STUDY PROTOCOL

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

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Investigators

Members of the Drug Safety Research Unit (DSRU), Southampton, SO31 1AA, UK

V Marshall BSc MBBS, Clinical Research Fellow
D Layton BSc MRPharmS MPhil DipPharm MSc PhD FHEA, Principal Research Fellow
SAW Shakir MB ChB LRCP&S FRCP FFPM FISPE MRCGP, Director

Address for correspondence

Saad AW Shakir
Drug Safety Research Unit
Bursledon Hall
Blundell Lane
Southampton
SO31 1AA
UK

Tel: 023 8040 8600
Fax: 023 8040 8609
Email: saad.shakir@dsru.org

Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	17/01/2010	All	Creation	-
2	12/04/2012	Methods	Amendment	Revised definitions
3	30/08/2012	Methods	Minor update	Review by MAH
4	20/08/2014	4.1 Study design and time frame; 4.9.1 Data monitoring	Amendment	Study extension (+2 years)

Glossary of terms

Abbreviation	Term
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CYP P450	Cytochrome P-450
DSRU	Drug Safety Research Unit
ECG	Electrocardiogram
EMEA	European Medicines Agency
EPS	Extrapyramidal Symptoms
FDA	Food and Drugs Administration
GGT	Gamma-Glutamyl Transferase
GP	General Practitioner
HLT	Higher Level Term
ID	Incidence Density
IQR	Interquartile Range
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
M-PEM	Modified Prescription-Event Monitoring
NDA	New Drug Application
NHS	National Health Service
NHSRxS	National Health Service Prescription Services
NMS	Neuroleptic Malignant Syndrome
OTC	Over-The-Counter
ODS	Organisation Data Service
PEM	Prescription Event Monitoring
PIP	Paediatric Investigation Plan
PSC	Project Steering Committee
QOF	Quality and Outcomes Framework
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCEM	Specialist Cohort Event Monitoring
SOC	System Organ Class
SPC	Summary of Product Characteristics
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
US	United States

Appendix 2 List of Rare and Iatrogenic Adverse Reactions (RAIDAR)

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EXECUTIVE SUMMARY

Asenapine is a novel atypical antipsychotic agent, developed for the treatment of moderate to severe manic episodes associated with bipolar I disorder and schizophrenia in adults. [1] It was approved by the FDA on 13 August 2009 and it has been marketed with the trade name SAPHRIS ® in the US since early October 2009. Early September 2010, the FDA approved supplemental NDAs, resulting in the following indications: treatment of schizophrenia, acute treatment of manic or mixed episodes associated with bipolar I disorder and adjunctive therapy with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder. [2;3] Asenapine sublingual tablet (SYCREST®) was approved by the European Commission on 1 September 2010 for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. To date, the clinical trial safety data for asenapine in patients with schizophrenia or bipolar I disorder is based on 3457 patients, of which 631 patients are classified as having bipolar I disorder in phase 2/3 clinical trials. In total, 350 patients are recorded as having been exposed for more than 12 months, with 16 classified as having bipolar I disorder. Additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of asenapine. A Risk Management Plan has been developed for asenapine by the manufacturer. This plan includes tools designed to monitor the important risks (including class effects and off-label use).

This post-marketing Modified Prescription-Event Monitoring (M-PEM) safety study of asenapine (SYCREST®) is to be carried out by the Drug Safety Research Unit (DSRU) as part of the Risk Management Plan required by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of asenapine in clinical practice. This study, the aim of which is to proactively capture safety and drug utilisation data in the post-marketing phase of license approval of asenapine as prescribed to patients by general practitioners in England is one of two complementary studies. The other, a Specialist Cohort Event Monitoring (SCEM) study, based in the mental health trust setting is designed to monitor the safety and drug utilisation of asenapine, as initiated by specialist psychiatrists in England.

This M-PEM study will enable the systematic collection and reporting of drug utilisation and safety data on patients newly initiated on treatment with asenapine in the primary care setting. The study aims to collect exposure and outcome data for a cohort of approximately 5000 evaluable patients.

Patients will be identified from dispensed National Health Service (NHS) prescription data for asenapine, sent to the Drug Safety Research Unit by the National Health Service Prescription

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Services (NHSRxS) in England. Data collection will be in two phases. At least 3 months after the first identified prescription has been issued for each patient, the prescribing doctor will be sent a M-PEM questionnaire to gather data on asenapine treatment prescribing patterns and baseline patient characteristics such as: the year of birth, sex and body mass index (BMI) of the patient (closest available measurement prior to initiation), confirmation of indication for treatment, start dose of asenapine, date of starting treatment, reasons for prescribing, past medical history, current medication use, including OTC and herbal remedies and selected events occurring early after starting treatment with asenapine. A second M-PEM questionnaire will be sent at least 9 months later to gather data on events occurring during treatment with asenapine and events after stopping up to the end of the observation period, including cause of death (where applicable); date of stopping treatment (including reason for discontinuing therapy if treatment was stopped), and changes in concomitant medication, including OTC and herbal remedies, during treatment.

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), this M-PEM study will monitor clinically important identified and potential risks within a cohort of patients treated with asenapine. The primary focus of the study will be to describe the incidence of selected identified risks which are not well-characterized (i.e., somnolence and sedation, weight gain, oral hypoaesthesia, swelling of the tongue and throat, and allergic reactions). The secondary focus will be on 1) describing the incidence of potential risks, class effects, and two identified risks that have been well-characterized for atypical antipsychotics (i.e., extrapyramidal symptoms and orthostatic hypotension in the elderly), and 2) describing off-label prescribing and use in populations with special label precautions. The study also includes several exploratory analyses to 1) evaluate outcomes that are important but subject to mis-ascertainment (e.g., reported adherence, reported non-compliance with dosing instructions, and reported misuse), 2) identify previously unrecognized adverse drug reactions, and 3) further explore events of special interest (oral events).

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1.0 BACKGROUND

1.1 Post-marketing surveillance

The clinical safety information available when a new medicine is marketed relates to a limited number of patients.[4] This applies to new formulations of licensed medicines. Pre-marketing data will usually give little information on drug utilisation and safety post-marketing. In the UK, the Yellow Card spontaneous reporting scheme and Prescription-Event Monitoring (PEM) provide complementary systems of post-marketing surveillance on a national scale of newly marketed drugs prescribed by general practitioners (GPs) in the primary care setting.

1.2 Prescription-Event Monitoring

Standard PEM provides surveillance on a national scale. Using a study questionnaire, general practitioners (GPs) who have prescribed the new medicine are asked to report all events* that have been recorded in the patients' notes during a specific time-period after beginning treatment with the medicine, regardless of whether any events are thought to be associated with any specific drug or treatment. By removing the need for the prescribing doctor to give an opinion about whether an event might have been caused by the medicine, PEM provides the opportunity to identify reactions that may not have been suspected as being due to the drug under surveillance. The technique of PEM has been described previously.[5]

1.3 Modified Prescription-Event Monitoring

The technique of PEM can be used to examine a variety of issues relating to the use of prescription drugs. In certain situations however, it may be desirable to modify this methodology – such studies are referred to as Modified Prescription-Event Monitoring studies (M-PEM) because the study will require modifications to the standard PEM methodology Customised data-collection questionnaires are designed for such studies. Examples of the modifications may relate to establishing baseline characteristics of patients in relation to pre-specified risks, identifying physician prescribing and decision making behaviour, and evaluating risks of adverse events over various timeframes, including periods prior to starting or after discontinuation of treatment.

The specific aims of this M-PEM study are to:

Primary

- Describe the incidence of selected identified risks of asenapine in the primary care setting

* The term 'event', as used in this study, is defined as, "*any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's note .*

Secondary

- Advance the understanding of the patient population prescribed asenapine in the primary care setting;
- Describe off-label prescribing and use outside of the approved indication and/or populations with special label precautions,

Exploratory

- Describe reported non-compliance (with 10-minutes abstinence from food or drink after dosing, misuse for illegal purposes),
- Describe collection of previously described and previously unrecognised ADRs

Modified PEM studies involve a payment to GPs for the data-collection questionnaires. Requests for 'follow-up' data are made, as in standard PEM studies, using a postal questionnaire. GPs receive an additional payment to cover any administrative costs for completed questionnaires for 'follow-up' information returned. Modified PEM studies are carried out under the same ethical guidelines as standard PEM studies (section 3.0).

1.4 Asenapine sublingual formulation and licensed prescribing indications

Asenapine is a novel atypical antipsychotic agent, developed for the treatment of moderate to severe manic episodes associated with bipolar I disorder and schizophrenia in adults. [1] It was approved by the FDA on 13 August 2009 and it has been marketed with the tradename SAPHRIS ® in the US since early October 2009. Early September 2010, the FDA approved supplemental NDAs, resulting in the following indications: treatment of schizophrenia, acute treatment of manic or mixed episodes associated with bipolar I disorder and adjunctive therapy with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder. [2;3] Asenapine sublingual tablet (SYCREST®) was approved by the European Commission on 1 September 2010 for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. Approval has also been granted in several other countries and further marketing applications are currently under review.

Asenapine exhibits high affinity and potency for blocking dopamine, serotonin, alphs (α)-adrenergic and histamine receptors, and no appreciable activity at muscarinic cholinergic receptors. [6] It is formulated as a fast-dissolving tablet containing 5 milligram (mg) or 10mg of active ingredient for sublingual administration, with recommendations for twice daily dosing when initiating treatment. The tablet dissolves in the saliva within seconds and is reported to have a bitter taste.[7] Bioavailability is approximately 35% when taken sublingually with peak plasma levels attained between 0.5-1.5 hours. However, patients are encouraged to avoid foods or liquid for 10 minutes after administration, as ingestion can reduce the bioavailability to < 2% due extensive hepato-gastrointestinal first-pass metabolism. This combination of strict compliance with administration procedures and twice daily dosing may prove a challenge to

patients as increases in dosing frequencies are negatively associated with adherence to antipsychotic medication regimens.[8]

1.4.1 Safety Profile and Undesirable Effects

To date, the clinical trial safety data for asenapine in patients with schizophrenia or bipolar I disorder is based on 3457 patients, of which 631 patients are classified as having bipolar I disorder in phase 2/3 clinical trials. In total, 350 patients are recorded as having been exposed for more than 12 months, with 16 classified as having bipolar I disorder. Additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of asenapine. A Risk Management Plan (RMP) has been developed for asenapine by the manufacturer. This plan includes tools designed to monitor the important risks (including class effects and off-label use). Evaluation by the Marketing Authorisation Holder (MAH) of all safety data and possible risk factors related to the use of asenapine or related to a class effect, revealed the following important risks[1]:

Important identified risks, including class effects, are
- Extrapyramidal symptoms (EPS)
- Somnolence and sedation (excess)
- Weight gain
- Increased exposure in patients with severe hepatic impairment
- Oral hypoaesthesia
- Swelling of tongue and throat
- Increased liver transaminases [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] and Gamma-Glutamyl Transferase (GGT)
- Orthostatic hypotension in the elderly
- Allergic reactions

Important potential risks, including class effects, are
- Neuroleptic Malignant Syndrome (NMS)
- Rhabdomyolysis
- Seizures
- Hyperprolactinaemia
- Cardiovascular effects (QT prolongation and orthostatic hypotension)
- Neutropenia
- Metabolic effects other than weight gain
- Overdose
- Non compliance with the 10-minute requirement for no food or fluids after sublingual administration

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(Atypical) antipsychotic agents are associated with a number of class effects. Effects that have at this point in time not been associated with the use of asenapine, but which may be expected based on class labelling, are the following:

- Increased mortality in elderly with dementia-related psychosis
- Suicide/self injury
- Liver related signs and symptoms
- Dysphagia
- Body temperature dysregulation.

Important missing information includes:

- Use during pregnancy and lactation
- Misuse for illegal purposes
- Off-label use
- Off-label paediatric use

No data are available to assess the safety in children aged < 12 years. A Paediatric Investigation Plan (PIP) has been approved, the aim of which is to contribute to the insight in the efficacy and safety profile of asenapine in paediatric populations with regard to the targeted indications of schizophrenia and bipolar mania.

Given that asenapine shares anaesthetic properties with lidocaine and the administration recommendations highlighted above, an additional potential issue which requires addressing are whether the particular formulation and administration of the product can cause unexpectedly high incidence of acute adverse events reactions at the application site (oral mucosa). Since US market introduction (early October 2009) up until 12 February 2011, 52 cases have been reported of swollen tongue (44 events) and/or Pharyngeal oedema (11 events). In addition, 10 cases with the MedDRA PT Hypersensitivity (10 events), 3 cases with the MedDRA PT Drug hypersensitivity (3 events), 2 cases with the MedDRA PT Anaphylactic shock (2 events) and 4 cases with MedDRA PT Anaphylactic reaction (4 events) were reported. [1] Oral events may be caused by a variety of factors (e.g., hypersensitivity, extrapyramidal symptoms, local toxic reaction, anaesthetic properties of the drug which causes oral numbness that may be perceived as swelling of the tongue, or they may be reported because of increased attention to oral sensations due to the route of administration or taste). It is not known which factors are most important in these oral events.

The MAH reports that asenapine has low potential for clinical addiction, however as all drugs acting on the Central Nervous System (CNS) have some potential for abuse, the possibility of misuse and abuse cannot be excluded.[1] The novel formulation may be clinically useful in patients who cannot swallow tablets or who cheek (spit out) medication, however the rapid

absorption and formulation of this product is associated with drug/formulation tampering and abuse.[9]. There have been anecdotal reports of abuse of another atypical antipsychotic, quetiapine, among inmates in jails and prisons. [10]

1.4.2 Considerations in initiating treatment for Bipolar I disorder.

Asenapine is approved for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. According to information from the MAH holder, out of total use, the proportion of use within primary care is estimated to be 80% [internal communication Merck & Co., Inc]. This will be comprised of patients newly initiated by GP and also patients initiated by a specialist psychiatrist for whom medicines management has been transferred to the GP. Thus, the GP may take on the primary role of treating the patient, with the option of referral to specialist services if and when required and support from the community mental health care service. Alternatively, the patient may have been primarily managed by the specialist psychiatric team within the secondary care setting, and the GP subsequently participates in co-ordinated arrangements with secondary care and/or mental health services managing pharmacological treatment and monitoring for side effects and subsyndromal depressive or manic symptoms and treatment non-adherence. [11] Guidelines for baseline and ongoing monitoring have recently been reviewed. [12] Treatment involves achieving remission of symptoms of acute manic episodes and/or depressives episodes, as well as longer-term maintenance (and specifically reducing risk of suicide).

1.5 Study Rationale.

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), this modified prescription event monitoring study will monitor clinically important identified and potential risks within a cohort of patients treated with asenapine. The primary focus of the study will be to describe the incidence of selected identified risks which are not well-characterized (i.e., somnolence and sedation,weight gain, oral hypoaesthesia, swelling of the tongue and throat, and allergic reactions). The secondary focus will be on 1) describing the incidence of potential risks, class effects, and two identified risks that have been well-characterized for atypical antipsychotics (i.e., extrapyramidal symptoms and orthostatic hypotension in the elderly), and 2) describing off-label prescribing and use in populations with special label precautions. The study also includes several exploratory analyses to 1) evaluate outcomes that are important but subject to misascertainment (e.g., reported adherence, reported non-compliance with dosing instructions, and reported misuse), 2) identify previously unrecognized adverse drug reactions, and 3) further explore events of special interest (oral events and somnolence/sedation).

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2.0 AIMS AND OBJECTIVES OF STUDY

2.1 Overall aim:

To study the utilisation and safety of asenapine in (asenapine naïve) new user patients and patients initiated in secondary care with shared care GP prescribing arrangements under normal conditions of use in primary care in England.

2.2 Specific objectives:

2.2.1 The primary objectives

These are given below. Their purpose is to provide timely information on:
(i) Cohort accrual, the type of clinician responsible for, and the setting of initiation of treatment.
(ii) To quantify the incidence rate of selected important identified and potential risks which are:

- Somnolence and sedation
- Weight gain
- Oral hypoaesthesia
- Swelling of the tongue and throat
- Allergic reactions (Type 1 hypersensitivity)

by: a) estimating the incidence density and b) exploring the hazard rates of these five event outcomes over time, respectively.

2.2.2 Secondary Objectives

These are given below. Their purpose is to provide timely information on:
(i) The baseline health profile of patients on treatment with asenapine in primary care setting and the treatment programme they received to advance the understanding of the asenapine patient population in actual clinical practice
(ii) To describe the risk profile of events reported in the 12 month observation period in the overall cohort and in patient subgroups of special interest [off-label arising from contraindications and those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; and limited information is available) .
(iii) To describe clinical features and management of cases of suicide/ self injury (including overdose) in the cohort exposed to asenapine.

2.2.3 Exploratory objectives

The specific objectives that follow are all exploratory. The purposes of these objectives are to provide timely information on:
(i) Changes of health profile of patients, assessment of adherence; number of indication related episodes and duration over the study period, plus any alterations of the treatment programme during the 12 months observation period.
(ii) Indicators of:

(a) non-compliance (with the 10-minute requirement for no food or fluids after sublingual administration);

(b) misuse (excessive dosage, formulation tampering, alteration in route of administration) and diversion to third parties;

(iii) Where possible, to quantify the incidence of other frequently and rarely reported events (including other important identified and potential risks not mentioned in Objective 2.2.1 ii) and to identify previously unrecognised adverse drug reactions (ADRs)

(iv) To estimate the relative incidence of newly diagnosed oral adverse events during the early high risk period after starting treatment compared to low risk time periods with asenapine using self controlled case series methodology.

3.0 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Sciences in collaboration with the World Health Organisation (2002).[13] The method of study also complies with the Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians.[14] In addition, the DSRU is mentioned in the 'Frequently Asked Questions' section of the General Medical Council booklet, 'Confidentiality: Protecting and Providing Information', as "a professional organisation that monitors the safety of medicines to which doctors should provide relevant information from patients' records wherever possible".[15] PEM is also included in the report detailing methods in which healthcare professionals can help improve reporting of adverse drug reactions.[16]

In addition, under Section 251 of the NHS Act 2006, the DSRU have received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research (October 2009).[17]

4.0 METHODS

4.1 Study Design & Time frame

This study will use an observational cohort design. Randomisation will not be required. The study will start upon notification of the date of market launch in England (Q1 2012) and continue for a maximum of 5 years, or until the target sample size has been achieved (whichever is the soonest; see section 4.2). The final cohort size and the duration of recruitment will be influenced by the level of prescribing of the atypical antipsychotic by GPs in England. Cohort recruitment rate for this study is based on prescribing data, incidence and

prevalence statistics. Slow uptake may impact the ability to meet the study objectives; in this instance due consideration should be given to the need to continue data collection and the feasibility of study completion should be open to re-evaluation. This will be an important area of review by the study team and MAH in order to monitor and agree upon any appropriate remedial actions.

Another important consideration is the capture of data on the initial period of usage. We anticipate that a proportion of patients (% as yet unknown) will be initiated within hospital and affiliated secondary care institutions. This study design will capture data on patients in primary care who continue therapy that was started in secondary care, as well as patients newly initiated on asenapine by the GP. Therefore, this design will not capture data on patients who start and stop treatment within the hosptial/secondary care setting. This could introduce error through selection bias (see section 5.3) into interpretation of results because the M-PEM study population may not be entirely representative of the total target population of new users of this product. However, as the data are sampled at national level, the cohort is representative of the population registered within the NHS in England in the general practice setting. As described previously, a complementary study to examine treatment initiation by specialist psychiatrists within the secondary care mental health care trust setting is proposed. A separate full final protocol is available.

Therefore, at 12 months (Q1 2013), cohort accrual will be examined to determine the proportions of patients initiated in primary care and in secondary care (based on response to relevant question on treatment initiation on the questionnaire) This is possible because GPs in England typically receive summary information on in-patient episodes and for out-patient care. In addition, in some cases, decisions by hospital doctors to start treatment with medicines are conveyed to GPs who issue the first prescriptions for the medicines recommended by the hospital based doctors; these are patients for whom shared care arrangements with GP are in place for prescribing.

All patients who receive a prescription from a GP for asenapine in the primary care setting will be eligible for inclusion (see section 4.3.1). Patients will be observed from start of treatment with asenapine (index date) and for a minimum of 12 months (or less if patient is censored because of treatment cessation or attrition) in order to allow for detection of acute outcomes associated with treatment initiation and events with delayed onset that might occur within 12 months after starting asenapine treatment. Data will be captured using a two-phased approach. The first questionnaire will be sent at least three months after the patient's first asenapine prescription and aims to capture information on baseline characteristics, acute adverse events associated with specific risks of interest including any early compliance/adherence issues. The second questionnaire will be sent at least 12 months after

the patient's first prescription and aims to capture time-variant data such as changes in health-status, disease severity, medications and adverse events with delayed onset associated with specific risks of interest, as well as awareness of misuse for illegal purposes.

4.2 Sample size

The ability to detect any particular adverse event is dependent on the expected incidence rate of the adverse event in those exposed to the drug, the background rate in those not exposed to the drug, and the total number of patients. The anticipated use of asenapine in the first years of marketing in the UK is projected to be modest, but is difficult to predict.

4.2.1 Sample size for general safety surveillance of events where background event rate is known

It is possible to estimate a sample size necessary to detect a specified adverse event with known background incidence rate (BR) by effect size (Table 1). Table 1 displays the sample sizes for a given power across a range of background rates and rate ratios or incidence density ratios (IDR). The table may also be used to interpret sample sizes for risk differences or incidence density differences (IDD) by the following formula:

$IDD = (BR \times IDR) - BR$

For this M-PEM study, a sample size of 5000 evaluable patients (see section 4.3.4) is desirable to detect an effect size (relative incidence rate) of at least 1.5 with power of 90 % at 5% significance for analysis of events of interest within the primary objectives (section 2.2.1) for which the hypothesised background rate is common (>1.0%), such as somnolence/sedation, weight gain and oral hypoaesthesia. [18]

As sample size calculations are based on overall cohorts, further unplanned subgroups or stratification of the data would underpower subsequent analyses. For this study, it is also desirable to have appropriate sample size sufficient to detect 2.0 fold increase in events of interest such as oral hypoaesthesia, weight gain and somnolence sedation for **sub-sets of asenapine users** (defined e.g by primary diagnosis) assuming the hypothesised background rate is common (>1.0%) or more in that population. Thus a sub-set sample size of 1423 would be sufficient to detect a 2.0 fold increase in such events with power of 90% at 5% significance, whilst a sub-set sample of 1250 would be sufficient to detect a 1.5 fold increase in somnolence/sedation events assuming the hypothesised background rate is 4.0% in that population with power of 90 % at 5% significance.

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Table 1. Sample sizes of evaluable patients for detection of a specified adverse event with known background incidence rate by effect size.

	Rate Ratio > 1.5	Rate Ratio > 2.0	Rate Ratio > 3.0	Rate Ratio > 3.5	Rate Ratio > 4.0
Background Rate (%)	Power 80%				
1.0	3578	992	292	200	147
2.0	1789	496	146	100	74
3.0	1193	331	97	67	49
4.0	894	248	73	41	37
5.0	716	198	58	40	29
Background Rate (%)	Power 90%				
1.0	4983	1423	437	304	227
2.0	2492	712	218	152	114
3.0	1661	474	146	101	76
4.0	1246	356	109	65	57
5.0	997	285	87	61	45

Notes: alpha = 0.05 (two-sided); Reference: Machin D, Campbell M, Fayers P, Pinol A. 1997. *Sample Size Tables for Clinical Studies*, 2nd edn, Blackwell Science: Oxford, pp. 144. [18]

4.2.2 Sample size for general safety surveillance of events where background event rate is unknown

For purposes of general safety surveillance (for events arising from exploratory objective (iii) section 2.2.3) for the population of interest, it is possible to estimate a sample size necessary to detect a minimum of three cases[†] based on an assumed rate in that exposed sub-group and assuming the background rate is zero. [20] For this study, a sample size of 5000 evaluable patients (see section 4.3) should allow for the detection of at least three cases of an adverse event, if the event occurs at a rate of at least one in 1000 patients (where the background rate is unknown); [20] a sample size of 1000 evaluable patients (see section 4.3) would allow for the detection of at least three cases of an adverse event with 85% power, if the event occurs at a rate of at least one in 200, whilst a sample size of 500 evaluable patients (see section 4.3) should allow for the detection of at least three cases with a rate of at least one in 100 at 85% power.

[†] In many situations involving rare reactions it is assumed that the frequency of the event is small, so that the occurrence of the event follows a Poisson distribution and the 95% CI calculated based on the number of events. If no events are observed in a study of X individuals then one can be 95% certain that the event occurs no more often that 3/X. [19]

4.2.3 Sample size for self-controlled case series analysis of oral events of interest

For this exploratory objective, the sample size is based on desired minimum effect size for the analysis of oral events (as primary endpoint for SCCSA) and is anticipated to be comprised of 5000 evaluable patients (see section 4.3), from which 255 cases of oral events would be expected.[‡] If this were true, with the first two weeks of exposure for each patient regarded as at 'high risk', and an average time in study of 0.5 x 3[§] = 1.5 years, and using a 2-sided test at 5% significance level, a study with a cohort size of 5000 from which the cases are sampled, would have 80% power to detect a relative incidence (high risk period compared to the others) of 2.4 (or greater); or 90% power to detect a relative incidence (high risk period compared to the others) of 2.7 (or greater). [Personal Communication P Farrington]

4.2.4. Cohort accrual considerations

Examination of sales projections by the manufacturer estimate initiation of treatment for approximately 2,500 patients within the UK during the first 12 months of marketing. Assuming that around 80% of these patients **end up** receiving prescriptions from their GPs, and a response rate from GPs of 50%, we can anticipate obtaining data on approximately 1000 patients of all indications during that first period. At the first interim (datalock at the beginning of Month 13), cohort accrual and the frequency rates for selected outcomes of interest can be reviewed and the adequacy of this sample size reassessed to determine the requirement for the final cohort size. Thus, although the speed of data collection during the study will be driven by the level of prescribing of asenapine in England, study duration and cohort size will ultimately be determined by the quantity and content of the data gathered. Due consideration should be given to the need to continue data collection as necessary to meet study objectives. Data collected during later years can be compared with earlier periods to identify any trends in drug utilisation that may be emerging.

4.3 Study Population

4.3.1 Inclusion Criteria

Patients will be identified by means of data extracted from dispensed National Health Service (NHS) prescriptions for asenapine, written by any GPs in England (irrespective of past

[‡] Estimates from clinical development programme give an approximate 25 cases of oral events in 482 patients in short term studies (3 months), this assumes the incidence (risk) of 5.1% is constant and equivalent to 2 cases per week in that trial. Using these data it can be assumed that if a sample size of 5000 evaluable patients followed-up over 3 year study duration, the expectation is that 5.1% of these would be cases which is effectively equivalent of 255 cases over that time, or 1.6 cases per week.

[§] A one-year average observation period is taken to account for different length of follow-up for each person. For example, for a three year study with staggered entry, the first person treated will have three years in study, the last may have only a few days (essentially time=0), so the average follow-up is 1.5 year.

participation within PEM studies[**]) and supplied in confidence to the DSRU by the NHS Prescription Services (NHSRxS) of the NHS Business Services Authority for England. M-PEM questionnaires are sent according to the chronological order of prescription issue date to those GPs who prescribed the newly marketed medicine until the target sample size is achieved. The intention as per study aim is to recruit a cohort prescribed asenapine, irrespective of indication. Thus, since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria apply to maximise external validity.

Patients for whom a study questionnaire containing useful information has been returned, will be included in the study cohort regardless of the dose or frequency of administration of asenapine, and irrespective of whether any medicines are concurrently administered.

4.3.2 Exclusion Criteria

Patients will also be excluded if the GP reports that the patient is no longer registered with the practice and no information is provided (NB.where information is available up to a specific date that data will be included). In addition, patients will also be excluded for whom the information provided on the M-PEM relates to either another antipsychotic drug, or the index date is an improbable date (i.e. before market launch date), or if the GP reports that the patient did not take or was never prescribed asenapine,

4.3.3 Post inclusion-exclusion criteria

Evaluable patients for primary objective (i) and secondary objective (i) will not include those where the initial 3-month survey questionnaire was returned blank (contain no clinical information) or has not been returned. Evaluable patients for all other objectives will not include those patients for whom both the 3-month or 12-month questionnaires were returned blank (contain no clinical information) or had not been returned.

4.4 Data Collection

4.4.1 M-PEM Questionnaires

Records-based data collection in this study will be conducted in two parts.

4.4.1.1 Three-month survey M-PEM questionnaires

For each eligible patient, at least 3 months post index date, data on relevant past medical history (see section 4.5) and additional exposure data contained within GPs' primary care medical records for will be requested from and abstracted onto a questionnaire, by the GP.

[**] Those GPs who have informed the DSRU that they do not wish to participate in PEM studies are excluded from receiving questionnaires

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Note that undertaking laboratory tests and ECG monitoring are not current standard practice when initiating antipsychotic medication; therefore such information will not be collected. These data will be submitted to the DSRU. A proportion of GPs are likely to fail to submit these questionnaires, so they will be sent a reminder request.

Data obtained from the 3-month survey will include:

- date and dose details of first asenapine prescription;
- setting and prescriber type;
- reason for prescribing (e.g. formulary decision, patients request etc);
- indications[††] (based on clinical diagnosis and supported by information recorded within the QOF mental health disease register based on READ codes held at each relevant practice, where available), and date of diagnosis of first ever recorded episode (mania or hypomania associated with Bipolar 1 disorder);
- date first treatment for any affective disorder including major depression relevant to indication;
- treatment as monotherapy or combination therapy
- treatment details of other drugs given as combination therapy (including lithium and valproate)
- If on lithium, the following laboratory values:TSH(mU/L), lithium (mMol/L) and eGFR(mL/min)
- demographic characteristics (age and gender)
- presence of general health factors (BMI status, weight -, date of most recent measurement);
- frequency of GP surgery attendance in past year
- risk factors for alcohol/substance misuse (ever at baseline);
- relevant medical history for important potential and identified risks of interest;
- exposure to psychoactive medications of interest (such as benzodiazepines) prior to and upon starting treatment;
- event reports of selected risks of interest associated with start of treatment (Somnolence/sedation; oral hypoaesthesia, pharyngeal hypoaesthesia, oropharyngeal

[††] General practitioner-based electronic medical records is not specifically designed to capture psychiatric disorders for research purposes. The Quality and Outcomes Framework (QOF) is the annual reward and incentive programme detailing GP practice achievement results.[21] It is a *voluntary* process for all surgeries in England and was introduced as part of the GP contract in 2004. One of the clinical domains reflects Mental health. It contains six quality indicators against which QOF achievement in that area is measured. The QOF mental health register is a count, for each GP practice, of the total number of people "with schizophrenia, bipolar disorder and other psychoses". The information is not captured from GP systems at any lower level of aggregation. The data are captured according to this definition to support QOF payments, and the data capture is designed only to meet payment requirements. Thus it is also not specifically designed to capture data 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 will initially be constructed whereby bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified (NOS), and cyclothymia will be categorised under the label 'bipolar disorder'". **READ** codes are a coded thesaurus of clinical terms used by clinicians to encode such data and which thus facilitate the access of information within patient records to enable reporting, auditing, research, automation of repetitive tasks, electronic communication and decision support.

swelling (swelling of tongue and throat), hypersensitivity/allergic reactions); suicide/self injury

- GP awareness of non-compliance to administration requirements in the first 3 months after starting treatment;
- GP awareness of general adherence problems in the first 3 months after starting treatment;
- GP awareness of aberrant behaviours, misuse for illegal purposes formulation tampering and alteration in route of administration during the first 3 months after starting treatment.
- date and reasons for stopping (if stopped within first 3 months after starting);
- treatment regimen changes (dose and/or frequency)
- if stopped and later restarted during 3 month period: date and reasons for re-starting
- date of death (if died) in the first 3 months after starting treatment;

4.4.1.2 12-Month M-PEM questionnaires

For each patient for whom a valid baseline questionnaire has been received, at least 12 months observation post index date (approximately nine months after the baseline M-PEM questionnaire was sent) , the GP will be prompted to complete a second M-PEM questionnaire which will gather information on clinical events of medical interest and serious adverse event reports [classified using the International Conference on Harmonisation definitions [22]].

Data obtained from this 12-Month M-PEM questionnaire will include:

- changes in general health factors (BMI status, weight,) and date last measured (closest to end of 12 month observation date);
- number of disease episodes of mania/depression (plus average duration);
- changes in medication treatment regimen (number of asenapine prescriptions with date, dose and frequency).
- event reports, with focus on selected delayed onset risks associated with longer-term exposure [metabolic effects other than weight gain i.e. hyperglycaemia and Diabetes Mellitus Type 2); extrapyramidal symptoms; cardiovascular events]; other events of interest [Somnolence/sedation; oral hypoaesthesia, pharyngeal hypoaesthesia, oropharyngeal swelling (swelling of tongue and throat), hypersensitivity/allergic reactions]; suicide (including overdose and self-injury); and any other events reported during the 12 months since starting treatment (including pregnancy) [‡‡]
- GP awareness of ongoing non-compliance to administration requirements

[‡‡] All reported pregnancies are followed up post estimated delivery date to capture additional information on outcomes relevant to the birth. Information on lactation is obtained through routine event reports.

- GP awareness of ongoing general adherence problems
- frequency of GP surgery attendance in 12 months post index date
- date and reasons for stopping (if stopped);
- date of death (if died)

The process of capture of patient data for this study is summarised in Figure 1.

Figure 1. MPEM study of asenapine

DSRU notifies NHS Prescription services (NHSRx) of **asenapine** study
↓
DSRU receives data from dispensed National Health Service prescriptions issued in England by GPs from the date of marketing approval
↓
Part 1: M-PEM baseline questionnaires sent to GPs (≥ 3 months after NHS FP10 1st prescription issued for patient)
↓
Part 2: M-PEM 12 month observation questionnaires sent to GPs (≥ 12 months after NHS FP10 1st prescription issued for patient)
↓
M-PEM questionnaires returned from Part I and II, scanned, reviewed and data entered onto DSRU database
↓
Selected events of medical interest, suspected ADRs, deaths (where cause not known) and pregnancies undergo further evaluation.

[Patient confidentiality maintained throughout]

4.4.1.3 Follow-up Questionnaires

During the course of the study, selected outcomes of interest (arising from Section 2.2) may undergo further evaluation to inform on any unusual features/manifestations, relevant risk factors, clinical course and behaviours. Where necessary, a supplementary follow-up questionnaire which is bespoke to the outcome of interest may be sent to gather additional relevant information. These events will be assessed for drug-relatedness by at least two trained DSRU research staff (of which at least one will be a medical physician). [23]

With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection will occur post the survey period. These data will be analysed at aggregate level partially at the time of compiling the interim report (because all information may be available then) and at study completion. Such aggregate analyses can help formulate possible hypotheses which then require further analytic study. Because of the epidemiological nature of the design of this cohort study, any *conclusions* on

drug-relatedness will be made on aggregate basis at study milestones, i.e. when the interim and final reports are written (see Section 4.9.1 on Communications).

If any other safety issues become apparent during the conduct of this study, additional events and/or event categories may be added to the list of events for follow up and this will be documented accordingly.

Specific outcomes of interest for further evaluation*:*

1. Pregnancies: All reported pregnancies will be specifically followed-up using a supplementary questionnaire to ascertain the outcome of pregnancy.

2. Deaths: All reported deaths will be followed-up to try to establish the cause of death.

3. Prescribing: If on lithium or valproate, number of prescriptions (date dose and frequency.

4. Prescribing: If taking moderate or strong CYP 450 1A2 inhibitors (Atazanavir, Cimetidine, Ciprofloxacin, Enoxacin, Ethinyloestradiol, Fluvoxamine, Mexiletine) or inducers (barbiturates, carbamazepine, primidone, rifampicin or smoker) details of dose (if drug) and duration (start/stop dates)

5. Events: Selected events of interest as defined in Table 2 will be followed-up for additional information on relevant risk factors.

6. Events: GP awareness of adherence with treatment, aberrant behaviours, misuse and unsanctioned diversion

7. Adverse events: Other adverse events deemed of medical importance by the DSRU which are considered to be possible safety signals (either arising from literature reports post marketing, or subsequent to interim data analysis) may also be followed-up for additional information on relevant risk factors for signal strengthening purposes.

8. Adverse events: Events within the list of Rare and Iatrogenic Adverse Reactions (RAIDAR) events compiled by the DSRU (Appendix 2) will be automatically followed up if a more likely alternative explanation for their occurrence is not given.

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Table 2. Selected events of interest requiring further evaluation

Risk/Missing Information	Proposed data capture	Comment
IDENTIFIED AND POTENTIAL RISKS		
Suicide/self-injury (inc Overdose)	Targeted outcome questions	Data on specific categories of symptoms will be collected (C-CASA). Events of overdose are those of clinical medical importance which require acute medical treatment (with or without) hospitalisation.
Extrapyramidal symptoms (EPS)	Targeted outcome question	Data on specific categories of symptoms will be collected
Somnolence and sedation	Targeted outcome question	
Weight gain	Targeted outcome question	Assessed by the prescriber
Increased exposure in patients with severe hepatic impairment	Targeted outcome question on other medications including prior or concomitant CYP 450 moderate/strong inducers	Data on CYP 450 Drug-drug interactions and special risk groups (elderly,,severe hepatic or renal disorder) will be collected
Oral hypoaesthesia	Targeted outcome question	
Swelling of the tongue and throat	Targeted outcome question	Data to distinguish between true swelling and sensations of swelling will be collected.
Increased liver transaminases and Gamma-Glutamyl Transferase (GGT); Bilirubin	General event report	Data on diagnosis of hepatic failure and where abnormal laboratory results indicate 3 X ULN relevant parameters will be collected.
Orthostatic hypotension	General event report	Data on (orthostatic) hypotension and syncope and falls will be collected
Neuroleptic Malignant Syndrome (NMS)	General event report	
Rhabdomyolysis	General event report	
Seizures	Targeted outcome question	
Hyperprolactinaemia	General event report	
Cardiovascular effects: QT prolongation **Thromboembolic events**	Targeted outcome question on arrythmias Targeted outcome question	Data on arrhythmias will be collected and follow-up for ECG confirmation
Neutropenia	Targeted outcome question	
Metabolic effects other than weight gain: **dyslipidemia,** **diabetes mellitus**	General event report Targeted outcome questions	Data on indicators of persistent abnormal blood glucose levels will also be collected
Non-compliance with the 10 minute requirement for no food or fluids after sublingual administration	Targeted outcome question	Data on GP awareness of non-compliance will be collected

Allergic reactions	General event report	Data on allergic reactions in hypersensitivity will be collected since misclassification with oral hypoesthesia is possible
IMPORTANT MISSING INFORMATION		
Use during pregnancy and lactation	Targeted outcome question	
Misuse for illegal purposes	Targeted outcome question	Data on risk factors for substance misuse at baseline, indicators of aberrant behaviour during treatment and GP awareness of unsanctioned diversion will be collected

4.4.2 Methods to Maximise Questionnaire Response Rate
4.4.2.1 Three- and 12- month M-PEM questionnaires

A proportion of GPs are likely to fail to respond to these questionnaires at this monitoring stage. Single reminder questionnaires are sent by post to those GPs who have not responded within one month of the date the initial questionnaire was sent.

4.4.2.2 Specific event follow-up questionnaires

A duplicate event follow-up questionnaire will be sent to GPs for the specific patient(s) for whom they have not responded to the initial follow-up questionnaire; within six weeks of the date the initial event follow-up questionnaire was sent. GPs will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

4.5 Data processing

GP and patient identifiable information will be stored within the DSRU PEM database. All original documents, individual correspondence from health care professionals will be stored for 10 years at the DSRU, with considerable care taken to preserve patient confidentiality (see below).

4.5.1 Review of data

All returned questionnaires with clinical data will be reviewed by a DSRU research fellow and coded onto the study database. Medically important adverse events that have been selected for follow-up will be coded as a priority. There will be regular monthly review of both the number of patients identified and study questionnaires returned, processed, and classified as void. This will assist in determining the point at which the final cohort size will be achieved. Aggregate data will be reviewed at interim and end of study milestones.

4.5.2 Coding of data

Data on indications, exposure, relevant medical history and medication use plus events of interest will be coded directly from the questionnaire which reference Medical Dictionary for Regulatory Activities (MedDRA) terminology and coded onto the DSRU PEM database.

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific PEM database region and will be maintained within the DSRU. Regular meetings of DSRU staff will be held to discuss study questionnaires that are difficult to code. A consensus opinion would be reached by medically qualified staff.

Methods to handle issues of missing or conflicting data, will be summarised within the detailed study specific Statistical Analysis Plan (SAP) which will be constructed to assist database development.

4.5.3 Confidentiality procedures

All DSRU staff sign confidentiality agreements and the DSRU is registered with the office of the Data Protection Registrar (Registration No. Z5438861).

DSRU information security policies are in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring the premises provides suitable physical and environmental security, all DSRU equipment is secure and protected against malicious software, the network can only be accessed by authorised DSRU staff, telecommunication lines to the DSRU premises are protected from interception by being routed overhead or underground and personnel receive training regarding security awareness.

All original documents, individual correspondence from health care professionals, will be stored for 10 years at the DSRU, with considerable care taken to preserve the confidentiality of data. The DSRU databases are well protected. To ensure patient anonymity, the names and addresses of patients will be deleted from the DSRU database after two years from receipt by NHSRxS (see section 3.0), as per current policy. Until this time, only appointed staff would have access to such data.

4.6 Quality Assurance

Good clinical data management is a high priority at the DSRU. A number of strategies exist to minimise biased PEM study results. The DSRU has a set of rules and processes associated with the conduct of pharmacoepidemiological studies. Data quality is assured through a number of

methods based on error-prevention, data monitoring, data cleaning and documentation. These include:

- Operator training;
- Vigilance of operators at the various stages of processing,
- On screen validation during data entry,
- Adoption of and adherence to study-specific data coding conventions,
- Coding review meetings,
- Code list and algorithms
- Double entry (random sample of 10% of M-PEM questionnaires),error reporting and correction of discrepancies between the entries by quality assurance staff
- Coding of M-PEM questionnaires are randomly reviewed by a quality assurance assessor.
- Routine data cleaning to screen for errors, missing values and extreme values and diagnose their cause; this being supported by bespoke software with objective, standardised logical checks and undertaken by the DSRU data manager or allocated staff.
- Relevant maintenance of reference tables, e.g., Event Dictionary
- Pilot testing of study documentation

4.7 Data analysis

4.7.1 Cohort accrual, the type of clinician responsible for, and the setting of initiation of treatment

The following relates to Section 2.2.1 Primary objective (i). Data on prescriber and valid cohort response rates will be presented, as will data on prescriber type and setting. These data will be used to inform on cohort accrual and study timelines to target sample size.

4.7.2 To quantify the incidence of selected events considered to be important identified and potential risks

The following relates to Section 2.2.1 primary objective (ii) and relates to somnolence and sedation, weight gain, oral hypoaesthesia, oropharyngeal swelling (swelling of tongue and throat) and allergic reactions (Type 1 Hypersensivity) events as reported in Table 2.

The incidence of these events will be explored by estimating the hazard rates of these events over time. Such methods account for truncation of exposure time and censoring; for these analyses the exposure time would be censored at the time of the first event. Smoothed hazard plots will be used to describe how the baseline risk of an event changes over time. Estimates of the hazard function will also be modelled to determine whether the baseline hazard (risk) of the event increases or decreases with time. A constant hazard over time may be consistent with a background (not caused by the drug) event rate, whereas a non-constant hazard over

time may be an indicator of a drug-event relationship. The null hypothesis that the hazard rate of the selected event in patients prescribed asenapine will be constant during the 12 week period following the start of treatment will be tested by fitting a parametric time to event model (e.g Weibull). Such models have a shape parameter that indicates whether the hazard is significantly increasing or decreasing over time. At least five reports of an event are deemed necessary for modelling purposes.* A sensitivity analysis will be performed to include in the numerator events reported within 30 days of stopping, and extend the denominator by 30 days

**When the shape parameter (p) for the Weibull model is equal to one, the hazard is estimated to be constant over time, if p greater than one the hazard is increasing, if p less than one the hazard is decreasing. The hazard function will be determined as non-constant if the 95% CI excludes the value one*.

Graphs of cumulative counts of events of interest, by month over the study period, will be examined for possible change in reporting over calendar time.

4.7.3. The baseline health profile of patients on treatment with asenapine in primary care setting and the treatment programme they received to advance the understanding of the asenapine patient population in actual clinical practice

The following relates to Section 2.2.2 secondary objectives (i) and (ii). Valid cohort demography (age and gender) will be presented, as reported at baseline. Carstairs Deprivation Score [24] will be determined for GP practice and used as surrogate marker of patient socioeconomic status. Other baseline general health factors [BMI, weight and height, BP (Systolic and diastolic)] and indication-related characteristics [primary (and secondary if provided) diagnosis , duration since first ever recorded episode of primary diagnosis as indicator of disease severity]; general pattern of treatment adherence of the patient [frequency of GP attendance in 12 month prior to index date] treatment initiation programme (asenapine starting dose and frequency, if first initiated by specialist – duration between initiation date and first GP NHS FP10 prescription date , treatment as mono- or combination therapy, drugs given as combination therapy) and prescribing reasons as reported on the M-PEM questionnaire will be described.

A synopsis of prior and baseline relevant morbidities and medication use will also be provided. Patient subgroups defined by whether asenapine naïve or past user, or other subgroups of special interest [Table 3 - off-label arising from contraindications and those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; and limited information is available] will be characterised in order to inform on missing information regarding use of asenapine. Where possible, these groups will be compared in terms of

demographic factors and other study variables. Further stratification by calendar period *may* also be undertaken to identify any cohort effects or trends that may be emerging.

The proportion of patients within each special population sub-group prescribed asenapine who had *one or more* relevant characteristics/conditions/co-prescribed medications at baseline will be summarised within each indicator group by simple aggregation of counts (see Table 3)

Table 3. Special population Indicators of Use

3a) Indicators of Contraindicated Use *(Patients can have up to 5 indicators)*
Children aged < 18 years
Treatment for indications other than BPD
Previous hypersensitivity to asenapine
Severe hepatic impairment
Elderly patients with dementia-related psychosis
3b . Indicators of Use with Special Warnings or Precautions *(Patients can have up to 11 indicators)*
Moderate hepatic impairment
History of seizure disorders
History of known cardiovascular disease
History of known cerebrovascular disease
Baseline or concomitant use of drugs associated with QT prolongation
Baseline or concomitant use of anticholinergics
History of Parkinson's Disease
History of Dementia with Lewy Bodies
Baseline use of psychoactive medications
Baseline use of products that are both CYPD26 substrates and inhibitors (e.g., paroxetine)
Breastfeeding
3c . Indicators of Use with Appropriate Clinical Monitoring Recommended *(Patients can have up to 4 indicators)*
History of suicide attempt/self injury
History of tardive dyskinesia
History of hyperglycaemia/diabetes mellitus
History of hyperprolactinaemia
3d . Indicators of Use in Patients with Limited Information *(Patients can have up to 3 indicators)*
Adults aged 65+years
Severe renal impairment
Pregnancy

3e. Indicators of Use with Potential Drug-Drug Interactions *(Patients can have up to 3 indicators)*
CYP1A2 inhibitors e.g fluvoxamine
Alpha1-adrenergic antihypertensives
Levodopa or dopamine agonists

4.7.4 To describe the risk profile of events reported in the 12 month observation period in the overall cohort and in patient subgroups of special interest [off-label arising from contraindications and those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; and limited information is available)

The following also relates to Section 2.2.2 secondary objective (ii). PEM methodology provides a numerator (the number of reports of an event) and a denominator (the number of patient-months at risk), both collected within a known time frame. This allows for the calculation of risk (percent of total valid cohort exposed) and incidence densities (ID; person-time incidence rates) for each event. Such analyses will be performed using 'Higher-level' event terms from the MedDRA dictionary. The risk profile of the overall cohort and sub-group of interest (based on characteristics defined at baseline, including whether asenapine naïve or past user) will be described by presenting summary tabulations (by rank) of counts and incidence risk of reported events, and crude event rates (IDs).

Crude Incidence Densities (ID) [§§]can be calculated by month in order quantify rates of events. IDs will be calculated, for each given time period (t), for all events reported in patients who continue to take asenapine for a given time period, or for whom the date of stopping is known. Only the first report of an event in an individual patient is used in the calculation of IDs. They are usually expressed as the number of first reports of an event per 1000 patient-months. This assumes pattern of use is continuous. The numerator will be the first reports of events reporting as occurring after the index date and during treatment.[***] For this study, IDs will be calculated for each event as for each month as follows:

[§§] It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

[***] Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.

ID_t = Number of first reports of an event during treatment for period t x 1000
Number of patient-months of treatment for period t

Thus, $ID_t = \frac{N_t \times 1000}{D_t}$

where: N_t = Number of first reports of an event during treatment for period t,

and D_t = Number of patient-days of treatment for period t
30

IDs will also be calculated for all 12 months during treatment combined (ID_A), and the first month after stopping (ID_{S1}) if patient stopped (and where patients are recorded as remaining on treatment for at least 4 weeks) after index date.

4.7.5 To describe clinical features and management of cases of suicide/ self injury (including overdose)[†††] in the cohort exposed to asenapine

The following relates to Section 2.2.2 secondary objectives (iii). This will be a qualitative assessment of the summary characteristics of patients reported with these events; detection and clinical features and management thereof, treatment and discontinuation details and event resolution; relevant investigations prior to and during therapy, the patient's relevant medical history and concurrent medication, and any sequelae. Data will be derived from the index, 12-month and supplementary questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table.

4.7.6 Changes of health profile of patients, assessment of adherence; number of indication related episodes and duration, plus any alterations of the treatment programme during the 12 months observation period

The following relates to Section 2.2.3 exploratory objective (i). Status of general health (BMI, weight, BP) and indication-related characteristics (alteration of primary (and secondary diagnosis; number and duration of episodes or mania and depression), number of GP visits post index date, GP awareness of general adherence, plus pattern of asenapine treatment adherence at the end of the 12 month observation period (as estimated from Medication Possession Ratio[‡‡‡]) will be summarised. The frequency and reasons for hospitalisation

[†††] Data on suicidal adverse events will be captured using terms reflecting the Columbia Classification Algorithm for Suicide Assessment (C-CASA). [25] This is a standardised suicidal rating system that provided data for paediatric suicidal risk analysis of antidepressants conducted by the Food and Drug Administration (FDA) in the US and which is considered to be reliable for application to assessing such risks in drugs used for psychiatric indications.

[‡‡‡] For this study, MPR will be defined as: No. days supply held during treatment x 100
No. days supply expected during treatment

including hospital referrals will also be summarised. Alterations in treatment programme (change in dose, other drugs) will be described, as will any reason(s) for stopping asenapine (including switching). Characteristics of censored patients (i.e those lost to follow-up during the study observation period for reason other than stopping) will be compared with those who remain in the study.

Changes in these general health factors, indication-related characteristics and treatment details will be examined by comparing values at baseline and at 12 months post index date. Exploratory analysis may include data mining and descriptive measures for describing alterations in treatment programme.

The number of pregnancies, trimester of first exposure and details of births, terminations and miscarriages will be presented. The number of deaths in the total cohort for each month of exposure will be calculated. Underlying causes of death (as recorded in patient notes by psychiatrist or GP) will also be described by system-organ class.

The proportion of patients within each special population sub-group prescribed asenapine who had *one or more* relevant characteristics/conditions/co-prescribed medications reported during treatment will be summarised (see Table 3).

4.7.7 To explore indicators of non-compliance with 10-minute administration regimen

The following relates to Section 2.2.3 exploratory objective (iia). Data will be based on the subjective opinion of GP awareness of non-compliance with administration regimen (as derived from enquiry on the questionnaire). This study can only examine what is reported in the study forms by doctors.

4.7.8 To explore indicators of misuse and diversion

The following relates to Section 2.2.3 exploratory objective (iib). The following data will be collected on indicators of aberrant behaviour [Overwhelming focus on drug related issues, escalating drug use (early refills/larger amounts for longer periods) unexplained by change in clinical condition, Reports lost, spilled, stolen medications, Exaggeration of symptoms, Requests for treatment from multiple prescribers,]; physical dependence (antipsychotic withdrawal syndrome during treatment or after stopping, asenapine restarted after stopping for reasons other than clinical need or physician direction); and prescriber awareness of

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Where no. days held will be calculated from information derived from 12 month questionnaire on number of prescriptions and average treatment length of prescriptions (usually given in 7, 14,28,56 day repeats); no. days supply expected will assume chronic use from start to end of study observation or treatment stop date (if stopped)

unsanctioned diversion/ accidental exposure to third parties, formulation tampering and alteration in route of administration.

Data on selected risk factors associated with substance abuse (past history any psychiatric disorder, past history of abuse, smoking and alcohol dependence) will also be examined.

It is noteworthy that with regard to inappropriate use, the study can only examine what is reported in the study forms by doctors.

4.7.9 Where possible, to quantify the incidence of other frequently and rarely reported events (including other events considered to be important identified and potential risks not mentioned in Objective 2.2.1 ii) and to identify previously unrecognised adverse drug reactions (ADRs)

The following relates to Section 2.2.3 exploratory objective (iii). Analysis of event data for purposes of signal detection includes calculating the difference (or ratio) between selected time periods, and also examining time to onset profiles for selected events.

The initial approach for generating signals will be to calculate the arithmetic difference and ratio between two time periods for each reported event (e.g. ID_{t1} and ID_{t2}) with a 95% confidence interval (CI) in order to examine the null hypothesis that the rate for the event is not increasing or decreasing between the two time periods.[26] This assumes that there is no difference in reporting between the two periods. ID differences and ratios can be used to identify events that occur significantly more frequently soon after starting treatment – e.g., if looking at the first three months of observation, where the ID_1-ID_{2-3} value for an event is positive, and the 95% confidence interval does not include zero, or where ID_1/ID_{2-3} is greater than one and the 95% confidence interval does not include the value one, then the rate of events in month one is significantly greater than the rate of events in months two to twelve. This result is considered to be a signal for an event occurring shortly after starting treatment with asenapine. Similarly, ID differences and ID ratios can be used to identify events that have a delayed-onset where the ID differences or ratio statistic is negative and the 95% confidence intervals exclude the value zero or one respectively, then the rate of events is significantly lower during month one than subsequent months. This result is considered to be a signal for a delayed-onset event.

As IDs for the overall cohort may sometimes mask significant signals in specific risk groups, the subgroups defined by specific characteristics (e.g previous history of type II diabetes, impaired glucose tolerance, previous/baseline use of selected medications, asenapine naïve or past user) will have IDs calculated and compared according to strata for relevant events, where appropriate.

It is acknowledged that the generalised approach to segregation of time periods may not be appropriate for all events with respect to their most relevant time periods of excess. It is possible to explore the time taken for an event of interest using parametric time to event models (e.g Weibull) as described previously, thus providing an additional tool for signal generation purposes. This approach will be explored for events of interest, where counts $\geq$ 5. If undertaken, a sensitivity analysis will be performed to include in the numerator events reported within 30 days of stopping, and extend the denominator by 30 days

4.7.10 To explore the feasibility of estimating the relative incidence of newly diagnosed oral adverse events during the early high risk period after starting treatment compared to low risk time periods with asenapine using self controlled case series methodology

The following relates to Section 2.2.3 exploratory objective (iv).To study whether there is a significant association between specific events of interest [Oral events:Swollen tongue, Pharyngeal oedema; Oral hypoaesthesia] and starting treatment with asenapine, application of the self-controlled case series methodology will be examined. [27;28]

The observation period for the case series analysis will start with date of treatment initiation, and end at data collection (12 months observation period), irrespective of whether asenapine treatment has stopped or not. The prior belief of high risk period is supported from information on time to onset from spontaneous case reports. The high risk period will be defined *a priori* as weeks 1 and 2 post index date, other periods (weeks 3-12, months 4-6; months 7-9; months 10-12) will be regarded as the control or reference period. [29] For individuals who come off treatment during the high risk period, a nominal risk period will be used equal to the average high risk period observed in the study; sensitivity of the results to this choice will be examined. If any individual dies, a nominal observation period will be used based on the average time from event to discharge in other cases; sensitivity of the results to this choice will be examined. The time-to-occurrence of selected events will be explored and reviewed for evidence of temporal patterns, using survival analysis statistics. Once a determination on the appropriateness of this approach has been thoroughly examined based on the available data at first interim, the specific statistical techniques selected for use in this study will be described in further detail as an addendum.

Using the case series analysis approach, relative risk estimates are automatically adjusted for all fixed confounders. Conditional regression modelling will provide the adjusted estimate of relative incidence (plus 95% Confidence Interval) of selected events for the high risk period relative to low risk periods, these periods having been empirically defined on observed data (see below). For each case information on relevant risk factors obtained from the baseline questionnaire and also the follow-up questionnaire will be included as fixed covariates within

the model to study interactions with the treatment, i.e. to see if the treatment effect varies according to these covariates. Time-varying covariates will be used to adjust the baseline risk.

4.7.11 Multiple comparison adjustments

The methods of signal surveillance require a large number of multiple comparisons on adverse events, which involve inferring statistical significance on multiple *p*-values. To control for an excess of false positive signals, suitable multiple comparison adjustments will be made with the false discovery rate (FDR) approach.[30] The Simes method [31;32]in addition to the double FDR method [30] will be implemented to maintain the false discovery rate at the acceptable 10% level for all statistical tests. Such approaches would allow for a balance between false positive and false negative signals.

4.8 Aggregate Assessment of Drug- Relatedness of Selected Events

As described previously (section 4.4.1.3) selected events of interest (Table 2) that require further characterisation and evaluation will be followed-up via a questionnaire sent to the patient's GP seeking further information. The information received at follow-up for events of medical significance or those which require further clarification will facilitate further evaluation at the aggregate level , including assessment of drug-relatedness, by experienced research staff at the DSRU (two qualified members of staff, independently, with a third adjudicator if necessary). This aggregate assessment of event data occurs at interim or final report for cases for which all requested information (i.e., 3 month questionnaire, 12 month questionnaire, and follow-up questionnaire if applicable) has been received. In the process of aggregate assessment of event data, the application of elements of the Austin Bradford Hill criteria , when the necessary information is available and the use of the method is considered appropriate, will be used.[33] This assessment takes into consideration of the points (see Box 1). [34]

Box 1. Points for consideration in evaluation of reported events

- *the temporal relationship (time to onset);*
- *the clinical and pathological characteristics of the event;*
- *the pharmacological plausibility based on previous knowledge of the drug and the therapeutic class if appropriate;*
- *whether the event was previously reported as an adverse reaction in clinical trials or postmarketing in the UK or in other countries;*
- *any possible role of concomitant medications or medications taken prior to the event;*
- *the role of the underlying or concurrent illnesses;*
- *the effect of de-challenge or dose reduction;*
- *the effect of re-challenge or dose increase;*

- *patient's characteristics, including previous medical history, such as history of drug allergies, presence of renal or hepatic impairment, etc.;*
- *the possibility of drug interactions.*

The following four categories are used to classify relatedness of events that are assessed as: probable, possible, unlikely or not assessable. [34]

Events are assessed as 'probable' if the event is well defined clinically and pathologically, if there is a reasonable time sequence, if it is more likely to be attributed to the study drug rather than to a concurrent disease or concomitant medication, if there is a positive dechallenge, rechallenge or response to dose increase, and if there are other supporting criteria (e.g. on the basis of lab tests or histological findings).

Events are assessed as 'possible' if the event has a reasonable clinical and pathological definition, if there is a reasonable time sequence, if it could also be explained by concurrent disease or concomitant medication, but dechallenge, rechallenge and confirmatory investigations are inconclusive or not fully available. Medical judgement will be necessary in some cases.

Events are assessed as unlikely if the event had a temporal relationship to the study drug administration that made a causal relationship improbable, or if concurrent disease or concomitant medication provided a far more plausible explanation.

Events are unassessable if insufficient information about the event has been provided and an appropriate evaluation is therefore not possible.

4.9 Data Monitoring

4.9.1 Communications

A cohort accrual progress report will be produced in time for inclusion in the scheduled Periodic Safety Update Reports for the product (i.e., every six months for the first two years after launch and then annually thereafter) or regular updates of the RMP for as long as the study continues.

Examination of aggregate event data will be limited to one interim report on a study cohort of 2500 valid patients or on the valid cohort achieved at approximately 18 months, whichever is the sooner; two annual reports based on the valid patient cohort achieved at approximately 36 and 48 months, respectively; and a detailed final report based on a study cohort of 5000 valid patients or on the valid cohort achieved at approximately 60 months, whichever is the sooner (unless an extension to study period is required).

4.9.2 Reporting

The DSRU shall on an ongoing basis notify the MAH when they consider, based on their evaluation, that any issues or matters of interest relating to the Study or its outcomes are of importance and shall provide the MAH with related results of the study and analyses thereof. The DSRU shall deliver interim and final reports in accordance with the Protocol and with content sufficient for the MAH to meet its obligations under Volume 9A, Section 7.4.3.

Since the clinicians are prescribing a licensed product, they will be reminded in the study documentation that it is their responsibility to report any suspected adverse reactions (including serious[§§§] adverse drug reactions) to the company and/or to the MHRA (using Yellow Cards) as they would normally do in their practice in support of routine pharmacovigilance. In cases where the DSRU receives, by mistake, such reports it will forward them to the MHRA and/or the MAH as appropriate.

5.0 STRENGTHS, LIMITATIONS AND POSSIBLE SOURCES OF BIAS

5.1 Strengths

- All patients who are dispensed asenapine in primary care are identifiable and will be eligible for inclusion. There are no exclusion criteria.
- The observational non-interventional nature of PEM study design is maintained; prescribing of relevant pharmacological therapy should not be affected because of participation in this study.
- Data is collected on large numbers of asenapine users in conditions of routine clinical practice.
- Special populations can be characterised
- Time-dependent effects can be examined

5.2 Limitations

- Possible delay in new user cohort accrual if adoption by primary care physicians is low.

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§§§ ***Definition of Serious Adverse Event*** *"Serious Adverse Event means an adverse event which is fatal or life-threatening, results in persistent or significant disability, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.*

- PEM prescription data will only identify those initiated in primary care. Treatment initiation date will be required from hospital discharge summary to obtain estimate of true index date.
- Only GP prescribers are identifiable from Organisation Data Service (ODS; which relate to General Medical Practitioner Codes and GP Practice Codes) data – hospital prescribers are not identifiable in PEM despite FP10 HP prescription data supplied by NHSRxS. A hospital event monitoring study is proposed to develop a systematic process for monitoring the safety of asenapine prescribed to patients by consultant specialist psychiatrists in the mental health care setting, to address possible selection bias arising through restriction of data collection in primary care..
- There is no comparator cohort, however where appropriate, within cohort comparisons will be considered.
- Design may preclude obtaining information on patients who have died, or have newly registered with UK primary care services from abroad and have limited information on past medical history.

5. 3 Potential for bias

As for other observational epidemiological studies, we recognise several potential sources of bias:

- Confounding by indication is a form of selection bias where the disease that forms the indication being treated (irrespective of severity) is not only associated with treatment but also an independent risk factor for selected outcomes (events of interest) in patients not exposed to atypical antipsychotics. This is likely and needs to be examined since such channelling may result in apparent association of increased risk of such events in this population. It may be introduced through prescribing of treatment based on certain characteristics of a patient. For this study, patients for whom prior alternative treatment was poorly tolerated or ineffective may be selectively prescribed the new treatment.
- Confounding by severity is possible, as is treatment switching of multiple-drug therapy in such a population with relapsing remitting cycling disease, and needs to be accounted for.
- Patients started and stopped in hospital will not be identified. Exclusion of this subset will introduce selection bias in that patients who may have more severe disease will not be included. See Appendix 1 for DSRU proposal for study to monitor the safety and use of asenapine in this cohort.
- Obtaining information on misuse for illegal purposes may be subject to information bias in that some prescribers may be less motivated to report such occurrences leading to an under-estimate of risk estimates.

- Immeasurable time bias in terms of inaccurate measurement of exposure is likely as a result of unidentified hospitalisation
- With this patient population, patient attrition and loss to follow-up is likely to be significant which may introduce selection bias.
- Non-response bias as a result of GPs being unwilling to complete a complex questionnaire with multiple outcomes is possible, however, this will be addressed by a) payment to cover administrative costs of completing a more complex questionnaire (response rate for M-PEM studies is approximately 64%, which is similar to average GP response rate to postal surveys in general([35] and b) sending two questionnaires (at three months and twelve months after the first prescription), either of these forms is less complex than sending one form.
- Under-reporting, including that of serious or fatal events, is possible in PEM, as for any other observational study. However, a ten fold difference in reporting of serious events between PEM and the Yellow card spontaneous reporting system has been identified, in favour of PEM. [36]
- Given the M-PEM questionnaires prompts prescribers to report on selected and often serious outcomes of interest through use of specific questionnaires, differential over-recording (and reporting) of serious to non-serious events is possible.
- Misclassification bias of outcomes may occur which is of particular importance for rare outcomes, however, it will be minimised by follow-up of medically important events. Patients with events of interest will be followed-up with regard to co-prescribed medicines and concurrent illness. Events that represent features of the respective indications will be taken into account when signals of potential ADRs to asenapine are investigated (i.e., confounding by indication).
- Misclassification of indication is possible. Of particular relevance to this study is the potential bias that may be introduced through variations in diagnosis and case definition between practitioners.
- Time bias may also become an issue if the study collection period, and thus the observation period, is extended because of low prescribing rates.
- Furthermore unidentified poor adherence may also lead to misclassification of exposure. In PEM, exposure is based on dispensed prescription data. These data are more accurate than exposure data based solely on written prescriptions, e.g. GPRD. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be ascertained. While it is not possible to be sure the patient used the medication, it is almost certain that the patient received it. Repeat prescriptions would indicate that a patient continued to obtain the medication, whilst GP awareness of adherence would inform on pattern of dosing.
- Calculating ID differences (plus 95%CI) is one of a number of quantitative evaluations of hundreds of events that can be used in PEM for signal generation purposes. It is

used as a means of alerting early potential signals as priorities for further evaluation. Medical judgment however is also part of this evaluation and prioritization process. As part of the initial inspection of event data, it is acknowledged that the generalised approach to segregation of time periods (month 1 vs months 2-6 combined) for calculating ID differences may not appropriate for all events with respect to their most relevant time periods of excess. In addition, when event counts are low in the periods being compared and the risk periods are of different lengths then there is a risk of false positives (Type I error). [37] However, since ID differences are tested at the 5% level, the probability of concluding that a relative difference is greater than the null (i.e a signal) when it is not, is low (2.5%). PEM methodology (which is hypothesis generating) enables further exploration of events for which the ID difference is significant, using other quantitative and qualitative methods before any conclusions on signals can be made.

6.0 STUDY SPONSORSHIP

This study is being undertaken by the DSRU as part of the Risk Management Plan for the product at the request of the Committee for Medicinal Products for Human Use (CHMP). The Drug Safety Research Trust is a registered independent charity (No, 327206) operating in association with the University of Portsmouth and is sponsor of the study. The DSRU is the academic sponsor and receives an unconditional grant from Merck.

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Appendix 2. Study Protocol

Appendix 1. UK SPC for asenapine (to be inserted)

Appendix 2. Study Protocol

(Appendix 2. Rare Adverse Events which are Serious and a high Proportion are due to drug)

Agranulocytosis
Alveolitis
Anaemia aplastic
Anaphylaxis
Angioneurotic oedema
Arrhythmia
Bone marrow abnormal
Congenital abnormality
Dermatitis exfoliative
Disseminated intravascular coagulation
Erythema multiforme
Erythroderma
Guillain-Barre syndrome
Hepatic failure
Hepatitis
Jaundice
Leucopenia
Multiorgan failure
Nephritis
Nephrotic syndrome
Neuroleptic malignant syndrome
Neutropenia
Pancreatitis
Pancytopenia
Pseudomembranous colitis
Renal failure acute
Retroperitoneal fibrosis
Rhabdomyolysis
Stevens Johnson syndrome
Sudden Unexpected Death
Thrombocytopenia
Torsades de pointe
Toxic epidermal necrolysis

Any event for which there is a positive rechallenge