Non-Interventional Post-Authorisation Safety Study
Final Study Report
Title Page

Title	An Observational Drug Utilization Study of SYCREST® (asenapine) in the United Kingdom
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Procedure number	EU/1/10/640/001 (5 mg, 20 sublingual tablets) EU/1/10/640/002 (5 mg, 60 sublingual tablets) EU/1/10/640/003 (5 mg, 100 sublingual tablets) EU/1/10/640/004 (10 mg, 20 sublingual tablets) EU/1/10/640/005 (10 mg, 60 sublingual tablets) EU/1/10/640/006 (10 mg, 100 sublingual tablets)
Marketing authorisation holder(s)	N.V. Organon Kloosterstraat 6 NL-5349 AB Oss The Netherlands
Joint PASS	No
Research question and objectives	• Describe on-label[1] use of asenapine among patients aged ≥ 18 years diagnosed with bipolar disorder by describing baseline demographic and physical characteristics and healthcare resource utilization. • Describe other use[2] of asenapine in the general practice setting among patients aged ≥ 18 years with no record of a diagnosis for bipolar disorder by describing baseline demographic and physical characteristics, healthcare resource utilization, and other psychiatric diagnoses among asenapine users • Describe recent historical, matched aripiprazole use in the general practice setting among patients aged ≥18 years in order to put asenapine use into context by describing "baseline" demographic and physical characteristics, healthcare resource utilization and on-

	and off-label psychiatric diagnoses among aripiprazole users observed in the CPRD and THIN. • Describe off-label use of asenapine in the general practice setting among patients aged 0-17 years by describing "baseline" demographic and physical characteristics, healthcare resource utilization, and off-label psychiatric diagnoses among these asenapine users observed in the CPRD and THIN. [1]On-label use is defined as use of the product as indicated in the label specific to the United Kingdom. [2]Other use is defined as use of the product for an indication that is not on the label specific to the United Kingdom.
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1 ABSTRACT

Title

An Observational Drug Utilization Study of SYCREST® (asenapine) in the United Kingdom
Final Report

PPD

Merck Research Laboratories
PPD

Keywords

Sycrest®, asenapine, atypical antipsychotic medications, utilization, prescribing

Rationale and Background

Bipolar disorders are chronic, typically cyclic, mood disorders. Asenapine is a novel atypical antipsychotic agent indicated for treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. In addition to routine pharmacovigilance, Merck conducted this drug utilization study of asenapine in primary care in the United Kingdom (UK). This study is part of a broader post-marketing commitment to evaluate the safety profile of asenapine in clinical practice and is conducted in tandem with protocol P08307 – An Observational Post-Authorization Safety Surveillance [PASS] Study of SYCREST® (asenapine) among Patients Aged 18 and Older Diagnosed with Bipolar Disorders. The present study complements the PASS study by providing a context of asenapine utilization in both bipolar patients and in patients with other conditions.

Research question and objectives

Primary Objectives:

1. Describe use of asenapine among patients diagnosed with bipolar disorder aged 18+ years by describing "baseline" demographic and physical characteristics and healthcare utilization.
2. Describe use of asenapine among patients with indications other than bipolar disorder aged 18+ years by describing "baseline" demographic and physical characteristics and healthcare utilization observed in the study databases
3. Describe recent historical, matched, aripiprazole use in general practice among patients aged 18+ to place asenapine use in context.
4. Describe off-label use of asenapine in UK general practice among patients aged 0-17.

Secondary Objectives:

Within the contemporary, non-matched, use of all atypical antipsychotics combined, and for aripiprazole, olanzapine, quetiapine, and risperidone separately among patients aged 18+ years in the general practice setting:

1. Describe the "baseline" demographic and physical characteristics
2. Describe psychiatric diagnoses among those atypical antipsychotic users observed in the databases

Study design

This study is an observational database study with only descriptive analysis of all patients who received asenapine or a comparator medication in a primary clinical care setting.

This study utilizes an inception cohort (new users) design [Ref. 5.4: 00QRC4]. The date of the first asenapine or aripiprazole prescription after meeting cohort entry criteria serves as the index prescription date. Patients are considered 'new users' if there is no use of asenapine or aripiprazole within 365 days prior to their first prescription after meeting cohort entry criteria. New users of asenapine or aripiprazole aged 18+ are categorized according to 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 without a diagnosis of bipolar disorder or schizophrenia, (4) other pre-defined psychiatric conditions that are not in any categories above and (5) none of the pre-defined conditions above (no diagnosis). Off-label users of asenapine are defined as patients aged 0-17 years at the time they receive their new user index prescription for asenapine.

Setting

This study utilizes two large general practice databases in the UK, CPRD (Clinical Practice Research Datalink) and THIN (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.

Variables and data sources

Variables include prescription of medications of interest, comorbidities 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 the data quality indicators for the databases in the

study time period of 1 January 2012 until 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 patients 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% depressive disorders, 38.1% nicotine dependence / smoking, and 26.2% pain. 93.0% and 83.3% patients were prescribed at least 1 other psychotropic medication within 365 days prior/after receiving the first prescription of asenapine, respectively.

For the primary comparator drug, aripiprazole, a total of 7,215 new users aged 18 years or older with at least a 365-day baseline period were included. The majority of these patients had other mental disorder diagnosis [n=4,259 (59.0%)], 1,537 (21.3%) of them had bipolar disorder diagnosis and 1,161 (16.1%) of users had schizophrenia diagnosis. Bipolar disorder appeared to be the predominant indication for asenapine use compared with aripiprazole users. The aripiprazole adult users at baseline showed a 16.1% prevalence of depressive disorders, 27.5% for nicotine dependence / smoking, and 30.8% for pain, compared with asenapine users at 19.0%, 38.1% and 26.2%, respectively. There were 85.8% and 79.1% of aripiprazole patients, respectively, who were prescribed at least one other psychotropic medication within 365 days prior/after receiving the first prescription of aripiprazole, which was slightly lower than that observed in the asenapine users.

There were no patients <18 years old who received a prescription of asenapine in either the 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 older 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 like the main comparator aripiprazole prescribed in the same study period.

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2 LIST OF ABBREVIATIONS

CPRD	Clinical Practice Research Datalink
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association)
EC	Ethics Committee
EMA	European Medicines Agency
GMS	General Medical Services
GP	General Practitioner
GPRD	General Practice Research Database
IRB	Institutional Review Board
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Services
NOS	Not otherwise specified
PASS	Post-Authorization Safety Study
SCEM	Specialist Cohort Monitoring Study
eSRC	Epidemiology Safety Review Committee
UK	United Kingdom
THIN	The Health Improvement Network

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	19-JUL-2011	27-JUL-2011	Internal protocol approved. IRB submission postponed until feedback received from CHMP. Milestone listed as background information.
Protocol amendment 1 , EMA approval	7-DEC-2011	27-SEP-2012	
Protocol amendment 1 , IRB approval	7-DEC-2011	26-NOV-2012	By the ISAC for the MHRA
Protocol amendment 2 , EMA approval	14-FEB-2014	30-APR-2014	
Protocol amendment 3	5-AUG-2014	5-AUG-2014	In response to eSRC recommendations
Start of data collection	24-JUN-2013	24-JUN-2013	"…date from which data extraction starts"
End of data collection	05-MAR-2014	05-MAR-2014	"…date from which the analytical dataset is completely available"
Registration in the EU PAS register	n/a		
Study progress report 1	12-OCT-2013	13-SEP-2013	First annual interim report (Interim Report #1)
Study progress report 2	12-OCT-2014	16-SEP-2014	Second annual interim report (Interim Report #2)
Study progress report 3	12-OCT-2015	SEP-2015	Third annual interim report (Interim Report #3)
Study progress report 4	12-OCT-2016	SEP-2016	Fourth annual interim report (Interim Report #4)
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 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 primary care data an appropriate research source for this study. Due to 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 proposed as part of a broader post-marketing commitment to evaluate the safety profile of asenapine in clinical practice and was conducted in tandem with protocol SP08307 – An Observational Post-Authorization Safety Surveillance Study of SYCREST® (asenapine) among Patients aged 18 and Older Diagnosed with Bipolar Disorders, hereafter referred to as the PASS study. This study complements the PASS study by providing the context of asenapine utilization in both bipolar patients and additionally patients with other conditions.

7 RESEARCH QUESTION AND OBJECTIVES

As stated in the study protocol, these are presented below for ease of reference.

7.1 Primary Objectives

3. Describe on-label[1] use of asenapine among patients aged 18+ diagnosed with bipolar disorders by:
    a. Describing the "baseline" demographic and physical characteristics, Including prior health status, comorbidities, concomitant medications and healthcare resource utilization

4. Describe other[2] use of asenapine in the general practice setting among patients aged 18+ with no record of a diagnosis for bipolar disorder by:
    a. Describing the "baseline" demographic and physical characteristics, including prior health status, comorbidities, concomitant medications and healthcare resource utilization
    b. Describing off-label psychiatric diagnoses among asenapine users observed in the CPRD and THIN

5. Describe the *recent historical, matched,* aripiprazole *use* in the general practice setting among patients aged 18+ in order to place asenapine use in context by:
    a. Describing the "baseline" demographic and physical characteristics, including prior health status, comorbidities, concomitant medications and healthcare resource utilization
    b. Describing on- and off-label psychiatric diagnoses among aripiprazole users observed in the CPRD and THIN

6. Describe off-label use of asenapine in the general practice setting among patients aged 0-17 by:
    a. Describing the "baseline" demographic and physical characteristics, including prior health status, comorbidities, concomitant medications and healthcare resource utilization
    b. Describing off-label psychiatric diagnoses among asenapine users observed in the CPRD and THIN

[1] On-label use is defined as use of the product as indicated in the label specific to the United Kingdom.

[2] Other use is defined as use of the product for an indication that is not on the label specific to the United Kingdom.

7.2 Secondary Objectives

To describe the contemporary, non-matched, use of all atypical antipsychotics combined (i.e. olanzapine, quetiapine, ziprasidone, iloperidone, risperidone, paliperidone, lurasidone, clozapine, amisulpride, sertindole, zotepine and aripiprazole) and aripiprazole, olanzapine, quetiapine, and risperidone separately among patients aged 18+ years in the general practice setting in order to put use of asenapine into context by:

a. Describing the "baseline" demographic and physical characteristics, including prior health status, comorbidities, concomitant medications and healthcare resource utilization
b. Describing other psychiatric diagnoses among *atypical antipsychotic* users observed in the CPRD and THIN

8 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	*07-DEC-2011*	A, B, C, D, & G	Clarified use of a recent historical, matched cohort of aripiprazole users as primary comparison cohort	Given asenapine' s lone approved indication and expected market entry in 2012, aripiprazole is the most appropriate recent historical comparator with two approved indications and having entered the market in 2004 when three other atypical antipsychotics already occupied the market
			Clarified justification for using of a recent historical, matched cohort of aripiprazole users as primary comparison cohort	Given that olanzapine and risperidone entered the market more than 15 years ago, the data available in CPRD during the early post-authorization time frame for each of those products may not be equivalent to what is currently available (i.e. number of general practices contributing data, changes in standard of care, etc.). Additionally, aripiprazole is more like asenapine since it has only two approved indications (bipolar I disorder mania and schizophrenia). In contrast, quetiapine and risperidone have more labelled indications making descriptive comparisons between all off-label asenapine use and these comparators more complex.
			Clarified contemporary, non-matched cohorts of atypical antipsychotic users as secondary comparison cohorts	CHMP requested to compare utilisation of asenapine with all other atypical antipsychotics

Number	Date	Section of study protocol	Amendment or update	Reason
2	*30-APR-2014*	D	To make the definition of pre-treated patients consistent with this used in the comparative CPRD study.	In CPRD >15% of patients received an atypical antipsychotic (olanzapine, risperidone) prior to their bipolar diagnosis. Thus, to ensure that we capture these patients, we revised the inclusion criteria accordingly.
3	*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

9 RESEARCH METHODS

9.1 Study design

This is a retrospective cohort study with descriptive analyses designed to describe asenapine prescribing patterns during the post-licensure period under conditions of usual care. Of note, this study does not involve active administration of asenapine by Merck Sharp & Dohme Corp. All recipients of asenapine who are followed have received the marketed drugs in the course of ordinary clinical practice after licensure of the drugs.

9.2 Setting

This study follows patients who received prescriptions of asenapine in general practice-based electronic healthcare databases. The asenapine prescriptions are 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[3].

9.3 Subjects

Due to very low accrual of asenapine prescribed users in the CPRD in previous analyses, the THIN database was added as another data source for the report. Both the CPRD and THIN include computerized, anonymous, longitudinal patient medical records retrieved from general practitioners 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 are duplicated when both databases are combined for analysis. Because the practices that are common to both databases are not publicly known, we used an algorithm to identify the common practices (Appendix 3) [Ref. 5.4: 04RLP9]. This algorithm has been applied in previous PASS in support of MSD marketed products. For those practices that are identified as contributing to both databases, the data from the CPRD database were used. Furthermore, since the developed algorithm to identify the common practices are 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.

The eligibility criteria are as follows:

Inclusion Criteria for Patients Treated with Asenapine

This drug utilization study identifies a cohort of patients treated with asenapine in the CPRD/THIN databases who meet the following criteria for inclusion:

1. ≥1 prescription for asenapine within the study period
2. A minimum of >365 days “up to standard” days of evaluable baseline observation time prior to the date of prescription for asenapine.

[3] The final report covers the study period between 01-Jan-2012 and 31-Dec-2016 with one-month fewer 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 available only up through 31 December 2016.

Inclusion Criteria for Patients Treated with a Comparator

This drug utilization study also identifies cohorts[4] of patients treated with olanzapine, quetiapine, risperidone, paliperidone, clozapine, amisulpride, and aripiprazole in CPRD/THIN that meet the following criteria for inclusion:

1. Age 18+ at the time the patient received a prescription for the comparator
2. ≥1 prescription for olanzapine, quetiapine olanzapine, quetiapine, risperidone, paliperidone, clozapine, amisulpride, or aripiprazole within the study period
3. A minimum of >365 days "up to standard" days of evaluable baseline observation time prior to the date of prescription for above drugs.

9.3.1 Database admission criteria, quality of records

Please refer to "Annex 2. Additional information" of this report that describes the steps involved in identifying the date a given practice is contributing "research" quality data according to quality standards set by CPRD/THIN.

9.4 Variables

9.4.1 Exposure

9.4.1.1 Definition of Primary Exposure

This study utilizes an inception cohort (new users) design [Ref. 5.4: 00QRC4]. The date of first asenapine prescription after meeting cohort entry criteria serves as the index prescription date. Patients are considered a 'new user' if there is no use of asenapine within 365 days prior to their first prescription after meeting cohort entry criteria (Figure 1). New users of asenapine are operationally defined into eight mutually exclusive groups according to indication:

1. Bipolar Disorder – Diagnosis before or at treatment:
    a. Patients aged 18+years with a diagnosis of Bipolar Disorder in their medical history at any time before or at the time they receive their new user index prescription for asenapine or aripiprazole.

2. Bipolar Disorder – Treatment before diagnosis:
    a. Patients aged 18+ years without a diagnosis of Bipolar Disorder in their medical history and subsequently receive a diagnosis of Bipolar Disorder within a period not greater than 730 days following the new user index prescription date.

[4] A separate cohort is created for each comparator exposure resulting in four comparison cohorts (olanzapine, quetiapine, risperidone, and aripiprazole). The cohorts are not mutually exclusive given that patients may have taken more than one of the comparator atypical antipsychotics over time.

3. Schizophrenia – Diagnosis before or at treatment:
    a. Patients aged 18+ years without a diagnosis of Bipolar Disorder but with a diagnosis of Schizophrenia in their medical history at any time before or at the time they receive their new user index prescription for asenapine or aripiprazole.

4. Schizophrenia – Treatment before diagnosis:
    a. Patients aged 18+ years without a diagnosis of Schizophrenia or Bipolar Disorder in their medical history and subsequently receive a diagnosis of Schizophrenia (but no Bipolar Disorder diagnosis) within a period not greater than 730 days following the new user index prescription date.

5. Alzheimer's disease:
    a. Patients aged 18+ years without a diagnosis of Bipolar Disorder or Schizophrenia but with a diagnosis of Alzheimer's disease in their medical history at any time prior to 730 days following the new user index prescription date.

6. Other diagnoses:
    a. Mental Disorders: Patients aged 18+ years without a diagnosis of Bipolar Disorder, Schizophrenia, or Alzheimer's disease but with a mental disorder diagnosis in their medical history at any time prior to 730 days following the new user index prescription date. Mental disorder diagnosis includes 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.

7. No diagnosis:
    a. Patients aged 18+ years without a diagnosis of Bipolar Disorder, Schizophrenia, or any Mental Disorders diagnoses or no diagnosis in their medical history at any time prior to 730 days following the new user index prescription date.

8. Off-label:
    a. Patients aged 0-17 years at the time they receive their new user index prescription for asenapine.

Table 1 below defines the disease classifications for patients prescribed asenapine or the comparator, aripiprazole, in this study:

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

Disease Classification	Asenapine	Aripiprazole
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 aripiprazole 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 aripiprazole 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 aripiprazole 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 aripiprazole 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 aripiprazole 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 aripiprazole 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 aripiprazole prescription

[1]Off-label indication for asenapine, but labeled indication for aripiprazole
[2]Off-label indication for asenapine and aripiprazole. 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

risk 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

9.4.1.2 Definition of Comparison Exposure

The primary comparison cohort is patients newly treated with aripiprazole in the same study period as the new users of asenapine. Due to low accrual of asenapine prescribed users in the UK, a cohort of patients treated with aripiprazole are not matched to the identified new asenapine users by the time since market entry (historical matched aripiprazole users). Instead, all new aripiprazole users identified in the same study period as new asenapine users are included for analysis in the final report.

To address the secondary objectives, this drug utilization study identifies cohorts of patients treated with olanzapine, quetiapine, risperidone as comparators separately, and combines all patients with olanzapine, quetiapine, risperidone, paliperidone, clozapine, amisulpride, and aripiprazole as a combined comparison group to asenapine.

9.4.1.3 Assumptions Related to Drug Utilization

Because this study measures general practitioners (GP) prescribing and not actual drug use by patients, any inferences about drug utilization by patients require that the following set of assumptions all hold true:

1. All prescriptions were dispensed to patients on the same day that they were issued by each practice's computer system;

2. Patients consumed a prescription as directed on consecutive days after the date that each prescription was issued; and

3. Patients consumed the entire quantity of drug supplied in each prescription.

Because the CPRD and THIN databases do not capture prescriptions issued by hospital-based specialists (e.g., psychiatrists), this study only measures the quantity of prescriptions

prescribed by GP's, which does not include all health care providers in the UK National Health Service (NHS).

9.4.2 Outcome

This is a descriptive study of drug utilization of asenapine. No outcomes are being assessed in this study.

9.4.3 Covariates

Variables include prescription of medications of interest, comorbidities of interest, and patient demographic information as recorded in the CPRD and THIN databases.

9.5 Data sources and measurement

The data source for this study is from the UK including both the CPRD and THIN databases.

9.5.1 Study Procedures

9.5.1.1 Informed Consent

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

Not applicable.

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

All analyses for this study are descriptive and are stratified within treatment groups according to diagnosis classification. Pediatric asenapine users are not described because none were identified from the CPRD/THIN in the study period. Characteristics presented as continuous data are summarized through means, standard deviations, medians, minimum and maximum values; whereas, categorical data are summarized as counts and proportions.

9.9.1.1 Baseline characteristics and concomitant treatment

For each patient, baseline characteristics are described using the clinical record accumulated 365 days prior to their first prescription index date. The related concomitants, which are prescribed within 365 days after the first prescription of asenapine and comparison drugs, are also described.

9.9.1.2 Description of related diagnoses

A pre-specified list of on- and off-label psychiatric diagnoses are described among medication users of interest.

9.9.2 Main statistical methods

The new users of asenapine, aripiprazole, olanzapine, risperidone, and quetiapine are classified into a pre-specified list of psychiatric diagnoses (section 9.4.1). Please note that these five cohorts are not mutually exclusive given that patients may have taken more than one of the comparator atypical antipsychotics over time.

Baseline characteristics for each of these five cohorts will be described using the clinical record in the 365 continuous registration days prior to their first new user index prescription date. The baseline characteristics in each of the five cohorts are stratified by the pre-specified list of psychiatric diagnoses as well.

The related concomitant medications, which are prescribed within 365 days after the first prescription of asenapine and comparison drugs, are also described.

Furthermore, to address the secondary objective, all other atypical antipsychotic new users identified in the CPRD/THIN during study period including aripiprazole, olanzapine, risperidone, quetiapine, amisulpride, clozapine and paliperidone are combined as one comparison group to asenapine users. The index date for the combined group is the earliest date of the listed drugs in the study period. The related psychiatric diagnoses and baseline characteristics of this combined group are described in the same way for the five cohorts mentioned above.

Pediatric asenapine users are not described because none were identified from the CPRD/THIN in the study period.

9.9.3 Missing values

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

9.9.4 Sensitivity analyses

Due to low accrual of asenapine prescribed users, no sensitivity analyses were performed in this report.

9.9.5 Amendments to the statistical analysis plan

Due to low accrual of asenapine prescribed users in the UK, a cohort of patients treated with aripiprazole are not matched to the identified new asenapine users by the time since market entry (historical matched aripiprazole users). Instead, all new aripiprazole users identified in the same study period as new asenapine users are included for analysis in the final report.

9.10 Quality control

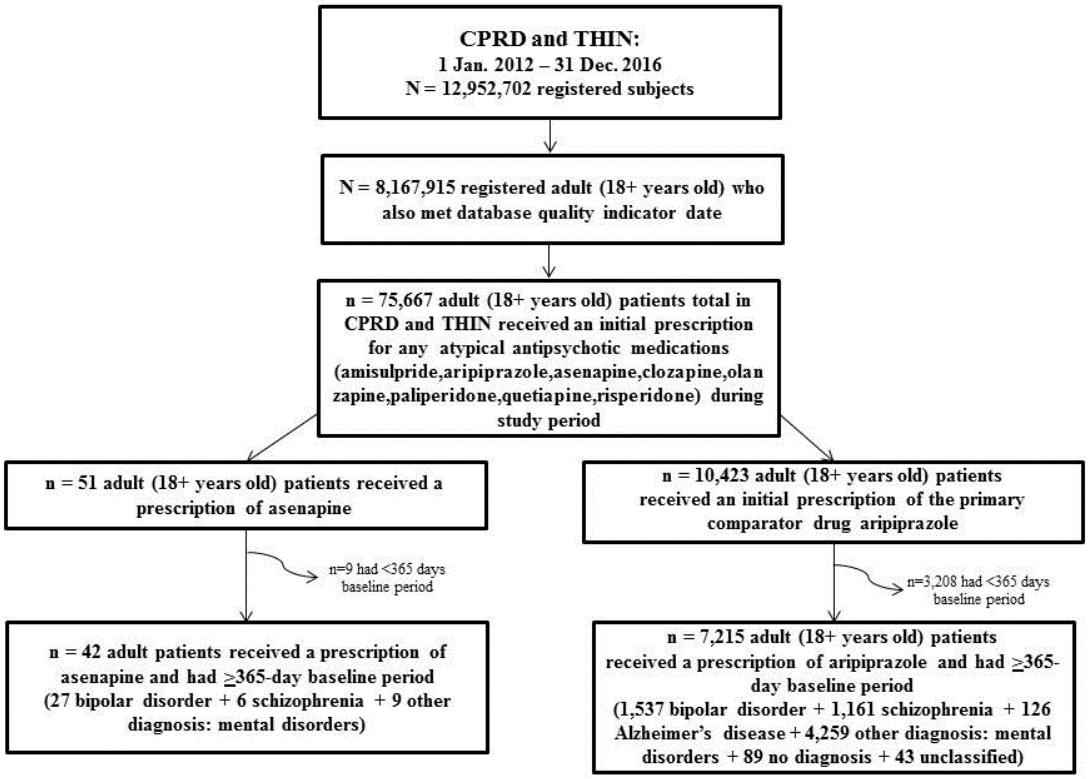
Descriptions of the CPRD and THIN Data Quality Markers are found in Protocol Number: P08308, which is also available in Appendix 1.

10 RESULTS

10.1 Participants

Patients registered in the CPRD/THIN databases 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 datasets (stratified results by CPRD or THIN are available in Appendix 4), which includes patients 18+ years old who received their first prescription for an atypical antipsychotic medication and the numbers of respective patients who received asenapine or aripiprazole. More detail about these patients and medications is provided in the subsection 10.2.

Figure 1: 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 contain 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 registered patients, respectively between 1/1/2012 and 12/31/2016. The registered adults (18+ years old) who also met the 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

No patient outcomes were assessed in this study.

10.4 Main results

Only results in the combined CPRD and THIN are described in this section. Details of other analyses including those from the stratified analyses by CPRD or THIN can be found in Appendix 4. 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 the 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 patients 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).

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 diagnosis before asenapine prescribing (40 vs.45 years old, respectively, Table 3, and Table A1 in Appendix 4). 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).

For the primary comparator drug, aripiprazole, a total of 7,215 new users aged 18 years or older with at least a 365-day baseline period were included. The majority of these patients had other mental disorder diagnosis [n=4,259 (59.0%)], 1,537 (21.3%) had bipolar disorder diagnosis and 1,161 (16.1%) had schizophrenia diagnosis. Bipolar disorders appeared to be the predominant indication for asenapine use (Table 2) compared with aripiprazole users. The aripiprazole adult users at baseline had the following prevalence of depressive disorders (16.1%), nicotine dependence / smoking (27.5%), and pain (30.8%) compared with asenapine users at 19.0%, 38.1% and 26.2%, respectively. There are 85.8% and 79.1% of aripiprazole patients, respectively, who were prescribed at least one other psychotropic medication within 365 days prior/after receiving the first prescription of aripiprazole, which was slightly lower than that observed in the asenapine users. Furthermore, users of aripiprazole had a lower percentage of females (59.6% vs. 71.4% in asenapine users, Table 3, Table A1 and A2 in Appendix 4). However, when restricting the comparison among the users of asenapine, aripiprazole and all other comparison groups to the sub-group with a diagnosis of bipolar disorder or schizophrenia, the differences in psychotropic medications use tended to attenuate; and ages among all of the comparison groups tended to be similar as well but there was still lower percentages of females, and lower prevalence of nicotine

dependence/smoking comparing all comparison groups to the asenapine users (Table 4, Table A7 in Appendix 4).

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).

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)		Aripiprazole[1] (N=7,215)		Risperidone[1] (N=12,812)		Olanzapine[1] (N=10,706)		Quetiapine[1] (N=21,966)		Combined (N=45,835)	
	N	%	N	%	N	%	N	%	N	%	N	%
Total Bipolar	27	64.3	1,537	21.3	813	6.3	1,397	13.0	2,424	11.0	4,830	10.5
Diagnosis before or at treatment	24	57.1	1,380	19.1	714	5.6	1,192	11.1	2,004	9.1	4,077	8.9
Treatment before diagnosis	3	7.1	157	2.2	99	0.8	205	1.9	420	1.9	753	1.6
Schizophrenia only[2]	6	14.3	1,161	16.1	856	6.7	888	8.3	759	3.5	3,230	7.0
Diagnosis before or at treatment	6	14.3	1,048	14.5	704	5.5	730	6.8	639	2.9	2,800	6.1
Treatment before diagnosis	0	0.0	113	1.6	152	1.2	158	1.5	120	0.5	430	0.9
Alzheimer's disease[3]	0	0.0	126	1.7	1,940	15.1	282	2.6	943	4.3	3,056	6.7
Other diagnoses: Mental Disorders[4]	9	21.4	4,259	59.0	8,782	68.5	7,791	72.8	17,265	78.6	33,326	72.7
No Diagnosis[5]	0	0.0	89	1.2	387	3.0	298	2.8	503	2.3	1,217	2.7
Unclassified[6]	0	0.0	43	0.6	34	0.3	50	0.5	72	0.3	176	0.4

[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 risk 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 and its comparators for patients 18 years and older in CPRD+THIN between 1/1/2012 and 12/31/2016

	Asenapine N = 42	Aripiprazole N = 7,215	Risperidone N = 12,812	Olanzapine N = 10,706	Quetiapine N = 21,966	Combined N = 45,835
Age (years)						
Mean	46.5	46.4	62	49.6	49.9	53.2
Median	44	45	68	47	46	50
Gender						
Male	28.6	40.4	44.2	49.1	42.2	44.2
Female	71.4	59.6	55.8	50.9	57.7	55.8
	%	%	%	%	%	%
Depressive disorders	19.0	16.1	11.7	21.1	23.5	18.9
Nicotine dependence / smoking	38.1	27.5	17.9	25.9	25.4	23.3
Pain	26.2	30.8	27.2	29.1	32.4	29.9
Prescription of at least 1 other psychotropic medications in the baseline	93.0	85.8	74	76.4	80.5	75.2
Prescription of at least 1 other psychotropic medication within 365 days after index date	83.3	79.1	71	74.7	75.5	100

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

	Asenapine N = 33	Aripiprazole N = 2,698	Risperidone N = 1,669	Olanzapine N = 2,285	Quetiapine N = 3,183	Combined N = 8,060
Age (years)						
Mean	47	46.2	50	48.3	45.5	47.9
Median	44	45	48	47	44	47
Gender	**%**	**%**	**%**	**%**	**%**	**%**
Male	24.2	42.7	47.3	50.6	41	46.1
Female	75.8	57.3	52.7	49.4	59	53.9
Depressive disorders	21.2	9.7	9.2	11.7	17	11.8
Nicotine dependence / smoking	45.5	32.4	31.8	32.8	32.4	32.3
Pain	27.3	30.5	26.1	25.2	30.5	27.4
Prescription of at least 1 other psychotropic medication in the baseline	90.9	86.5	76.3	74	84.3	76
Prescription of at least 1 other psychotropic medication within 365 days after index date	78.8	80.5	75.4	74.7	76.5	100

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 data 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 the primary comparator aripiprazole (7,215) was considerably higher during the study period. Based on available data from the combined CPRD/THIN databases, bipolar disorder appeared to be the indication in about two-thirds of asenapine users; and comparing all comparators including the primary comparator aripiprazole, bipolar disorder appeared to be the predominant indication for asenapine users.

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 like the main comparator aripiprazole, prescribed in the same study period.

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

11.2 Limitations

This study has a number of limitations that potentially affects the validity of findings or the interpretation of the results:

1. There was very limited prescribing of asenapine in the CPRD and THIN databases, with only 42 available new asenapine users. In addition, treatment initiation and diagnostic information originating in secondary care may be missed if the general practitioner was not aware of or did 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.

11.3 Interpretation

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

Available data indicated that bipolar disorder appeared to be the most common indication for prescribing asenapine in the CPRD/THIN databases, and that the pattern of comorbidity and concomitant psychotropic drug use was consistent with clinical expectations for patient receiving atypical antipsychotic agents like the main comparator, aripiprazole, prescribed in the same study period. 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).

11.4 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 being prescribed for bipolar disorder, the licensed indication in UK and was not prescribed in patients less than 18 years older 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 like the main comparator aripiprazole prescribed in the same study period.

14 REFERENCES

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15 APPENDICES

Appendix 1 List of stand-alone documents

Number	Document reference number	Date last amendment	Title
1	(Protocol Number: P08307)	31-JUL-2015	An Observational Post-Authorization Safety Surveillance (PASS) Study of SYCREST® (asenapine) among Patients aged 18 and older Diagnosed with Bipolar Disorder
2	(Protocol Number: P08308)	05-AUG-2014	An Observational Drug Utilization Study of SYCREST® (asenapine) in the United Kingdom
3	(Protocol Number: P08309)	15-MAY-2014	An Observational Post-Authorization Modified Prescription-Event Monitoring Safety Study To Monitor The Safety And Utilization Of Asenapine (SYCREST®) In The Primary Care Setting In England
4	(Protocol Number: P08310)	15-MAY-2014	An Observational Post-Authorization Safety Specialist Cohort Event Monitoring Study (SCEM) To Monitor The Safety And Utilization Of Asenapine (SYCREST®) In The Mental Health Care Setting In England And Wales