will be implemented. If a medical record does not exist in the database, it is assumed that the patient does not have that disease or condition. This large-scale empirical adjustment strategy should address expected confounders, including demographics, prior cardiovascular risk factors, schizophrenia diagnosis, and health service utilization behavior. The study will be subject to the limitation that some confounders may be unmeasured or inadequately represented in US claims data, including weight, smoking status, and lifestyle behaviors, such as diet and exercise.

8.3.1. Therapy

8.3.1.1. Primary Therapy

N/A

8.3.1.2. Secondary Therapy

N/A

8.3.2. Evaluation of Safety

Adverse Drug Reactions

N/A see section 10

8.3.3. Evaluation of Effectiveness/Clinical Response

Effectiveness/Clinical Response

N/A

Patient-Reported Outcomes

N/A

Effectiveness/Clinical Response Variables

Primary Endpoint(s)

The human-readable textual description of the outcome definition is listed above in section 8.2.2.1, and the listing of concepts and associated source codes for each concept-set in italics is provided in Annex 1. The complete specification for the cohort definition, including

human readable textual description, listing of all included concepts and associated source codes, and computer-executable SQL, has been generated using the OHDSI open-source analytics tool, ATLAS. The hyperlinks below are available internally within JNJ. In the following cohort definitions please note that here, "event" is used to refer to an outcome event, without consideration of exposure status.

The primary safety endpoint is defined as the following:

O1: Stroke as a Principal Inpatient Diagnosis

Complete Specification:

Initial Event Cohort

People having any of the following:

- a condition occurrence of *stroke_ICD10Update*
    - Condition type is any of Inpatient detail - primary, Inpatient header - primary, Primary Condition
    - Visit occurrence is any of: Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date
limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

Outcomes are first defined independently of exposure and then associated with the target and comparator cohorts during analysis.

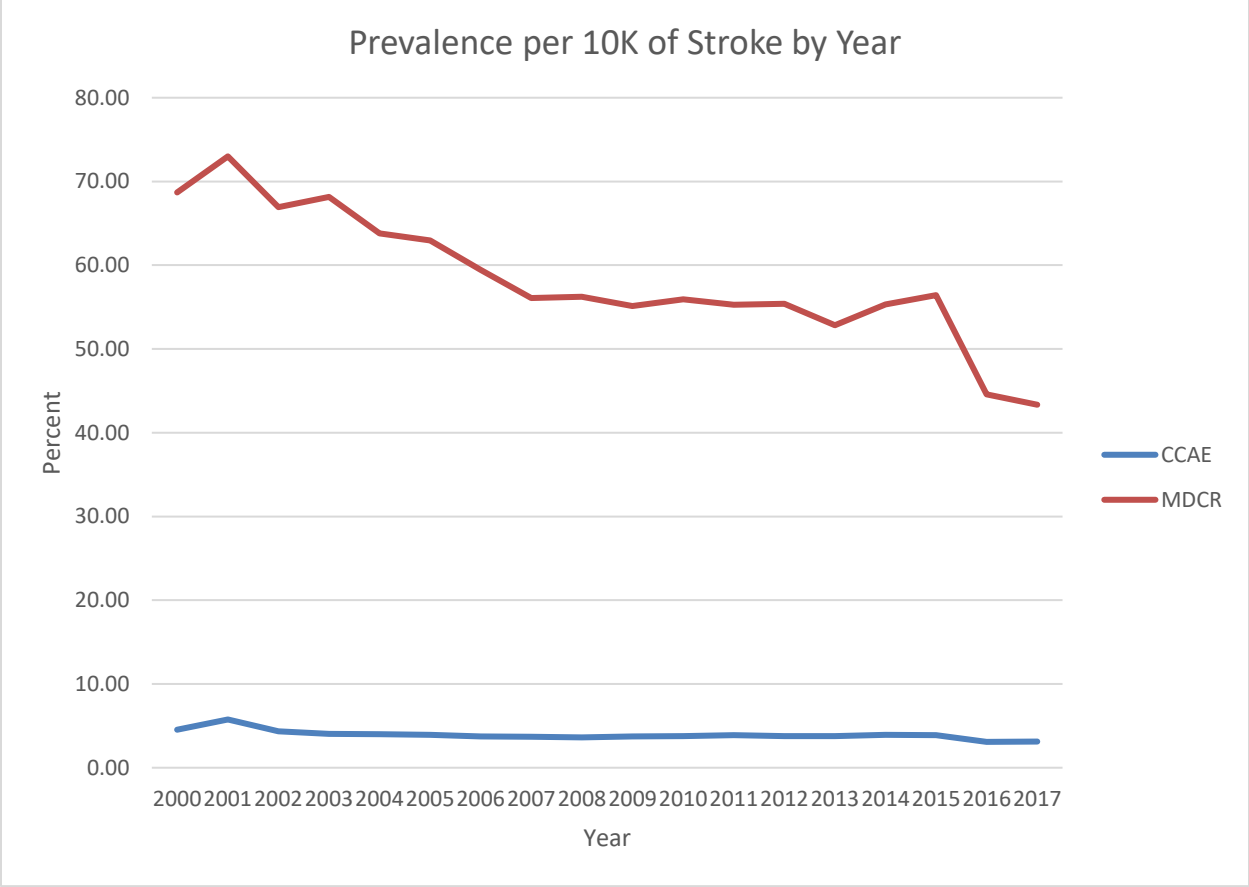
The above definition includes both ICD9CM codes and ICD10CM codes to identify patients with stroke. Since this study covers data from the year 2000 through the year 2017, it includes data both prior to and after the switch to sole use of ICD10CM coding practices in the U.S, which occurred on 01-Oct-2015. One concern around this switch was the ability of the outcome definition to accurately identify patients who experienced strokes after that date. Below, table 1 shows a decline over the study period in the rate per 10,000 people of patients with stroke by database and year and figure 1 represents that information graphically. In each of the two databases CCAE and MDCR, there is a dip between 2015 and 2016 in stroke risk, from 3.88 per 10K to 3.09 per 10K and from 56.41 to 44.59 per 10K, respectively. This dip is likely to be a mix of the overall downward trend during the study period and an artifact of coding system shift. The latter does not appear to be large enough to require a change to the definition.

Table 1: Number and Percent of Patients with Stroke by Year

	CCAE			MDCR		
Year Cohort Entry	**Number of Subjects With Stroke**	**Total Patients Contributing Time**	**Rate of Stroke per 10K People**	**Number of Subjects With Stroke**	**Total Patients Contributing Time**	**Rate of Stroke per 10K People**
2000	1,460	3,216,791	4.54	3,387	493,220	68.67
2001	3,016	5,233,589	5.76	7,398	1,013,499	72.99
2002	4,290	9,841,132	4.36	8,797	1,314,125	66.94
2003	6,185	15,343,831	4.03	14,757	2,165,424	68.15
2004	7,606	18,933,004	4.02	16,872	2,645,183	63.78
2005	8,337	21,195,662	3.93	18,326	2,910,198	62.97
2006	8,470	22,553,771	3.76	13,497	2,271,073	59.43
2007	8,929	24,191,867	3.69	13,051	2,327,102	56.08
2008	10,357	28,511,214	3.63	13,676	2,431,757	56.24
2009	12,088	32,462,939	3.72	14,318	2,597,712	55.12
2010	13,244	34,987,693	3.79	16,178	2,893,170	55.92
2011	15,487	39,954,916	3.88	19,100	3,456,068	55.27
2012	15,528	41,153,109	3.77	17,279	3,118,698	55.40

2013	13,023	34,366,245	3.79	17,489	3,310,460	52.83
2014	14,115	36,027,524	3.92	15,230	2,752,415	55.33
2015	10,287	26,535,188	3.88	11,779	2,088,213	56.41
2016	8,095	26,215,027	3.09	8,910	1,998,050	44.59
2017	7,753	24,842,599	3.12	6,980	1,610,420	43.34

Figure 1: Time Series Showing the Prevalence per 10K of Patients with Stroke by Year



Negative Control Outcomes

Negative control outcomes, outcomes known not to be causally associated with any of the exposure cohorts (6), are to be used for empirical calibration (7). Evidence comes from the Common Evidence Model (CEM). The evidence base is comprised of evidence found in

published literature, product labels and spontaneous reports. Use the evidence sources below to find out what evidence has been associated to the concepts included in this concept set. The same analysis performed for each target-comparator-outcome combination will also be performed for each negative control outcome. Because of the a priori assertion of no effect, we assume the true relative risk for each negative control outcome is 1, and the difference between RR=1 and the observed effect estimate will be classified as error. The sample of negative controls will therefore be used to construct an empirical distribution of the error distribution, which will be used to calibrate the p-values from the unknown outcomes of interest. Analyses performed for negative control outcomes should not be considered formal hypothesis tests and should not be included in any multiplicity adjustment. The negative control outcomes used in this study are listed in the table below:

Table 2: Negative Control Outcomes

Concept ID	Concept Name
443585	Abrasion and/or friction burn of multiple sites
318222	Acute lymphadenitis
4155909	Anesthesia of skin
132736	Bacteremia
374367	Bilateral hearing loss
4216972	Bursitis of hip
4344258	Bursitis of shoulder
4213540	Cervical somatic dysfunction
140842	Changes in skin texture
372925	Cholesteatoma
4068241	Chronic instability of knee
196454	Colostomy and enterostomy malfunction
46269889	Complication due to Crohn's disease
377888	Conductive hearing loss
437366	Contracture of tendon sheath
4022071	Convalescence
42873170	Dependence on supplemental oxygen
40481547	Dependence on ventilator
434887	Disorders of bilirubin excretion
198846	Enthesopathy of hip region
374801	Foreign body in ear
438111	Hematologic neoplasm of uncertain behavior

79864	Hematuria syndrome
197911	Hernia of anterior abdominal wall without obstruction AND without gangrene
440021	Herpes simplex without complication
440329	Herpes zoster without complication
435511	Hypercalcemia
4295287	Hypercoagulability state
440072	Hypogammaglobulinemia
40481385	Imaging of abdomen abnormal
40484908	Imaging of brain abnormal
374375	Impacted cerumen
4344500	Impingement syndrome of shoulder region
440276	Infection AND/OR inflammatory reaction due to internal prosthetic device, implant AND/OR graft
139099	Ingrowing nail
4288544	Inguinal hernia
4168222	Intra-abdominal and pelvic swelling, mass and lump
4168681	Irritability and anger
74052	Labyrinthitis
133088	Late amputation stump complication
434814	Late effect of medical and surgical care complication
435516	Lipoprotein deficiency disorder
443600	Localized infection of skin AND/OR subcutaneous tissue
4166126	Localized swelling, mass and lump, trunk
44783760	Mammographic calcification of breast
439082	Menopausal syndrome
441536	Mixed acid-base balance disorder
137967	Muscle, ligament and fascia disorders
43530648	New daily persistent headache
40480893	Nonspecific tuberculin test reaction
4194981	Pain due to any device, implant AND/OR graft
4091513	Passing flatus
375292	Perforation of tympanic membrane
78162	Peripheral vertigo
437092	Physiological development failure
46286594	Problem related to lifestyle
4049367	Psychologic conversion disorder
436246	Reduced libido
138845	Rheumatism

36713918	Somatic dysfunction of lumbar region
77079	Spinal stenosis
4008710	Stenosis due to any device, implant AND/OR graft
440233	Strain of supraspinatus muscle AND/OR tendon
199065	Stricture of ureter
374053	Sudden hearing loss
376382	Tension-type headache
193251	Umbilical hernia without obstruction AND without gangrene
4094742	Unstable knee
201916	Ureteric stone
79873	Urolith
133327	Viremia
439981	Wound dehiscence
435723	Wound seroma
440193	Wristdrop

For each negative control outcome, events will be defined as follows:

Initial Event Cohort
People having any of the following:

- a condition occurrence of <*negative control outcome*>

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Date Offset Exit Criteria
This cohort definition end date will be the index event's start date plus 0 days

Positive Control Outcomes

In addition to negative control outcomes, we will also include synthetic positive control outcomes. These are outcomes based on the real negative controls, but where the true effect size is artificially increased to a desired effect size by injection of additional, simulated outcomes. To preserve confounding, these additional outcomes are sampled from predicted probabilities generated using a fitted predictive model. For each negative control outcome, three positive control outcomes will be generated with true relative risk is 1.5, 2, and 4, respectively. Using both negative and positive controls, we will fit a systematic error model and perform confidence interval calibration.

Other Variables of Interest

See section 8.3

8.3.4. Medical Resource Utilization and Health Economics

N/A

8.3.5. Sample Collection and Handling

N/A

8.4. Data Sources

This study will be conducted in two observational health databases:

- IBM MarketScan® Commercial Database (CCAE)
- IBM MarketScan® Medicare Supplemental Database (MDCR)

Based on all available data, i.e., from Jan 1, 2002 through Dec 31, 2017

Each analysis will be done in the database that corresponds to the age range examined in that analysis to produce one database specific result for each analysis. For example, all analyses performed in the 18-64 year old population will be done in CCAE and all analyses performed in the population greater than 64 years old will be done in MDCR. A small proportion of patients do transition from CCAE to MDCR when they retire from their employer and purchase supplemental Medicare insurance, but in these cases, the patients would not be duplicated at the same period of time, but rather their person time would be split between the two databases.

Each database is described below:

IBM MarketScan® Commercial Database (CCAE) Version 870

The IBM MarketScan® Commercial Database (CCAE) is a medical and drug insurance claims database that include active employees, early retirees, COBRA continuers, and their dependents insured by employer-sponsored plans. The database contains inpatient admission records, outpatient services, prescription drugs, populations, eligibility status, and costs of services. This administrative claims database includes a variety of fee-for-service, preferred provider organizations, and capitated health plans.

As of 5 December 2018 (data lock on version CDM_IBM_CCAE_v813), the latest available version of CCAE contains more than 142 million patients with observations from January 2000 through August 2018. The major data elements contained within this database that will be used within this analysis include: outpatient pharmacy dispensing claims – which provide dispensing date, National Drug Code (NDC) to identify the prescription product, days' supply, and quantity; inpatient and outpatient medical claims – which provide service date, procedure codes (coded in CPT-4, HCPCS, ICD-9-CM or ICD-10-PCS), and diagnosis codes (coded in ICD-9-CM or ICD-10-CM); and enrollment records – which
provide the dates of insurance eligibility, as well as year of birth and sex. The database does contain selected laboratory test results (those sent to a contracted third-party laboratory service provider) for a non-random sample of the population, but this data will not be used within these analyses. As an administrative claims database, records exist for each reimbursement transaction, such that it is possible for the database to document multiple drugs, diagnoses, and procedures during inpatient and outpatient medical services for a given person over time,

during the enrollment period. Claims submitted using the CMS-1500 form are limited to 12 diagnoses per claim. A person may experience
discontinuation in their eligibility and the database may contain observations during multiple discontinuous periods of time for a given individual.

The following limitations of IBM CCAE should be noted:

- The commercially insured patients represent a higher socioeconomic status than the overall US population.
- Data are based on financial claims filed for reimbursement; disease coding may reflect financial incentives for reimbursement rather than clinically and systematically verified definitions.
- Prescriptions are those filled at outpatient pharmacies, not those prescribed or administered within inpatient services. The extent to which prescribed records went unfulfilled is not known. It is also not known whether medications were actually taken as directed, although repeated dispensing of the same drug would suggest that this is the case.

IBM MarketScan® Medicare Supplemental Database (MDCR) Version 871

MDCR is an administrative health claims database for Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans (predominantly fee-for-service plans). Only plans where both the Medicare-paid amounts and the employer-paid amounts were available and evident on the claims were selected for this database. MDCR captures person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug. It also includes results for outpatient lab tests processed by large national lab vendors.

As of 5 December 2018 (data lock on version CDM_IBM_MDCR_v871), the latest available version of MDCR contains more than 10 million patients with observations from January 2000 through August 2018. The major data elements contained within this database that will be used within this analysis include: outpatient pharmacy dispensing claims – which provide dispensing date, National Drug Code (NDC) to identify the prescription product, days' supply, and quantity; inpatient and outpatient medical claims – which provide service date, procedure codes (coded in CPT-4, HCPCS, ICD-9-CM or ICD-10-PCS), and diagnosis codes (coded in ICD-9-CM or ICD-10-CM); and enrollment records – which
provide the dates of insurance eligibility, as well as year of birth and sex. The database does contain selected laboratory test results (those sent to a contracted third-party laboratory service provider) for a non-random sample of the population, but this data will not be used within these analyses. As an administrative claims database, records exist for each reimbursement transaction, such that it is possible for the database to document multiple drugs, diagnoses, and procedures during inpatient and outpatient medical services for a given person over time, during the enrollment period. Claims submitted using the CMS-1500 form are limited to 12 diagnoses per claim. A person may experience
discontinuation in their eligibility and the database may contain observations during multiple discontinuous periods of time for a given individual.

The following limitations of IBM MDCR should be noted:

- The commercially insured patients represent a higher socioeconomic status than the overall Medicare population.
- Exact birth date is not available, only year of birth.
- Data based on financial claims filed for reimbursement, disease coding may reflect financial incentives for reimbursement rather than clinically and systematically verified definitions.
- Prescriptions are those filled, not those prescribed. We do not know the universe of prescribed records that went unfulfilled.

Both databases have been standardized into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM),[a] which includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts and enables consistent application of analyses across multiple disparate data sources (2, 3). Complete specifications for the extract, transform,
and load (ETL) process for each database is available at: https://github.com/OHDSI/ETL-CDMBuilder.

The standardized vocabularies within OMOP CDM enable disparate source codes to be mapped into a common referent standard for each clinical domain, such as conditions, drugs, and procedures. As an example that is of particular relevance for this analysis, the standard vocabulary for conditions is SNOMED-CT and source vocabularies that have been mapped into SNOMED-CT include both ICD-9-CM and ICD-10-CM. In the US, with the transition of diagnosis recording from ICD-9-CM to ICD-10-CM occurring in October 2015, the use of OMOP standardized vocabularies is quite valuable because it means a common definition for exposures, outcomes, and covariates can be applied to all data, both pre- and post-October 2015 using SNOMED concepts instead of ICD-9-CM or ICD-10-CM codes. The source codes that map to all standard concepts are provided in Annex 1, and the full OMOP standard vocabulary is available for download at: http://athena.ohdsi.org/.

8.5. Study Size

The sample size of the cohorts is listed below. These patient counts represent the initial population, prior to statistical adjustment, so provide an upper bound of exposure available for each analysis.

Table 3: Initial cohort sizes

Cohort Definition Name	***Database***	***Num. Persons***
T1*. New users of typical antipsychotics aged 18 to 64 years without a recent dementia diagnosis*	**CCAE**	104,205
T2*. New users of haloperidol aged 18 to 64 years without a recent dementia diagnosis*	**CCAE**	54,987
T3*. New users of typical antipsychotics aged >= 65 years*	**MDCR**	43,711

[a] https://github.com/OHDSI/CommonDataModel

***T4**. New users of haloperidol aged >= 65 years*	**MDCR**	29,780
***T5**. New users of typical antipsychotics aged 18 to 64 years*	**CCAE**	105,061
***T6**. New users of haloperidol aged 18 to 64 years*	**CCAE**	55,628
***C1**. New users of atypical antipsychotics aged 18-64 years without a recent dementia diagnosis*	**CCAE**	967,283
***C2**. New users of atypical antipsychotics aged >= 65 years*	**MDCR**	232,353
***C3**. New users of atypical antipsychotics aged 18-64 years*	**CCAE**	990,689

For the descriptive analyses as part of clinical characterization, these cohorts should provide sufficient sample to adequately summarize and compare baseline characteristics within the cohorts.

For population-level effect estimation, where our aim is to produce an unbiased estimate of the average treatment effect, the precision we will achieve will vary by the incidence rate of each outcome. Because our focus is to estimate the magnitude of the effect, it is acceptable to be underpowered for the analyses, recognizing that this will manifest as wider confidence intervals that account for the random sampling error inherent to the analysis. Smaller sample size for specific comparisons may limit the internal study validity of estimates. Small samples may also limit the ability to fit adequate propensity models and thus limit our ability to control confounding. In comparison to the sentinel report, these sample sizes are larger.

8.6. Data Management

Raw data is stored securely within the Amazon Web Services (AWS) Simple Storage Service (S3) and encrypted in both transit and at rest. Transformed data is stored in AWS Redshift. AWS manages a comprehensive controlled environment for each of their service offerings which comply with various IT security standards including ISO 9001/ISO 27001. The services are run within a Virtual Private Cloud (VPC) that restricts database access to Johnson & Johnson network users with specific authorization. Details of the AWS security are available here: https://d0.awsstatic.com/whitepapers/aws-security-whitepaper.pdf.

In addition to data storage access is controlled leveraging Johnson & Johnson Identity Management Services (IDMS) which restricts access to the rHEALTH analytics platform. Each data set is further restricted by individual user. To obtain access users must agree to standard platform guidelines and if provisioned can be required to attest to data-specific usage requirements. Each request for data access is reviewed by a data set owner (or their designated backup) at which time the request can either be 'Approved' or 'Rejected'. Once approved, access is granted in an automated manner at the top of each hour.

All requests for access are tracked, along with connections and queries to/against the data set. User passwords are rotated every 90 days.

Processes are in place to enable users to complete analysis directly within the environment limiting the need to remove data from the system. rHEALTH provides services such as an RStudio Server and SAS Enterprise Server in an effort to decrease the removal of data from rHEALTH. In scenarios where data analysis cannot be completed directly in Redshift, processes are in place to enable compliant/secure sharing of this data with non-J&J third parties, should the data provider and J&J business owner want to enable this feature.

8.7. Data Analysis

See section 8.1.2

8.7.1. Patient Stratification

Patients will be stratified by age (18-64 and >=65). Additionally, analyses were conducted with and without the restriction of no recent dementia diagnosis.

8.7.2. Main Summary Measures

Cohort characterization: this type of descriptive analyses is intended to provide a characterization of the baseline covariates. Baseline variables include demographics (age, gender, index year), as well as conditions, drugs, procedures, and measurements observed during the 183d on or prior to exposure, as listed in section 8.3. Cohort characterization will be performed on all 9 exposure cohorts, as listed in section 8.2.2.1.

Cohort comparison: this type of descriptive analysis provides an explicit head-to-head comparison between two cohorts of baseline covariates, using standardized difference as a metric to compare individual factors. Covariates with standardized difference > 10% will be highlighted as potential imbalanced confounding factors. Cohort characterization will be performed for all 6 target-comparator comparisons, as listed in section 8.2.2.

Incidence (rates and proportions) will be computed for the outcome across all 6 target cohorts and all three comparator cohorts. The number of persons and person-years-at-risk for each exposure-outcome-database combination will be provided, along with the number of events during the time-at-risk periods. Incidence summary will be stratified by gender and schizophrenia diagnosis.

As distinct from the incidence rate ratios, all clinical characterization analyses involve direct observation of the experience of patients, which can provide context about the real-world patterns of utilization in different populations, but cannot be used for causal inference or to draw comparative conclusions about the effects of any treatment.

8.7.2.1. Safety Analyses

Adverse Events

N/A See section 10

Other Safety Parameters (eg, clinical laboratory tests, ECG parameters, vital signs)

N/A

8.7.2.2. Analysis of Effectiveness/Clinical Response

N/A

8.7.3. Main Statistical Methods

Population-level effect estimation: this type of analysis attempts to provide an unbiased estimate of the average treatment effect of an exposure on an outcome. These questions using a comparative cohort design take the following form: We will compare <insert target cohort here> with <insert comparator cohort here> for the <Cox proportional model hazard ratio> of <stroke> in the <on treatment with censoring at switch time-at-risk>.

For each of the 6 comparisons listed in section 8.2.2, we will perform an effect estimation analysis the outcome listed in section 8.3.3. Therefore, the total analyses per database will be 6 comparisons * 1 outcomes * 1 database * 3 propensity score approaches {Sentinel approach, large-scale regularized regression approach, none} = 18 target-comparator-outcome combinations. (For consistency with the Sentinel report, we will include the crude comparisons, so the total will be 18 target-comparator-outcome combinations.)

For each target-comparator combination, we will use a collection of negative control outcomes, as listed in section 8.3.3, as a diagnostic tool to quantify residual bias and empirically calibrate statistics generated during the analysis.

In this study, we compare the target cohorts with the comparator cohorts as specified in section 8.2.2 for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model.

For both cohorts, we impose a requirement that patients must have at least 1 day of continuous observation after the time-at-risk start, 1 day from the cohort start date.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window, 1 day from cohort
start date, until the earliest event among 1) occurrence of the outcome post-index before (<=) 0 days from cohort end date, 2) the end of the time-at-risk window, 0 days from cohort end date, and
3) the end of the observation period that spans the time-at-risk start. The diagrams below show how the time-at-risk will be calculated:

Figure 2: Cohort end date as the end of the persistent period of exposure

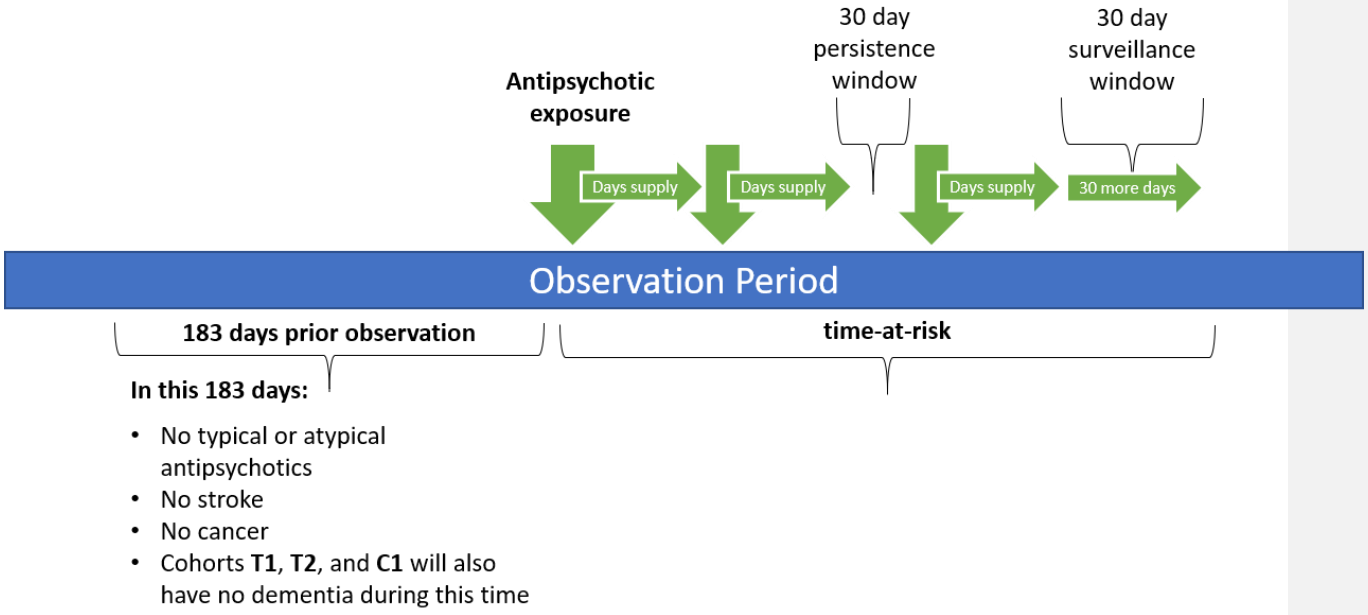


Figure 3: Patient has outcome of interest

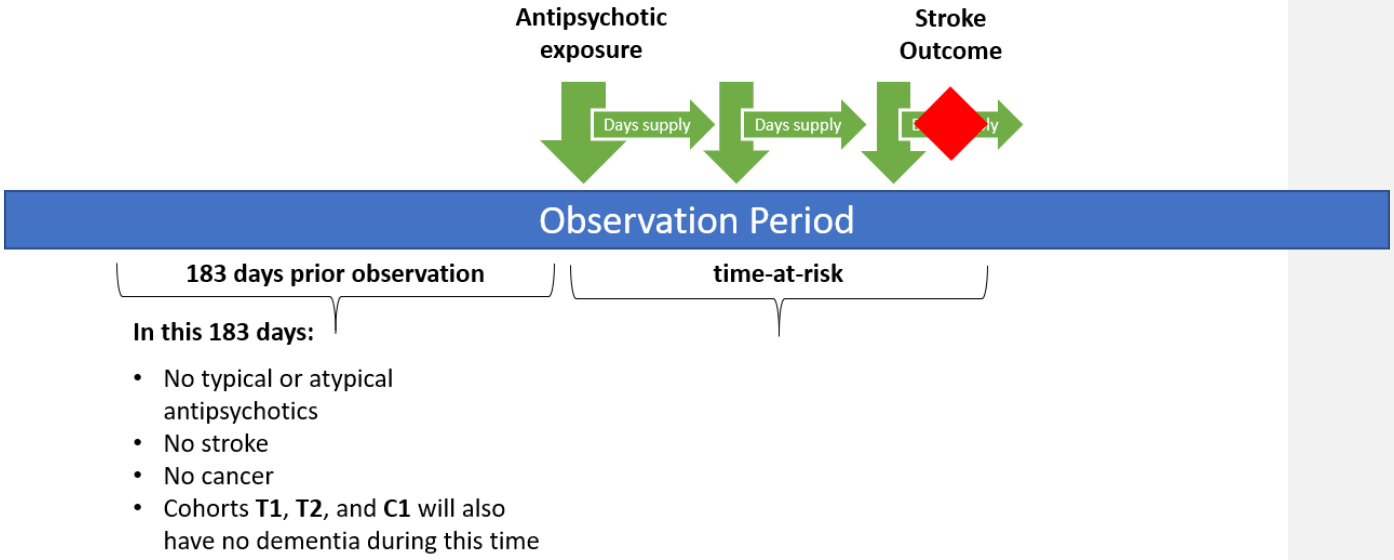


Figure 4: Cohort end date as the end of observation period

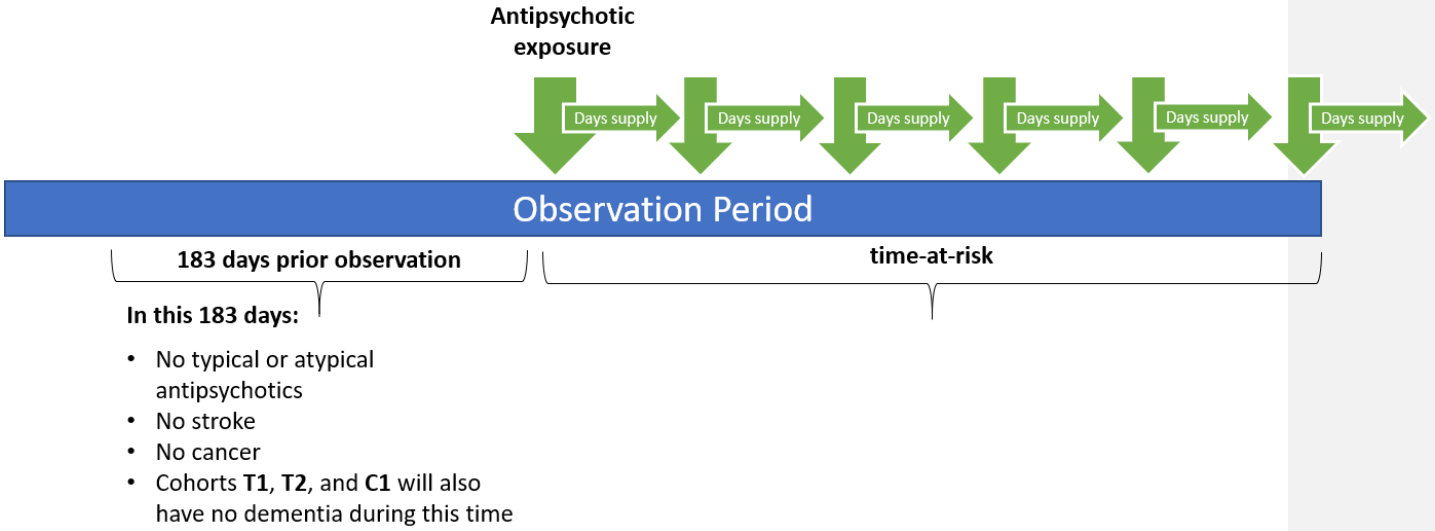
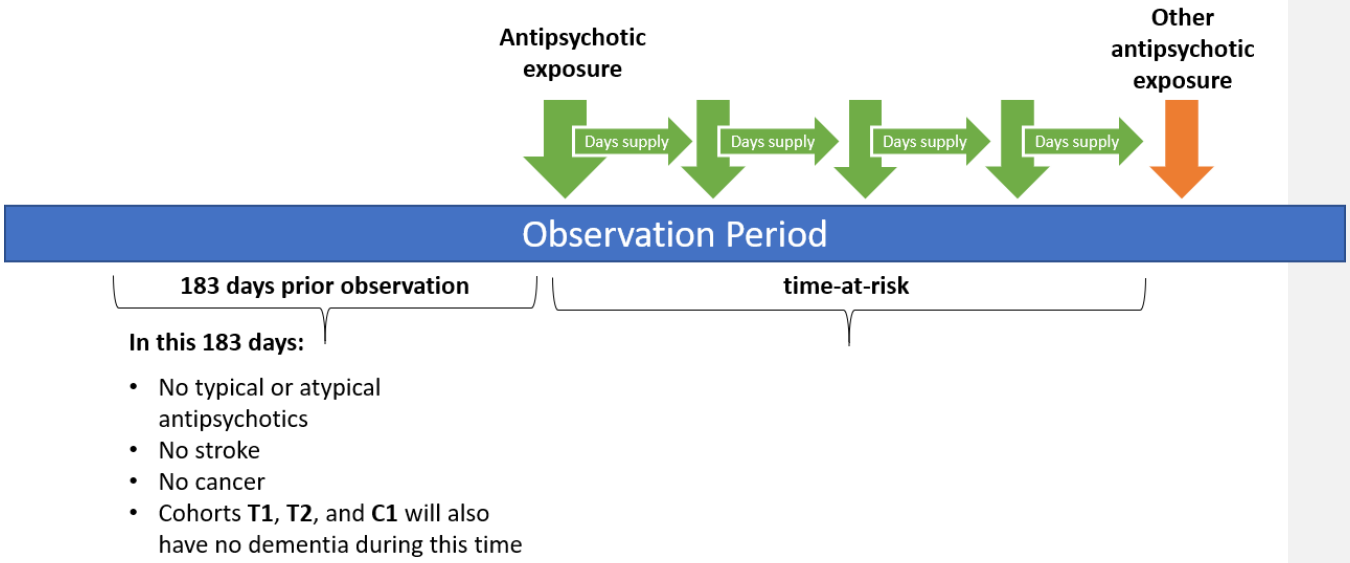


Figure 5: Cohort end date as the date of dispensing of comparator antipsychotic type (e.g. if index exposure is a typical antipsychotic a dispensing of an atypical antipsychotic will end the patient's time-at-risk)



Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity

score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. In this study, three approaches will be used to calculate propensity scores:

1. **Sentinel propensity score replication:** a propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model. Covariates to be used in the propensity score model are listed in section 8.3, as was applied in the Sentinel study. The target and comparator cohorts will be matched using variable ratio matching on the propensity using a caliper of 0.05 on the propensity score scale, with a maximum ratio of 1.

2. **Large-scale regularized regression model:** a propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e -7 (9). Covariates to be used in the propensity score model are listed in section 8.3, as was applied in prior studies (10). Typically, the regression model includes more than 10,000 variables, which are systematically coded (prior to any comparative analyses) based on the OMOP Common Data Model and applied consistently in our studies using regularized logistic regression models to calculate the exposure propensity scores. The propensity score will be estimated only once for each person in each cohort of a pairwise comparison. The target cohort and comparator cohorts will be matched using variable ratio matching on the propensity using a caliper of 0.2 times the standard deviation of the logit of the propensity score distribution, with a maximum ratio of 10. Four concepts will be excluded from the large-scale regularized regression model. These include:

    i. 21600490 – Antiemetics and Antinauseants
    ii. 21600491 – Antiemetics and Antinauseants
    iii. 21600492 - Serotonin (5HT3) antagonists
    iv. 10000560 – Ondansetron

    The above concepts are excluded because they are highly correlated with use of haloperidol for end of life care.

3. In addition, a third approach will be applied whereby no propensity scores are calculated and no matching or outcome adjustments are made. This is referred to as the **unadjusted approach**.

Output and Evaluation

Covariate balance will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score models are fit, we will plot the propensity score distributions of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The area under the Receiver Operating Characteristic (ROC) curve (AUC) will be reported. The

covariates selected within the propensity score model, with associated coefficients will also be reported.

A plot showing the propensity score distributions for both cohorts before and after matching will be provided. Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before propensity score stratification against the standardized mean difference for each covariate after propensity score stratification.

An attrition diagram will be provided to detail the loss of patients from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied.

For the Sentinel replication the final outcome model will be an unconditional Cox proportional hazards model, summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

For the analysis utilizing the large-scale regularized regression model the final outcome model will be a conditional Cox proportional hazards model, summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

Evidence Evaluation
For population-level effect estimation analyses:

Within each target-comparator-outcome-propensity score approach combination, we will execute diagnostics to determine if the analysis can be appropriately conducted. However, in the interest of replicating the Sentinel results and extending them to age >= 65 years, the first two analyses below will be completed even if the diagnostics suggest that they cannot be appropriately conducted.

For the unadjusted approach the diagnostics will include:

- Cohort characterization for target and comparator

For the Sentinel replication propensity score approach the diagnostics will include:

- Cohort characterization for target and comparator
- Propensity score distribution
- Covariate balance before and after PS matching
- Empirical null distribution

For the large-scale regularized regression approach the diagnostics will include:

- Cohort characterization for target and comparator
- Propensity score distribution

- Covariate balance before and after PS matching
- Empirical null distribution

For the large-scale regularized regression approach, analysis of negative control outcomes will be used to evaluate the potential impact of residual systematic error in the study design and to facilitate empirical calibration of the effect measure, confindence interval, and p-value for the outcomes of interest. Negative control outcomes are conditions known not to be associated with either the target or comparator exposures, such that we assume the true relative risk should equal 1. For each negative control outcome, the study design described above will be implemented and the effect estimate will be recorded. Further, we leveraged the negative control outcomes to generate synthetic positive control outcomes of known effect sizes by injecting simulated outcomes by a survival process during the target and comparator time-at-risk periods. The distribution of effect estimates across all negative and positive control outcomes will be used to fit an empirical null distribution which models the observed residual systematic error and the study design. The null distribution is used to compute HRs and confidence intervals (CIs) calibrated to reflect the observed residual error of the analysis. Empirical calibration serves as an important diagnostic tool to evaluate if the residual systematic error is sufficient to cast doubt on the accuracy of the unknown effect estimate. The calibration effect plot and calibration probability plots will be generated for review. We will report the numerical values of the risk estimates, CIs, and traditional p-values, and empirically calibrated risk estimates, CIs, and p-value for the outcome of interest.

8.7.4. Missing Values

Missing values are considered non-existent. Meaning if a patient does not have a value it is assumed they do not have the diagnosis, condition, procedure, etc.

8.7.5. Sensitivity Analyses

N/A

8.7.6. Interim Analysis

N/A

8.8. Quality Control

In order to make sure that the written program conforms to the specifications detailed in this document two analysts are assigned to the study. One analyst writes the program initially and the second analyst investigates the program against the protocol document. This method ensures that all logic is fully accounted for and correctly implemented.

8.9. Limitations of the Research Methods

- Causality between drug exposure and any given event cannot be drawn for individual cases
- Socioeconomic variables (such as race/ethnicity, education, income), behavioral variables (such as diet, alcohol consumption, eating disorders) are not available or may not be

completely captured from these databases, which will lower the validity for outcome identification, risk factor/confounding adjustment, or causal interpretation.

- Free drug samples are not captured in insurance claims databases, which may result in misclassification of some exposure as non-exposure, prevalent drug use as new use (potentially missing incident events or incident events following exposure misclassified as historical events). Although some Health Maintenance Organizations (HMOs) forbid direct access to sales representatives and therefore may not have the free-sample issue, sensitivity analyses are not done due to limited sample size and changing of insurance over time.
- Adjustment by propensity score may not completely remove confounding bias (11)

9. PROTECTION OF HUMAN SUBJECTS

The use of the IBM MarketScan databases were reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research. In addition, this study is also confined to the following facts: (i) the study is using only de-identified data, (ii) that confidentiality of patient records will be maintained at all times and (iii) that identification of individual patients or physicians is not possible.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports. The study results will be assessed for medically important results.

10.1. Definitions and Classifications

10.1.1. Adverse Event Definitions

N/A

10.1.2. Attribution Definitions

N/A

10.1.3. Severity Criteria

N/A

10.2. Special Situations

N/A

10.3. Procedures

N/A

10.3.1. Retrospective Study Period

N/A

10.3.1.1. Adverse Drug Reactions

N/A

10.3.1.2. Pregnancy

N/A

10.3.2. Prospective Study Period

10.3.2.1. All Adverse Events

N/A

10.3.2.2. Serious Adverse Events

N/A

10.3.2.3. Pregnancy

N/A

10.3.3. Product Quality Complaints

N/A

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The protocol will be registered at www.clinicaltrials.gov after finalization. Results will be reported to the FDA. Additionally, results will be submitted for peer-reviewed publication.

12. REFERENCES

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ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Standalone Documents

Title	Reference No	Date
List of variable definitions and code sets for variables included in the protocol	1	
Sentinel reference reports	2	

Annex 1.2: Information to be Provided to Investigators

N/A

Annex 1.3: Regulatory Documentation

N/A

Annex 1.4: Ethics Compliance

Independent Ethics Committee or Institutional Review Board

N/A See section 9

Annex 1.5: Patient Consent

N/A See section 9

Annex 1.6: Patient Identification and Enrollment

N/A See section 9

Annex 1.7: Patient Data Protection

N/A See section 9

Annex 1.8: Case Report Form Completion

N/A

Annex 1.9: Monitoring

N/A

Annex 1.10: On-Site Audits

N/A

Annex 1.11: Record Retention

N/A

Annex 1.12: Study Completion/Termination

N/A

Annex 1.13: Use of Information and Publication

All information, including but not limited to information regarding [DRUG] or the sponsor's operations (eg, patent applications, formulas, manufacturing processes, basic scientific data, prior

clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information obtained in the study will be used by the sponsor in connection with the continued development of [DRUG], and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information obtained to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish the primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish data specific to the associated participating site after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	22, Is haloperidol associated with an increased risk of stroke…
1.1.2 The objectives of the study?	☒	☐	☐	22, The primary objective of this study…
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	22, to patients aged 65 and older regardless of dementia status…
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	23, To compare the risk of stroke in each of the target cohorts..
1.2.3 if applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☒	☐	☐	29, section 8.2.2
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	54, section 8.4
2.2.2 Age and sex?	☒	☐	☐	29, section 8.2.2
2.2.3 Country of origin?	☒	☐	☐	54, section 8.4
2.2.4 Disease/indication?	☒	☐	☐	29, section 8.2.2
2.2.5 Co-morbidity?	☒	☐	☐	45, section 8.3
2.2.6 Seasonality?	☐	☒	☐	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	29, section 8.2.2

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	50, section 8.3.3
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	61, section 8.7.3
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	61, section 8.7.3
3.4 Is sample size considered?	☒	☐	☐	57, section 8.5
3.5 Is statistical power calculated?	☐	☐	☒	Section 8.5

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				54, section 8.4
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	
4.1.3 Covariates?	☒	☐	☐	
4.2 Does the protocol describe the information available from the data source(s) on:				54, section 8.4
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	54, section 8.4
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	50, section 8.3.3
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	67, section 8.7.3, negative control outcomes will be used to evaluate the potential impact of residual systematic error…
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	28, section 8.2.2.1
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	50, section 8.3.3
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	67, section 8.7.3, negative control outcomes will be used to evaluate the potential impact of residual systematic error…

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address: 7.1.1 Selection biases?	☒	☐	☐	67, section 8.7.3, negative control outcomes will be used to evaluate the potential impact of residual systematic error…
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	Section 8.7.3 In this study, three approaches…
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	
7.4 Does the protocol address other limitations?	☒	☐	☐	68, section 8.9

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	60 Incidence (rates and proportions) will
8.2 Is the choice of statistical techniques described?	☒	☐	☐	62 Population-level effect estimation:
8.3 Are descriptive analyses included?	☒	☐	☐	60 Cohort characterization
8.4 Are stratified analyses included?	☒	☐	☐	60 Patients will be stratified by age
8.5 Does the plan describe the methods for identifying:				45 Propensity scores will be used - 47
8.5.1 Confounders?	☒	☐	☐	
8.5.2 Effect modifiers?	☐	☒	☐	
8.6 Does the plan describe how the analysis will address:				45 Propensity scores will be used – 47
8.6.1 Confounding?	☒	☐	☐	
8.6.2 Effect modification?	☐	☒	☐	

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Section 8.6
9.2 Are methods of quality assurance described?	☒	☐	☐	68 program conforms to
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	47 No missing data imputation
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	58 Table 2
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	18, section 5
9.5.2 Any progress report?	☒	☐	☐	
9.5.3 End of data collection?	☒	☐	☐	
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12
9.7 Are communication methods to disseminate results described?	☒	☐	☐	72, section 11
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	69, section 9
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☐	☐	☒	Section 8.6

Comments:

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Coordinating Investigator [delete when not required]:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): _____

Institution: [Insert applicable Janssen Company Name]

Signature: _____ Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor; a protocol amendment will not be required.

LAST PAGE