NON-INTERVENTIONAL POST-AUTHORIZATION STUDY
Final Study Report
Title Page

Title	An Observational Post-Authorization Safety Surveillance (PASS) Study of SYCREST® (asenapine) among Patients aged 18 and older Diagnosed with Bipolar Disorder
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Medicinal product	Sycrest®, Asenapine ATC Code: N05AH05
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Joint PASS	No
Research question and objectives	To assess the incidence rates of identified and potential risks among patients aged 18+ prescribed asenapine and to compare these rates to those prescribed risperidone and olanzapine in primary care in the UK. This research is primarily conducted among bipolar disorder patients who are on-label users of asenapine, and secondarily in schizophrenia patients who are the most frequent off-label users of asenapine. Use of asenapine for other diagnoses will also be examined in this study.
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1 ABSTRACT

Title

An observational post-authorization safety surveillance (PASS) study of SYCREST® (asenapine) among patients aged 18 and older diagnosed with bipolar disorder

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Keywords

Sycrest®, asenapine, atypical antipsychotic medications, database study, safety, inception cohort

Rationale and Background

Bipolar I disorder is a severe and chronic mood disorder characterized by the occurrence of at least one manic or mixed episode according to the criteria of DSM-IV-TR. Asenapine is a novel atypical antipsychotic agent indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), Merck Sharp & Dohme Corp. conducted this active post-licensure observational safety study to monitor clinically important identified and potential risks within a cohort of patients diagnosed with bipolar disorder and treated with asenapine. The European Medicine Agency (EMA) requested that the PASS specifically monitor the occurrence of allergic reactions, diabetes mellitus, dyslipidaemia, extrapyramidal symptoms, hyperprolactinaemia, neuroleptic malignant syndrome (NMS), neutropenia, orthostatic hypotension, rhabdomyolysis, seizures, somnolence and sedation. This study is part of a broader post-marketing commitment to augment routine evaluation of the safety profile of asenapine in clinical practice. In addition to this PASS, the commitment includes a drug utilization study of asenapine conducted by Merck Sharp & Dohme Corp. in the Clinical Practice Research Datalink (CPRD) / The Health Information Network (THIN) and two independent safety monitoring studies conducted in primary and specialty care in the United Kingdom by the Drug Safety Research Unit.

Research question and objectives

This study was designed to assess the incidence rates of identified and potential risks among patients aged 18+ prescribed asenapine and to compare these rates to those prescribed risperidone and olanzapine in primary care in the United Kingdom (UK). This research was primarily conducted among bipolar disorder patients who are on-label users of asenapine, and secondarily in schizophrenia patients who are the most frequent off-label users of asenapine. Use of asenapine for other diagnoses was also examined.

Primary Objectives:

1) Describe the baseline demographic and physical characteristics, of patients aged 18+ diagnosed with bipolar disorder newly treated with asenapine in routine post-licensure use
2) Assess the incidence rate of identified and potential risks in patients aged 18+ diagnosed with bipolar disorder and newly treated with asenapine in routine post-licensure use.
3) For comparison purposes, describe the baseline demographic and physical characteristics as described above and calculate incidence rate ratios of identified and potential risks between new users of asenapine and two control cohorts:
    - A post-licensure concurrent control cohort of patients aged 18+ diagnosed with bipolar disorder and newly treated with risperidone.
    - A post-licensure concurrent control cohort of patients aged 18+ diagnosed with bipolar disorder and newly treated with olanzapine

Secondary Objectives:

The secondary objectives are similar to the primary objectives but are investigated in two separate off-label groups of asenapine users:

1) Schizophrenia patients
2) Patients without diagnoses for bipolar disorder or schizophrenia

Study design

This PASS is a database study using a new-user cohort design for the purposes of conducting analyses of safety data related to asenapine when the product is used in the post-licensure period under conditions of usual care. This study evaluates asenapine use in the following operational definitions of indication: 1) bipolar disorder, which is the on-label use of asenapine; 2) schizophrenia, which is the most frequent off-label use of asenapine; 3) Alzheimer's disease (another off-label use) without a diagnosis of (1) or (2) above categories; 4) other pre-defined psychiatric conditions that are not in any categories above and 5) none of the pre-defined conditions above (no diagnosis).

Two comparator exposures are also evaluated, risperidone and olanzapine.

Setting

Two large general practice databases in the UK, CPRD (Clinical Practice Research Datalink) and THIN (the Health Improvement Network).

Subjects and study size, including dropouts

Subjects are those prescribed asenapine or comparator medication over the 5 year study period from 01 January 2012 to 31 December 2016 in the CPRD/THIN. All patients are required to have at least 365 days of observation time in the general practice before cohort entry, which occurs at the first prescription of asenapine or one of the comparator medications. The study protocol targets an enrolment of 3,000 new asenapine users.

Variables and data sources

Variables include events of interest (i.e., extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidemia, and diabetes mellitus) which are all potential and identified risks from the Risk Management Plan of asenapine that are measurable in CPRD/THIN, prescription of medications of interest, and patient demographic information, all as recorded in the CPRD/THIN.

Results

In the study population from the combined CPRD and THIN after removal of probable duplicate subjects, a total of 8,167,915 patients ≥18 years old were registered in the combined CPRD+THIN and also met their corresponding data quality indicator in the study time period of 1 January 2012 to 31 December 2016 during the first 5 years of asenapine launch. Of those patients, 75,667 had their first prescription of an atypical antipsychotic medication during that time period. The total number of patients initially prescribed asenapine in the combined CPRD and THIN was small (n=51), of which 42 had a 365-day baseline period. Of the 42 patients prescribed asenapine, 27 (64.3%) had a diagnosis of bipolar disorder (n=24 received asenapine on or after diagnosis, n=3 received asenapine before diagnosis), 6 (14.3%) had a diagnosis of schizophrenia, and 9 (21.4%) had a diagnosis of other mental disorders.

The median age among asenapine adult users (≥18 years old) was 44 years. The comorbidity profile of asenapine adult users at baseline showed the following prevalence: 19.0% of depressive disorders, 38.1% of nicotine dependence / smoking, and 26.2% of pain. 93.0% and 83.3% asenapine users were prescribed at least 1 other psychotropic medication within 365 days prior or after receiving the first prescription of asenapine, respectively.

For the comparator drugs, risperidone and olanzapine, a total of 12,812 and 10,706 new users of these drugs, respectively, aged 18 years or older with at least a 365-day baseline period were included. The majority of these patients received drugs for other mental disorder diagnosis [n=8,782 (68.5%) for risperidone and n=7,791 (72.8%) for olanzapine]. Six point three percent of risperidone patients and 13.0% of olanzapine had bipolar disorders diagnoses; six point seven percent of risperidone patients and 8.3% of olanzapine patients had schizophrenia diagnosis.

None of asenapine users were found to have diagnoses of the pre-specified clinical outcomes during follow-up for the identified risks for asenapine, which include extrapyramidal symptoms, somnolence, neuroleptic malignant syndrome, seizure, hyperprolactinemia, orthostatic hypotension, allergic reactions, dyslipidemia and diabetes mellitus, and the potential risks for asenapine, which include rhabdomyolysis and neutropenia.

There were no patients <18 years old who received a prescription of asenapine in either CPRD or the THIN during the study period (01 January 2012 – 31 December 2016).

Discussion

During the first 5 years of launch in the UK, asenapine was largely being prescribed for bipolar disorder, the licensed indication in UK and was not prescribed in patients less than 18 years old in the CPRD and THIN databases. The pattern of comorbidity and concomitant drug use indicated a high prevalence of comorbid conditions and concomitant medication use, consistent with clinical expectations for patient receiving atypical antipsychotic agents. None of asenapine users were found to have the pre-specified clinical incident events for the identified and potential risks for asenapine during follow-up. However, there was very limited prescribing of asenapine in the CPRD and THIN with only 42 available new asenapine users. Therefore, we were not able to calculate incidence rate ratios of identified and potential risks for asenapine compared to olanzapine and risperidone.

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2 LIST OF ABBREVIATIONS

AMR	Acceptable Mortality Reporting
DDD	Defined Daily Dose
DFDR	Double False Discovery Rate
DSRU	Drug Safety Research Unit
EMA	European Medicines Agency
EPIC	Epidemiology and Pharmacology Information Core
EPS	Extrapyramidal Symptoms
FDR	False Discovery Rate
GP	General Practitioner
CPRD	Clinical Practice Research Datalink
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare products Regulatory Agency
M-PEM	Modified Prescription–Event Monitoring Study
MREC	Multi-Centre Research Ethics Committee
NMS	Neuroleptic Malignant Syndrome
PASS	Post-Authorization Safety Study
SCEM	Specialist Cohort Event Monitoring Study
eSRC	Epidemiology Safety Review Committee
THIN	The Health Improvement Network
UK	United Kingdom
UPS	Up-to-Standard

3 INVESTIGATORS

The investigators are PPD

4 OTHER RESPONSIBLE PARTIES

Not applicable

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Original protocol submitted to EMA	18-JUL-2011	27-JUL-2011	Internal protocol approved. IRB submission postponed until feedback received from CHMP. Milestone listed as background information.
Registration in the EU PAS register	N/A	24-MAY-2017	EUPAS17631No.: EUPAS17631
Protocol amendment 1 , EMA approval	7-DEC-2011	27-SEP-2012	In response to CHMP recommendation
Protocol amendment 2, EMA approval	4-JUN-2012	4-JUN-2012	In response to CHMP recommendation
Protocol amendment 3	21-FEB-2013	21-FEB-2013	In response to ISAC recommendation
Protocol amendment 4	5-AUG-2014	5-AUG-2014	In response to eSRC recommendations
Start of data collection	30-SEP-2013	01-JUL-2013	
End of data collection	31-OCT-2017	19-APR-2017	
Interim report 1	13-OCT-2014	16-SEP-2014	First annual interim report (Interim Report 1)
Interim report 2	13-OCT-2015	16-SEP-2015	Second annual interim report (Interim Report 2)
Interim report 3	13-OCT-2016	16-SEP-2016	Third annual interim report (Interim Report 3)
Final report of study results	31-JAN-2018	31-JAN-2018	

6 RATIONALE AND BACKGROUND

The group of disorders commonly referred to as 'bipolar disorders' are chronic, typically cyclic, mood disorders and are is comprised of bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified (NOS). Mania is the hallmark of bipolar disorders, with individuals experiencing periodic episodes, which may be manic (or hypomanic), depressive (meeting criteria for major depressive episode), or mixed (i.e., the criteria are met for both a manic episode and a major depressive episode, except for the duration requirement). Bipolar I disorder is a severe and chronic mood disorder characterized by the occurrence of at least one manic or mixed episode according to the criteria of DSM-IV-TR. Often, individuals have experienced one or more episodes of major depression. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood.

Bebbington and Ramana conducted a review of studies examining the epidemiology of bipolar affective disorder, also referred to as the group of bipolar disorders. The annual incidence of bipolar affective disorder ranges from 2.6 to 20.8 cases per 100,000 persons [Ref. 5.4: 00QS0Y]. Based on studies in the US, Germany and Switzerland, current prevalence estimates for bipolar spectrum disorders are reported to be in the range of 2.8-6.5% [Ref. 5.4: 00QS0X].

Management of bipolar disorders is comprised of effective treatment of the acute phases of manic, mixed, hypomanic and depressive episodes, and maintenance treatment aimed to prevent relapses. The treatment of bipolar depression differs substantially from the treatment of unipolar depression due to the increased risk of a switch into mania, and mood stabilizers are recommended when antidepressants are used. Asenapine is a novel atypical antipsychotic agent indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

In addition to the routine pharmacovigilance activities, Merck Sharp & Dohme Corp. agreed to conduct a database study of asenapine prescribing in the primary care setting in the United Kingdom (UK). In the UK, "up to one half of people who have a serious mental illness are seen only in a primary care setting," [Ref. 5.4: 00QRC3] making the use of the primary care data an appropriate study population source. Due to very low counts of asenapine prescribed subjects in the CPRD, the THIN database was added as another data source in 2015 (section 9). This study is part of a broader post-marketing commitment to evaluate the safety profile of asenapine in clinical practice, which is conducted in tandem with protocol P08308 – An Observational Drug Utilization Study of SYCREST® (asenapine) in UK, hereafter referred to as the Drug Utilization (DU) study. The DU study complements this study by providing the context for asenapine utilization in both bipolar disorders patients and patients with other conditions.

7 RESEARCH QUESTION AND OBJECTIVES

The research question and objectives are stated in the study protocol, and presented below for ease of reference.

Overall Aim:

To assess the incidence rates of identified and potential risks among patients aged 18+ years that are prescribed asenapine, and compare these rates to those prescribed risperidone and olanzapine in a primary care setting in the UK. This research is primarily conducted among bipolar disorder patients who are on-label users of asenapine, and secondarily in schizophrenia patients who are the most frequent off-label users of asenapine. Other uses of asenapine with other conditions were also examined.

Primary Objectives:

1. Describe the baseline demographic and physical characteristics, including prior health status, comorbidities, and concomitant medications of patients aged 18+ years diagnosed with bipolar disorder who are newly treated with asenapine in routine post-licensure use
2. Assess the incidence rate of identified and potential risks, including extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidemia and diabetes mellitus, in patients aged 18+ years diagnosed with bipolar disorder and who are newly treated with asenapine in routine post-licensure use
3. For comparison purposes, describe the baseline demographic and physical characteristics as described above and calculate incidence rate ratios of identified and potential risks, including extrapyramidal symptoms, somnolence and sedation, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidemia and diabetes mellitus, between new users of asenapine and two control cohorts:
    a. A post-licensure concurrent control cohort of patients aged 18+ years diagnosed with bipolar disorder and are newly treated with risperidone
    b. A post-licensure concurrent control cohort of patients aged 18+ years diagnosed with bipolar disorder and are newly treated with olanzapine

Secondary Objectives:

The secondary objectives are similar to the primary objectives, but are investigated in two separate off-label groups of asenapine users:

1) Schizophrenia patients

2) Patients without diagnoses for bipolar disorder or schizophrenia

8 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	8-Dec-2011	List of Abbreviations	Added DDD = Defined Daily Dose	Clarification was needed
		B.2	Added Secondary Objectives which are the same as primary objectives but for Schizophrenia Patients and for other off-Label users of asenapine	In response to CHMP recommendation
		C.2 and C.3	Study Population amended so that Schizophrenia Patients and other off-Label users of asenapine are included.	In response to CHMP recommendation
		D.1	Definition of Primary Exposure extended to Schizophrenia Patients and other off-Label users of asenapine	In response to CHMP recommendation
			Clarification of definition of first ever atypical antipsychotic treatment.	In response to CHMP recommendation
			Clarification of handling of missing or erroneous data.	In response to CHMP recommendation
2	4-Jun-2012	C.1	Modification of criteria for determining the end of the study	In response to CHMP recommendation
3	21-Feb-2013	B.2 and C.1	Modification of sample size needed to trigger comparative analyses	In response to ISAC recommendation
		C.1	Clarification of strategy for reporting observed 'null' effects for outcomes where the sample size is underpowered	In response to ISAC recommendation
			Clarification on handling of missing or erroneous data.	In response to ISAC recommendation
		D.1	Inclusion in the bipolar disorder sub cohort of patients with first written prescription for asenapine within 2 years before their diagnosis of bipolar disorder (pre-treated patients)	In CPRD, among olanzapine and / or risperidone patients receiving a bipolar disorder diagnosis before initiation of treatment, the cumulative distribution shows approximately 75% have a duration of time between last bipolar disorder diagnosis and first prescription of olanzapine or risperidone of less than 2 years

4	5-Aug-2014	All references to "off-label" group	Off-label group defined into three groups: i) Alzheimer's disease, ii) "Other diagnoses: Mental disorders", and iii) "No diagnosis"	In response to eSRC recommendation
		Bipolar disorder and schizophrenia cohorts	Patients can have diagnosis at any time prior to prescription date	In response to eSRC recommendation
		Schizophrenia cohort	Patients now can have treatment before diagnosis of schizophrenia	In response to eSRC recommendation
		"On-label" and "Pre-treated" classifications	Modified to "Diagnosis before or at treatment" and "Treatment before diagnosis", respectively	In response to eSRC recommendation
5[1]	31-July-2015	C.3	Removed inclusion II and III when defining Bipolar Disorder Cohort	In response to eSRC recommendation
		D.1	Removed the requirement that the index date of Asenapine new users must be the first written prescription after entry into the Bipolar Disorder Cohort (now the index date is the date for the first written prescription for asenapine)	In response to eSRC recommendation

9 RESEARCH METHODS

9.1 Study design

This PASS is a retrospective database study utilizing a new user cohort design for the purposes of conducting analyses of safety data related to asenapine when the product is used in the post-licensure period under conditions of usual care. The same definition of new users is applied regardless of the conditions. This study is, however, structured according to the 3 following groups of conditions: (i) bipolar disorder, which is the on-label use of asenapine, (ii) schizophrenia, which is the most frequent off-label use of asenapine and (iii) other conditions that are neither bipolar disorders nor schizophrenia, which includes Alzheimer's disease, other diagnosis of mental disorders, and no diagnosis. The chart below defines the disease classifications for patients prescribed asenapine or one of the comparators, risperidone or olanzapine, in this study. Due to expected heterogeneity of the disease conditions, no safety analyses are performed across these different conditions.

[1] See Appendix 1. Summary of Changes for more detail

Table 1: Disease classification definitions for patients who received an incident atypical antipsychotic prescription between 01 Jan 2012 and 31 December 2016 in the CPRD/THIN

Disease Classification	Asenapine	Olanzapine	Risperidone
Bipolar disorder Diagnosis before or at treatment	Bipolar disorder diagnosis date on or before first asenapine prescription date	Bipolar disorder diagnosis date on or before first olanzapine prescription date	Bipolar disorder diagnosis date on or before first risperidone prescription date
Bipolar disorder Treatment before diagnosis	Bipolar disorder diagnosis date within 2 years after asenapine prescription date	Bipolar disorder diagnosis date within 2 years after olanzapine prescription date	Bipolar disorder diagnosis date within 2 years after risperidone prescription date
Schizophrenia only[1] Diagnosis before or at treatment	No bipolar disorder diagnosis. Schizophrenia diagnosis date on or before the first asenapine prescription date	No bipolar disorder diagnosis. Schizophrenia diagnosis date on or before the first olanzapine prescription date	No bipolar disorder diagnosis. Schizophrenia diagnosis date on or before the first risperidone prescription date
Schizophrenia only[1] Treatment before diagnosis	No bipolar disorder diagnosis. Schizophrenia diagnosis date within 2 years after asenapine prescription date	No bipolar disorder diagnosis. Schizophrenia diagnosis date on or before the first olanzapine prescription date	No bipolar disorder diagnosis. Schizophrenia diagnosis date on or before the first risperidone prescription date
Alzheimer's disease[2]	No bipolar disorder and no schizophrenia diagnosis. Alzheimer's diagnosis date at any time up to 2 years after asenapine prescription date	No bipolar disorder and no schizophrenia diagnosis. Alzheimer's diagnosis date at any time up to 2 years after olanzapine prescription date	No bipolar disorder and no schizophrenia diagnosis. Alzheimer's diagnosis date at any time up to 2 years after risperidone prescription date
Other diagnoses: Mental Disorders[3]	No bipolar disorder diagnosis, no schizophrenia diagnosis, and no Alzheimer's disease diagnosis. Any mental disorder diagnosis date at any time up to 2 years after asenapine prescription	No bipolar disorder diagnosis, no schizophrenia diagnosis, and no Alzheimer's disease diagnosis. Any mental disorder diagnosis date at any time up to 2 years after olanzapine prescription	No bipolar disorder diagnosis, no schizophrenia diagnosis, and no Alzheimer's disease diagnosis. Any mental disorder diagnosis date at any time up to 2 years after risperidone prescription
No Diagnosis	No bipolar disorder diagnosis, no schizophrenia diagnosis, and no other diagnosis: mental disorders at any time up to 2 years after asenapine prescription	No bipolar disorder diagnosis, no schizophrenia diagnosis, and no other diagnosis: mental disorders at any time up to 2 years after olanzapine prescription	No bipolar disorder diagnosis, no schizophrenia diagnosis, and no other diagnosis: mental disorders at any time up to 2 years after risperidone prescription

[1]Off-label indication for asenapine, but labeled indication for olanzapine and risperidone

[2]Off-label indication for asenapine and olanzapine. Risperidone is "indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is of harm to self or others"

[3]Includes at least one of the following: Depressive disorders; Major depressive disorder; Psychotic disorders; Schizophreniform disorder; Schizoaffective disorder; Anxiety Disorders; Mixed Anxiety and Depression; Generalized anxiety disorder; Panic disorder; Post-traumatic stress disorder; Personality disorders; Paranoid personality disorder; Schizotypal personality disorder; Borderline personality disorder; Suicide and self-inflicted injury; Delirium, dementia, amnestic and other cognitive conditions; Mental retardation; Miscellaneous mental disorders; Disorders usually diagnosed in infancy, childhood, or adolescence; Gilles de la Tourette's disorder; Attention deficit, conduct, and disruptive behavior disorders (Including Oppositional Defiant Disorder); Conduct Disorder; Attention deficit disorder and attention deficit hyperactivity disorder; Autism; Developmental disorders; Impulse control disorders, not elsewhere classified; Alcohol dependence/abuse (Including dependence and withdrawal); Drug dependence/abuse; Nicotine dependence/smoking; Anxiety symptoms; Miscellaneous childhood symptoms

Of note, this PASS is non-interventional and does not involve active administration of asenapine by Merck Sharp & Dohme Corp. All recipients of asenapine who are followed in this study have received the marketed drug in the course of ordinary clinical practice after licensure of asenapine in the UK (16 January 2012).

9.2 Setting

To answer the primary objective of the research question, this PASS is conducted in a cohort of patients diagnosed with bipolar disorder as identified through Read diagnosis codes in general practice-based electronic healthcare databases. The bipolar disorder cohort is extracted from both CPRD and THIN in the United Kingdom (UK). The study period for the final report is from 1 January 2012 to 31 December 2016[2].

9.3 Subjects

Due to very low accrual of asenapine prescribed subjects in the CPRD, the THIN database was added as another data source for the reports. Both the CPRD and THIN include computerized, anonymous, longitudinal patient medical records retrieved from general practices in the UK. The bipolar disorder cohort is extracted from both the CPRD and THIN. Since some general medical practices in the UK contribute data to both the CPRD and THIN, some patient records may be duplicated when both databases are combined. Because the medical practices that are common to both databases are not publicly known, we utilized an algorithm to identify the common practices (Appendix 2) [Ref. 5.4: 04RLP9]. This algorithm has been applied in a previous PASS in support of MSD marketed products. For those practices that are identified as contributing to both databases, the data from the CPRD are used. Furthermore, since the developed algorithm that identifies common practices is based on probabilistic linkage between the CPRD and THIN, analyses are conducted for the combined dataset, as well as for the CPRD and THIN datasets separately.

Patients registered in the CPRD/THIN who received an atypical antipsychotic prescription from 1 January 2012 through 31 December 2016 are the source population for the present analyses. Flowcharts of the population attrition for this study are stratified by the source populations (the combined CPRD and THIN, the CPRD only, or the THIN only), which consists of patients 18+ years of age who received their first prescription for an atypical antipsychotic medication and the numbers of respective patients. Patients who received asenapine, risperidone or olanzapine are the target population in this final report.

[2] The final report covers the study period between 01-Jan-2012 and 31-Dec-2016, which is one-month fewer of data than what was planned (01-Jan-2012 to 31-Jan-2017). The reason for this is that at the time this report was written and reviewed by the independent Epidemiology Safety Review Committee, both the data for CPRD and THIN were only available up through 31 December 2016.

Inclusion criteria for the Bipolar Disorder Cohort [3]:

Subjects who had a diagnostic code for bipolar disorders[4] in the databases are included in the bipolar disorder cohort. The date that each patient had the first bipolar disorder diagnosis in the database is his/her bipolar disorder cohort entry date. Patients that enter the bipolar disorder cohort are stratified into those with incident or prevalent disease. Incident patients are defined as a set of patients who have accumulated ≥ 365 days before first recorded diagnosis of bipolar disorder. Because there is no evidence that these patients received a diagnosis of bipolar disorder during the 365-day period prior to this first recorded diagnosis of bipolar disorder, they are considered incident bipolar disorder patients. Prevalent patients are defined as a set of patients who have accumulated < 365 days before first recorded diagnosis of bipolar disorder.

9.4 Variables

9.4.1 Exposure

Asenapine Inception (new user) Cohort

This study utilizes an inception cohort (new users) design (Figure 1). [Ref. 5.4: 00QRC4]. Patients treated with asenapine are identified within the bipolar disorder cohort, and must meet the following criteria:

- First written prescription for asenapine after entry into the bipolar disorder cohort or first written prescription for asenapine within 2 years before entry into the bipolar disorder cohort during study period.
- No use of asenapine within 365 days prior to the first written prescription for asenapine defined above.
- ≥ 365 days “up to standard” days of accumulated time prior to the first prescription of asenapine.

[3] The schizophrenia cohort is defined with similar inclusion criteria with addition of an exclusion criterion where patients with a prior and/or concomitant diagnosis of bipolar disorder are excluded.

[4] Given that CPRD/THIN are general practitioner-based electronic medical record databases, they are not specifically designed to capture psychiatric disorders for research purposes. As such, the diagnostic information recorded may lack the specificity required to differentiate between bipolar I disorder, the condition associated with the indication, from other bipolar disorders. As a result, the bipolar cohort is initially are constructed using a general coding algorithm that would categorize bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified (NOS) under the label 'bipolar disorder'.

Figure 1: Definition of inception cohort (new user) in CPRD/THIN

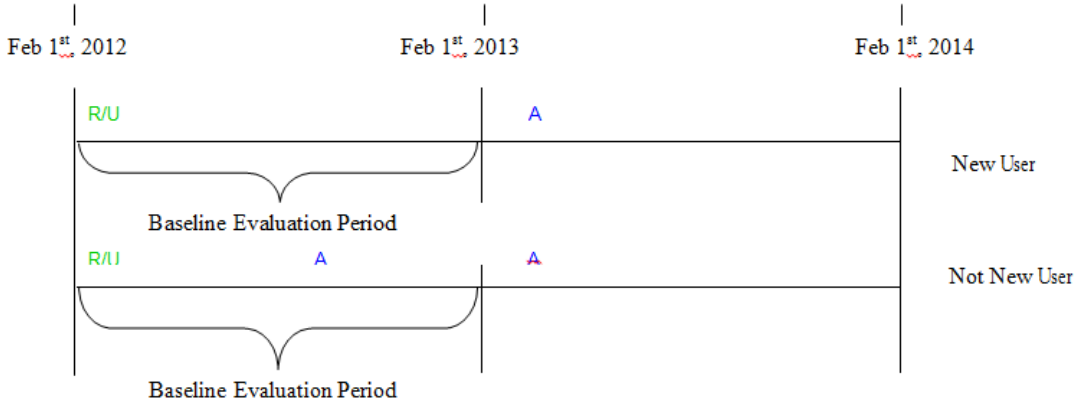


Figure 1. Definition of an inception cohort (new user) in CPRD

A = Asenapine Prescription
BD = Bipolar Disorder Diagnosis
18+ = Date Patient Turned 18
R/U = Max of Registration and UTS Dates

For each patient who meets all of above criteria, the date of the first written prescription for asenapine is identified as their index date.

Definition of Comparison Exposure

New users of risperidone or olanzapine during the study period are defined using the same above criteria for asenapine users and served as the comparison groups.

9.4.2 Outcomes

The outcomes of interest are the identified and potential risks for asenapine that are included in the Risk Management Plan and are measurable in the databases including: extrapyramidal symptoms, somnolence, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidemia and diabetes mellitus. The operational definitions of incident cases of above risks are defined in section 9.9 in the report.

9.4.3 Covariates

Covariates included in the study are those determined to be potential confounders or risk factors for a given outcome of interest including the covariates that are used for descriptive analyses. A list of potential confounders and risk factors for each outcome of interest are listed in Appendix D of the protocol, which is also available in Appendix 1 of this report.

9.5 Data sources and measurement

The data sources for this study are from the UK, including both CPRD and THIN.

9.5.1 Study Procedures

The CPRD and THIN databases are licensed by MSD. Inc., and contain de-identified data; therefore, MSD does not have access to any individual patient's medical information. Prior to finalization, the study protocol was reviewed by the EMA and underwent review and approval by the Independent Scientific Advisory Committee (ISAC) of the CPRD and the Multi-Centre Research Ethics Committee (MREC) for the Epidemiology and Pharmacology Information Core (EPIC) Company.

9.6 Bias

Given the very low accrual of asenapine prescribed subjects in the UK, only descriptive analyses are performed in this final report (please refer the section 9.9.5 for the summary of amendments to the statistical analysis plan for the final report), and no formal comparison between users of asenapine and the two comparison cohorts are performed because such comparison will be underpowered. Discussions on limitations on descriptive analyses are under the section 11.2.

9.7 Study size

As stated in the study protocol, this study is designed to end at the first occurrence of either 5-years post-launch (approximately 2012-2017) or until at least 3,000 patient /3,000 patient-years of exposure to asenapine are accrued, whichever comes earlier.

9.8 Data transformation

Not applicable.

9.8.1 Data management

All statistical analyses were conducted using SAS version 9.3.1.

9.9 Statistical methods

9.9.1 Main summary measures

Description of Baseline Characteristics and Concomitant Treatment

The baseline period is a period of 365 days prior to the first prescription of asenapine and the comparison drugs. Baseline characteristics described for asenapine and the comparison cohorts include:

- Demographics
- Pre-existing conditions and comorbidities
- Baseline medications

The concomitant treatment that was prescribed within 365 days after the first prescription of asenapine and comparison drugs is also described.

Calculation of Incidence Rates for each Identified and Potential risk

The incidence rates and corresponding 95% confidence intervals for each of the identified and potential risks is calculated separately for new users of asenapine and the comparison cohorts.

9.9.2 Main statistical methods

Given the very low accrual of asenapine prescribed subjects in the UK, only descriptive analyses are performed in this final report (please refer the section 9.9.5 for the summary of amendments to the statistical analysis plan for the final report), and no formal comparison between users of asenapine and the two comparison cohorts are performed because such comparison will be underpowered.

The descriptive analyses include the following:

1. Description of the frequency and proportion of asenapine, olanzapine, and risperidone cohorts by psychiatric diagnosis

   Patients treated with a study drug of interest (asenapine and comparison drugs), are stratified by a list of pre-defined psychiatric diagnoses (please refer to section 9.1, Table 1 for detailed descriptions of the list of the psychiatric diagnoses). This list of conditions/diagnoses had been reviewed and agreed by an external eSRC.

2. Descriptions of baseline characteristics and concomitant treatment

   For each patient, baseline characteristics are described using the clinical record data in the 365 days prior to the prescription index date. Furthermore, related concomitant treatment is also described within 365 days after the index date entry in asenapine, olanzapine, and risperidone cohorts.

   Baseline characteristics described include:

   - Demographics
   - Pre-existing conditions and comorbidities
   - Baseline medications

   Characteristics presented as continuous variables are summarized using means, standard deviations, medians, minimum and maximum values; whereas, categorical data are summarized as counts and proportions.

3. Calculation of Incidence Rates for each Identified and Potential risk
   a. Follow-up

i. The date of the first written prescription for asenapine is identified as the index date. All patients in the asenapine inception cohort had at least 365 day of baseline data prior to their index date, per cohort definition.
ii. Given the limited number of asenapine users during the study period, there are limited options to impute missing data related to prescription days-supply. It is also impractical to estimate an allowable prescription gap for asenapine users. As an operational definition, the following algorithm was used to define the duration of asenapine exposure during follow-up: the asenapine exposure duration is calculated as the duration between the 1st prescription and the last prescription plus 30 days (please see further details of justification for such operational definition at section 9.9.5).
iii. Each patient is followed starting with the prescription index date and ending with the earliest of:
    1. Exposure end date (as determined by the above algorithm for exposure duration)
    2. Date of transfer out of the practice
    3. Date of the last data collection from the practice
    4. Date of the clinical event of interest (since multiple outcomes are being evaluated, this date will vary for each patient by outcome)
    5. The end of the study period
    6. Date of death
iv. In order to retain more follow-up time from very limited asenapine exposures, the follow-up for new users of asenapine is not censored if they added other antipsychotic drugs and were still on asenapine per the asenapine exposure duration defined above. This same rule is also applied to the comparison drugs exposures.
v. Accrued person-time for patients on asenapine is accumulated from the index date until the end of follow-up, as defined above. Accrued person-time for new users of patients receiving prescription for risperidone or olanzapine (comparison cohorts) during follow-up is also calculated this same way as for users of asenapine.

b. Incidence of Outcomes of Interest
i. Each of the identified and potential risks is analysed separately. During follow-up, incidence (the first occurrence) of each identified and potential risk for each patient is identified. An event is attributed to a given exposure if observed in the risk window as defined in the "follow-up" section. Given the new user design, all patients have 365 days of baseline data. Patients with a history of a given outcome 365 days prior to the prescription index date are considered prevalent cases and are excluded from the incidence analysis for that type of event. Only the first event of a given type during follow-up is counted in the analysis.

c. Calculation of incidence rates and corresponding 95% confidence interval
   i. The incidence rate for an exposure group is calculated as the number of first occurrences of each identified or potential risk divided by the total person-time accrued by all patients in that exposure group. A given patient may contribute different amounts of person-time for each separate analysis of an identified or potential risk, depending on whether or not he/she experiences one of the identified or potential risks of interest. Incidence rates are calculated for each exposure group and reported per 1,000 person-years.
   ii. The exact Poisson 95% confidence intervals for the estimated incidence rates are calculated given the limited asenapine exposure.

9.9.3 Missing values

Counts and proportions of missing data for each variable of interest are included in the tables for the descriptive analyses, if any.

9.9.4 Sensitivity analyses

Due to low accrual of asenapine prescribed subjects, no sensitivity analyses per-protocol is conducted for this report.

9.9.5 Amendments to the statistical analysis plan

Due to very low accrual of asenapine prescribed users in the UK, a number of analytic deviations from the per-protocol specified analyses are summarized below by study objectives:

Primary Objectives

All descriptive analyses for baseline characteristics are NOT stratified by incidence or prevalence of bipolar disorder; or by the inception cohort strata (1st ever atypical antipsychotic or prior recent atypical antipsychotic use). Instead, the descriptive analyses are conducted in ALL available new users of asenapine patients identified in the CPRD/THIN stratified by the pre-defined three groups of conditions when the patients were prescribed asenapine: i) bipolar disorder, (ii) schizophrenia, and (iii) other conditions that are neither bipolar disorder nor schizophrenia, which includes Alzheimer's disease, other diagnosis: mental disorders, and no diagnosis (Please refer to the details descriptions on the list in section 9.1 at Table 1). This list of categories to group conditions had been reviewed and agreed by external eSRC.

Calculation of incidence rates for each identified and potential risk in new users of asenapine are NOT stratified by either incidence or prevalence of bipolar disorder; or by the inception cohort strata (1st ever atypical antipsychotic or prior recent atypical antipsychotic use).

The follow-up of new users of asenapine including comparison drugs were not censored when they added other antipsychotic drugs during follow-up as long as they were still on

asenapine. This is also applied to the comparison drugs. The use of the simplified algorithm to calculate asenapine exposure duration is driven by missing data of daily dosing and extreme values of quantity for asenapine prescriptions recorded in the databases. In all recorded asenapine prescriptions, around 10% (10 mg tablet) and 39% (5 mg tablet) are missing daily dosing information, and the ranges for quantity are between 2 to 60 pills (10 mg tablet), and 1 to 120 pills (5 mg tablet). Furthermore, around 55% (23 out of 42 new asenapine users) are found to have fewer than 3 asenapine prescriptions, and 31% of all asenapine users had only one asenapine prescription in the study period.

For comparison purposes, all the descriptive analyses of baseline characteristics and calculation of incidence rates for each identified and potential risk are conducted in the new users of two comparison cohorts (risperidone and olanzapine) using the same logic as the asenapine users. However, no formal direct comparative analyses between the users of asenapine and the two comparison groups are performed for the final report because of very low accrual of asenapine prescribed users, such comparisons will be underpowered.

Secondary Objectives

Descriptive analyse of baseline characteristics were provided for subgroups. The incidence rates for each identified and potential risk in new users of asenapine were NOT calculated for subgroups of psychiatric diagnoses including schizophrenia and others because of low numbers of asenapine available in the study period.

9.10 Quality control

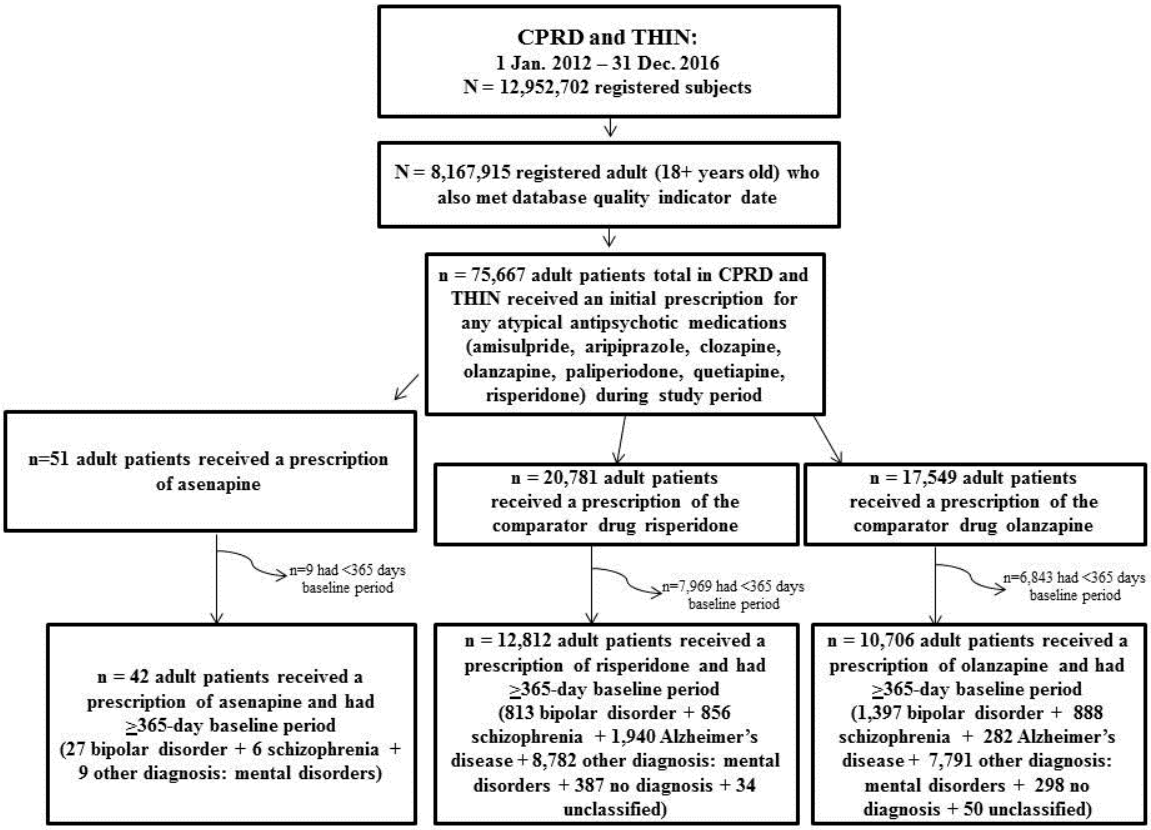
Descriptions of the CPRD and THIN Data Quality Markers are found in Protocol Number: P08307, which is also available in Appendix 1.

10 RESULTS

10.1 Participants

Patients registered in the CPRD/THIN who received an atypical antipsychotic prescription from 1 January 2012 through 31 December 2016 served as the source population for the present analyses. Figure 2 shows a flowchart of the target patient population for this study in the combined CPRD and THIN (the flowcharts stratified by CPRD or THIN are available in Appendix 2), which consists of patients equal to or greater than 18 years old who received their first prescription for an atypical antipsychotic medication and the numbers of respective patients who received asenapine, risperidone, or olanzapine. More detail about these patients and medications is provided in the subsection "10.2 Descriptive data."

Figure 2: Flow Chart of Available Study Population in the CPRD and THIN



10.1.1 Protection of Human Subjects

The CPRD and THIN databases are licensed by MSD and contains de-identified data; therefore, MSD does not have access to any individual patient's medical information. Prior to being finalized, the study protocol was reviewed by the CHMP of the EMA and underwent review and approval by the Independent Scientific Advisory Committee (ISAC) of the CPRD and the Multi-Centre Research Ethics Committee (MREC) for the Epidemiology and Pharmacology Information Core (EPIC) Company.

10.2 Descriptive data

The CPRD and THIN had a population of 9,392,090 vs. 9,449,026, respectively with registered subjects between 1/1/2012 and 12/31/2016. The registered adults (18+ years old) who also met the corresponding database quality indicators were 5,763,950 and 6,198,080 in the CPRD and THIN, respectively. During the study period, there were a total of 668 general medical practices in the CPRD, and 722 GPs in the THIN. The algorithms (section 9.3) identified a total of 407 common medical practices between the CPRD and THIN. The details of descriptive results on asenapine new users are covered in the section 10.4 "Main results".

10.3 Outcome data

In the combined CPRD/THIN, none of the new asenapine users are found to have any pre-specified clinical incident events for the identified and potential risks for asenapine during follow-up, including: extrapyramidal symptoms, somnolence, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidemia and diabetes mellitus in the study period. More details are described in the section 10.4 "Main results".

10.4 Main results

Only results in the combined CPRD and THIN are described under this section. Details of other analyses including those from stratified analyses by CPRD or THIN can be found in Appendix 2. For the study time period of 1 January 2012 until 31 December 2016, representing the first 5 years of asenapine launch, a total of 8,167,915 patients ≥18 years old were registered in the combined CPRD+THIN and also met their corresponding data quality indicator (for those identified as the common practices for both databases, the data in the CPRD were used). Of those patients, 75,667 had their first prescription of an atypical antipsychotic medication during that time period. The total number of patients initially prescribed asenapine in the combined CPRD and THIN was small (n=51), of which 42 had a 365-day baseline period. Of the 42 patients prescribed asenapine, 27 (64.3%) had a diagnosis of bipolar disorder (n=24 received asenapine on or after diagnosis, n=3 received asenapine before diagnosis), 6 (14.3%) had a diagnosis of schizophrenia, and 9 (21.4%) had a diagnosis of other mental disorders (Table 2).

For the comparator drugs, risperidone and olanzapine, a total of 12,812 and 10,706 new users of these drugs, respectively, aged 18 years or older with at least a 365-day baseline period were included. The majority of these patients had other mental disorder diagnoses [n=8,782 (68.5%) for risperidone, and n=7,791 (72.8%) for olanzapine]; 813 (6.3%) risperidone and 1,397 (13%) olanzapine users received the drugs for bipolar disorder, and 856 (6.7%) risperidone and 888 (8.3%) olanzapine users had the drugs for schizophrenia (Table 2).

The median age among asenapine adult users (≥18 years old) was 44 years, and patients who received asenapine prior to a bipolar disorder diagnosis were younger than those who received a bipolar diagnosis before being prescribed asenapine prescribing (40 vs. 45 years old, respectively, Table 3, and Table A1 in Appendix 2). The comorbidity profile of asenapine adult users at baseline showed high prevalence of depressive disorders [n=8 (19.0%)], nicotine dependence / smoking [n=16 (38.1%)], and pain [n=11 (26.2%)]. Thirty nine (93.0%) and 35 (83.3%) patients, respectively, were prescribed at least one other psychotropic medication within 365 days prior/after receiving the first prescription of asenapine (Table 3, Table A1 in Appendix 2).

Compared to users of risperidone and olanzapine, users of asenapine were younger (median age was 47 and 68 years in risperidone and olanzapine, respectively vs. 44 years for asenapine users); and had a higher percentage of females (71.4% in asenapine vs. 50.9% and 55.8% in olanzapine and risperidone users, respectively), and higher baseline prevalence of nicotine dependence/smoking (38.1% vs. 25.9% and 17.9% in olanzapine and risperidone, respectively) and psychotropic medications use at baseline (93.0% vs. 76.4% and 74.0% in olanzapine and risperidone respectively, Table 3). When restricting the comparison to the sub-group with a diagnosis of bipolar disorder or schizophrenia, the mean and median ages of the cohorts were closer but there were still a higher percentage of females, higher prevalence of nicotine dependence/smoking and psychotropic medication use at baseline in asenapine users (Table 4).

The mean follow-up duration for asenapine users was 0.76 year. In an additional analysis of asenapine prescriptions, around 55% (23 out of 42 new asenapine users) were found to have fewer than 3 asenapine prescriptions, and 31% of all asenapine users had only one asenapine prescription in the study period. Though the average follow-up duration for asenapine users was slightly less than the follow-up durations of risperidone (mean: 0.82 year) and olanzapine (mean: 1.00 year), all three drugs had generally short follow-up durations in the study period (Table 5).

Among the 42 new asenapine users, there were two patients who had the clinical outcome of seizure and one patient who had dyslipidemia in their baseline periods. After excluding patients with a history of the events of interest, none of asenapine users were found to have any of pre-specified clinical outcomes for the identified and potential risks for asenapine during follow-up (Table 7). This could be due to the very small sample of asenapine users coupled with the low incidence rates of these outcomes in the study population. For example, even for the outcome of somnolence and sedation that has an incidence rate of 18.8 per 1000 person-years among risperidone users, one would expect to see only 0.59 cases of somnolence and sedation among the around 32 patient years of asenapine exposure captured

in this study. An analysis of the incidence rates of outcomes of interest restricted to users with a diagnosis of bipolar disorder produced similar low incidence rates, but with wider 95% CIs (Table 8).

There were no patients <18 years old who received a prescription of asenapine in the combined CPRD+THIN dataset during the study period (01 January 2012 – 31 December 2016).

Table 2: Frequency and Proportion of Atypical Antipsychotic Treatment by Psychiatric Diagnosis among Patients Aged 18+ Years Atypical Antipsychotic Prescription Date: 01/01/2012 - 12/31/2016 in the Combined CPRD and THIN

Psychiatric Diagnosis	Asenapine (N=42)		Risperidone[1] (N=12,812)		Olanzapine[1] (N=10,706)	
	N	%	N	%	N	%
Total Bipolar	27	64.3	813	6.3	1,397	13.0
Diagnosis before or at treatment	24	57.1	714	5.6	1,192	11.1
Treatment before diagnosis	3	7.1	99	0.8	205	1.9
Schizophrenia only[2]	6	14.3	856	6.7	888	8.3
Diagnosis before or at treatment	6	14.3	704	5.5	730	6.8
Treatment before diagnosis	0	0.0	152	1.2	158	1.5
Alzheimer's disease[3]	0	0.0	1,940	15.1	282	2.6
Other diagnoses: Mental Disorders[4]	9	21.4	8,782	68.5	7,791	72.8
No Diagnosis[5]	0	0.0	387	3.0	298	2.8
Unclassified [6]	0	0.0	34	0.3	50	0.5

[1]Schizophrenia is a labeled indication for this treatment

[2]After excluding patients with Bipolar Disorder

[3]Risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer´s dementia unresponsive to non-pharmacological approaches and when there is of harm to self or others

[4]After excluding patients with Bipolar Disorder, Schizophrenia or Alzheimer´s

[5]Excludes patients with Bipolar Disorder, Schizophrenia, or any Mental Disorders diagnoses

[6] the subjects who had a diagnosis of bipolar or Schizophrenia outside 730 days since the first prescriptions of the interest of drugs

Table 3: Patients' demographics, some selected baseline comorbidities, and pre/post psychotropic mediations in new users of asenapine, risperidone and olanzapine 18+ years in CPRD+THIN between 1/12012 and 12/31/2016

	Asenapine	Olanzapine	Risperidone
Age (years)	**N=42**	**N=10,706**	**N=12,812**
Mean	46.5	49.6	62
Median	44	47	68
Gender	**%**	**%**	**%**
Male	28.6	49.1	44.2
Female	71.4	50.9	55.8
Depressive disorders	19.0	21.1	11.7
Nicotine dependence / smoking	38.1	25.9	17.9
Pain	26.2	29.1	27.2
Prescription of at least 1 other psychotropic medication in the baseline	93.0	76.4	74
Prescription of at least 1 other psychotropic medication within 365 days after index date	83.3	74.7	71

Table 4: Patients' demographics, some selected baseline comorbidities, and pre/post psychotropic mediations in new users of asenapine, risperidone and olanzapine 18+ years with a Diagnosis of Bipolar Disorder or Schizophrenia in CPRD+THIN between 1/12012 and 12/31/2016

	Asenapine	Olanzapine	Risperidone
Age (years)	**N=33**	**N=2,285**	**N=1,669**
Mean	47	48.3	50
Median	44	47	48
Gender	**%**	**%**	**%**
Male	24.2	50.6	47.3
Female	75.8	49.4	52.7
Depressive disorders	21.2	11.7	9.2
Nicotine dependence / smoking	45.5	32.8	31.8
Pain	27.3	25.2	26.1
Prescription of at least 1 other psychotropic medication in the baseline	90.9	74	76.3
Prescription of at least 1 other psychotropic medication within 365 days after index date	78.8	74.7	75.4

Table 5: Follow-up duration (years) of New Users of Asenapine, Risperidone, and Olanzapine during the 01/01/2012 - 12/31/2016 in the CPRD and THIN

	Asenapine N = 42	Risperidone N = 12,812	Olanzapine N = 10,706
Mean	0.761	0.820	1.001
Std. Dev.	1.114	1.001	1.147
Minimum	0.049	0.003	0.003
Median	0.205	0.392	0.512
Maximum	4.005	4.992	4.997

Table 6: Follow-up duration (years) of New Users of Asenapine, Risperidone, and Olanzapine within a diagnosis of Bipolar Disorder during the 01/01/2012 - 12/31/2016 in the CPRD and THIN

	Asenapine N = 27	Risperidone N = 813	Olanzapine N = 1,397
Mean	0.507	0.883	1.103
Std. Dev.	0.821	1.061	1.184
Minimum	0.049	0.008	0.005
Median	0.162	0.411	0.644
Maximum	3.181	4.912	4.984

Table 7: Incidence of Identified and Potential Risks during Follow-up among new users of asenapine, risperidone, and olanzapine between 01/01/2012 and 12/31/2016 in the CPRD and THIN

Clinical Outcome	Asenapine			Risperidone			Olanzapine		
	N (%)	Incidence/ 1,000 py[1]	95% CI	N (%)	Incidence/ 1,000 py[1]	95% CI	N (%)	Incidence/ 1,000 py[1]	95% CI
Extrapyramidal symptoms	0	0.00	NA	60 (0.47%)	5.76	4.393-7.410	44 (0.41%)	4.15	3.019-5.577
Somnolence and sedation	0	0.00	NA	190 (1.49%)	18.38	15.859-21.187	50 (0.47%)	4.70	3.487-6.194
Neuroleptic malignant syndrome	0	0.00	NA	4 (0.03%)	0.38	0.104-0.975	2 (0.02%)	0.19	0.023-0.675
Rhabdomyolysis	0	0.00	NA	1 (0.01%)	0.10	0.002-0.530	1 (0.01%)	0.09	0.002-0.520
Seizure	0	0.00	NA	82 (0.65%)	7.97	6.340-9.895	59 (0.56%)	5.61	4.271-7.238
Hyperprolactinemia	0	0.00	NA	36 (0.28%)	3.44	2.407-4.758	12 (0.11%)	1.12	0.580-1.960
Orthostatic hypotension	0	0.00	NA	36 (0.28%)	3.46	2.420-4.784	23 (0.22%)	2.16	1.367-3.237
Neutropenia	0	0.00	NA	2 (0.02%)	0.19	0.023-0.688	2 (0.02%)	0.19	0.023-0.675
Allergic reactions	0	0.00	NA	78 (0.61%)	7.54	5.959-9.408	57 (0.54%)	5.40	4.087-6.991
Dyslipidemia	0	0.00	NA	51 (0.40%)	4.92	3.665-6.471	67 (0.63%)	6.35	4.924-8.069
Diabetes mellitus	0	0.00	NA	136 (1.08%)	13.31	11.167-15.744	141 (1.33%)	13.44	11.311-15.847

[1] py = person-year

Table 8: Incidence of Identified and Potential Risks during Follow-up among new users of Asenapine, Risperidone, and Olanzapine with a diagnosis of Bipolar Disorder between 01/01/2012 and 12/31/2016 in the CPRD and THIN

Clinical Outcome	Asenapine			Risperidone			Olanzapine		
	N (%)	Incidence/ 1000 py[1]	95% CI	N (%)	Incidence/ 1000 py	95% CI	N (%)	Incidence/ 1000 py	95% CI
Extrapyramidal symptoms	0	0.00	NA	6 (0.74%)	8.43	3.092-18.339	16 (1.16%)	10.62	6.072-17.252
Somnolence and sedation	0	0.00	NA	2 (0.25%)	2.80	0.339-10.113	8 (0.57%)	5.25	2.267-10.346
Neuroleptic malignant syndrome	0	0.00	NA	0	0.00	NA	1 (0.07%)	0.65	0.016-3.617
Rhabdomyolysis	0	0.00	NA	0	0.00	NA	0	0.00	NA
Seizure	0	0.00	NA	2 (0.25%)	2.80	0.339-10.105	10 (0.72%)	6.62	3.173-12.167
Hyperprolactinemia	0	0.00	NA	7 (0.86%)	9.84	3.956-20.273	4 (0.29%)	2.61	0.710-6.670
Orthostatic hypotension	0	0.00	NA	5 (0.62%)	7.11	2.308-16.588	0	0.00	NA
Neutropenia	0	0.00	NA	0	0.00	NA	0	0.00	NA
Allergic reactions	0	0.00	NA	8 (0.99%)	11.28	4.871-22.230	11 (0.80%)	7.29	3.637-13.035
Dyslipidemia	0	0.00	NA	6 (0.74%)	8.49	3.117-18.488	14 (1.01%)	9.30	5.083-15.599
Diabetes mellitus	0	0.00	NA	9 (1.13%)	13.15	6.013-24.963	23 (1.66%)	15.30	9.696-22.952

[1] py=personal year

10.5 Other analyses

Not applicable.

10.6 Adverse events/adverse reactions

Not applicable.

11 DISCUSSION

11.1 Key results

During the first 5 years of asenapine launch, accrual of asenapine users in the study was low, despite adding the THIN to the CPRD data. Only 51 patients were identified as receiving at least one asenapine prescription, of which 42 had at least 365 days of baseline observation in the combined CPRD and THIN databases. The corresponding number of patients exposed to risperidone (12,812) and olanzapine (10,706) were considerably higher. Based on available data from the combined CPRD/THIN dataset, bipolar disorder appeared to be the indication in about two-thirds of asenapine users, as compared with 6.3% and 13.0% for risperidone and olanzapine cohorts, respectively.

Consistent with clinical expectations, results also indicated that several comorbid conditions were prevalent among asenapine users, including depressive disorders, anxiety symptoms, alcohol dependence, nicotine dependence/smoking, and pain.

None of the asenapine users were found to have the pre-specified clinical events for the identified and potential risks for asenapine during follow-up, which include extrapyramidal symptoms, somnolence, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidemia and diabetes mellitus.

There were no patients <18 years old who received a prescription of asenapine in the combined CPRD+THIN during the study period (01 January 2012 – 31 December 2016).

11.2 Limitations

This study has a number of limitations that potentially affect the validity of findings or the interpretation of the results. Some of the limitations most pertinent to the analysis described in this protocol are as follows:

1. **Limited sample size:** There was very limited prescribing of asenapine in the CPRD and THIN with only 42 available new asenapine users. Therefore, we were not able to calculate incidence rate ratios of identified and potential risks for asenapine compared to olanzapine and risperidone. In addition, treatment initiation and diagnostic information originating in secondary care may be missed if the general practitioner was not aware of or does not record the information provided in the discharge summaries.

2. **Identification of bipolar disorder (**(specifically bipolar I disorder)**):** Given that the CPRD and THIN databases are general practitioner based electronic medical record databases, they are not specifically designed to capture psychiatric disorders for research purposes. As such, the diagnostic information recorded often lacks the specificity required to differentiate between bipolar I disorder, the condition associated with the indication, from other bipolar disorders. In addition, during the baseline period, some patients with long histories of bipolar disorder may have been misclassified as not having the diagnosis. Similarly, some patients with bipolar disorder may still be undiagnosed and could still be treated as such.
3. **Ascertainment of identified and potential risks:** Since the CPRD and THIN databases include general practitioner-based electronic medical records, under-reporting or misclassification of identified and potential risks may occur. Events occurring in emergency care can also be missed. Diagnostic codes or laboratory data may lack the specificity needed to determine if an event of interest occurred.

11.3 Interpretation

Exposure to asenapine was very limited during the first 5 years of launch in the UK. The limited usage in UK was consistent with two additional asenapine surveillance studies which were also conducted in the UK under the direction of the DSRU, one in specialty care (P08310) and one in primary care (P08309).

Results indicated that bipolar disorder appeared to be the most common indication for prescribing asenapine in the CPRD/THIN, and that the pattern of comorbidity and concomitant psychotropic drug use was consistent with clinical expectations for patient receiving atypical antipsychotic agents. There were no patients <18 years old who received a prescription of asenapine in the combined CPRD+THIN dataset during the study period.

None of asenapine users were found to have the pre-specified clinical events for the identified and potential risks for asenapine during follow-up which include extrapyramidal symptoms, somnolence, neuroleptic malignant syndrome, rhabdomyolysis, seizure, hyperprolactinemia, orthostatic hypotension, neutropenia, allergic reactions, dyslipidemia and diabetes mellitus in the study period.

However, there was very limited prescribing of asenapine in CPRD and THIN with only 42 available new asenapine users. Therefore, we were not able to calculate incidence rate ratios of identified and potential risks for asenapine compared to olanzapine and risperidone.

11.4 Generalizability

The data sources for this study were the CPRD/THIN in the UK. The databases are generally representative of the UK general population.

12 OTHER INFORMATION

This study is funded and conducted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA.

13 CONCLUSION

During the first 5 years of launch in the UK, asenapine was largely prescribed for bipolar disorders, the licensed indication in UK and was not prescribed in patients less than 18 years old in the CPRD and THIN databases. The pattern of comorbidity and concomitant drug use indicated a high prevalence of comorbid conditions and concomitant medication use, consistent with clinical expectations for patients receiving atypical antipsychotic agents. None of the asenapine users were found to have the pre-specified clinical incident events for the identified and potential risks for asenapine during follow-up. However, there was very limited prescribing of asenapine in CPRD and THIN with only 42 available new asenapine users. Therefore, we were not able to calculate incidence rate ratios of identified and potential risks for asenapine compared to olanzapine and risperidone.

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