STUDY PROTOCOL

AN OBSERVATIONAL POST-AUTHORIZATION SAFETY SPECIALIST COHORT EVENT MONITORING STUDY (SCEM) TO MONITOR THE SAFETY AND UTILIZATION OF ASENAPINE (SYCREST) IN THE MENTAL HEALTH CARE SETTING IN ENGLAND, WALES AND SCOTLAND

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Investigators

Members of the Drug Safety Research Unit (DSRU), Southampton, SO31 1AA, UK in collaboration with psychiatrists in England, Wales and Scotland:

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

Principal Investigator

tbc

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

(see Appendix 4)

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
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

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 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. 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 which includes tools designed to monitor the important risks (including class effects and off-label use).

This postmarketing safety study of asenapine (SYCREST®) is to be carried out by the Drug Safety Research Unit (DSRU) as part of a broader Post-Authorisation Commitment requested by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of asenapine in clinical practice. This study which is designed to monitor the safety and drug utilisation of asenapine as initiated by specialists and used in the mental health care setting in England, Wales and Scotland is one of two complementary studies conducted by the DSRU. The other, based in primary care, is a Modified Prescription-Event Monitoring (PEM) 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.

The aim of this Specialist Cohort Event Monitoring (SCEM) study is to proactively monitor the short-term (up to 12 weeks) safety and drug utilisation of asenapine as prescribed to patients by

psychiatrists in a mental health care setting in England, Wales and Scotland. The study aims to collect exposure and outcome data for a cohort of approximately 1000 evaluable patients.

Patients will be identified by psychiatrists in England, Wales and Scotland. At start of treatment (index date) consent will be obtained from appropriate patients to be entered into the study and details of indication, drug exposure, co-morbidities and other factors will be collected as relevant to index date from patient medical charts. After 12 weeks of observation (from index date), a data-collection end of observation questionnaire about early utilisation of asenapine, treatment and safety will be completed. Information requested on the index questionnaire will include both prescribing and patient information such as: the year of birth, sex and body mass index (BMI) of the patient, confirmation of indication for treatment that is the clinical conditions which require asenapine treatment (from notes and utilising codes utilised in clinical practice, where available), start dose of asenapine, date of starting treatment, reasons for prescribing, past medical history and current medication use, including OTC and herbal remedies. The end of observation (12 weeks) questionnaire will collect information on any dose changes (and relevant dates), date of stopping treatment (including reason for discontinuing therapy if treatment was stopped), care status-specialist or GP (including date of discharge). Data on events occurring during treatment with asenapine and events after stopping up to the end of the observation period will be collected, including cause of death (where applicable). In addition, information will be requested on co-morbidities and concomitant medication, including Over the Counter (OTC) and herbal remedies, during treatment.

This study will enable the systematic collection and reporting of safety data on patients newly initiated on treatment with asenapine, with a particular focus on obtaining information on patients who stop taking asenapine prior to transfer of care to their GP. Its purpose will be to provide information on a large number of such patients and the treatment they received in a mental health care clinical practice setting. In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), this 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 in excess affecting quality of life, excessive 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 (arising from contraindications) and use in populations with special label precautions (those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; limited information is available). 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 for the 10 minute requirement for no food or fluids after sublingual administration and reported misuse/diversion), 2) identify previously unrecognized adverse drug reactions, and 3) further explore events of special interest (oral events).

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. The technique of PEM has been described previously. [5] 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. A Modified PEM study of the product will be conducted by the DSRU in parallel.

1.2 Specialist Cohort Event Monitoring (SCEM)

In the UK, often the choice of drugs prescribed in primary care is guided by clinical experience and recommendations from experts and therapeutic committees in secondary care. The principle of 'event monitoring' can be adapted to monitor the use and safety of a new drug prescribed to a patient population under the care of specialists, including those who may be more complex in terms of underlying disease, co-morbidities and concomitant medications than in the general disease population. In particular, this methodology enables the capture of important information on patients who may discontinue treatment prior to transfer of care to general practitioners in the primary care setting and therefore, risk estimates will be less subject to the influence of selection bias based on concurrent health status/disease severity by capturing first ever prescriptions from specialists. Also, this method enables reliable examination of exposures in relation to outcomes. For this study, monitoring the target patient population will

* 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.*

be achieved through an active research network of clinicians (with the assistance of the MHRN), established and maintained by the administration team at the DSRU and study research nurses/facilitators. This observational cohort study design offers the opportunity for the systematic collection and reporting of safety data on patients newly initiated on treatment with asenapine in a mental health clinical practice setting, after consent has been obtained. Extensions to monitor longer-term safety and use are also possible.

The specific aims of this SCEM study are to:

Primary

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

Secondary

- Advance the understanding of the patient population prescribed asenapine in the mental health 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

The DSRU has already established a network of psychiatrists across the country, in conjunction with the MHRN. Those psychiatrists who express an interest will be invited to participate in the study and contacted at regular intervals to enquire whether any patients under their care have been initiated on treatment with asenapine. Psychiatrists, designated member of clinical care teams, or study facilitator [†] from the DSRU will be asked to obtain consent from patients for whom asenapine has been prescribed based on clinical need and enrol them into a product registry. Whilst both the SCEM and M-PEM are complementary observational studies that can address questions regarding treatment, risk factors and clinical events in a defined population exposed to asenapine, the principal difference is how patients are initially identified and sampled (psychiatrists are required to pro-actively register patients in the SCEM study), the type of patient (estimates of risk and rate of outcomes of interest may be influenced by differences in selection in the two settings) and the ability for further extension (through

[†] Including Clinical Study Officers (CSOs) from the MHRN

obtaining consent in the SCEM study) to collect information on long-term follow-up and future indications, as appropriate.

1.3 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, α-adrenergic and histamine receptors, and no appreciable activity at muscarinic cholinergic receptors.[6] It is formulated as a fast-dissolving tablet containing 5mg 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 instructed 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]

1.3.1 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 has been developed for asenapine which includes tools designed to monitor the important risks (including class effects and off-label use). Evaluation by the Marketing Authorization Holder (MAH) of all safety data and possible risk factors related to the use of asenapine, 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

(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
• Suicidality

• 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 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 sublingual 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). [9] 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. [9] 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 report that asenapine has low potential for clinical addiction, however as all CNS drugs have some potential for abuse, the possibility of misuse and abuse cannot be excluded, although the potential is very low. [1] The sublingual 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. [10] There have been reports of abuse of another atypical antipsychotic, quetiapine, among inmates in jails and prisons.

1.3.2 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, out of total use, the proportion of use within primary care is estimated to be 80% [internal communication Merck & Co., Inc]. This is 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).

1.4 Study Rationale

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), this 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).

2.0 AIMS AND OBJECTIVES OF STUDY

2.1 Overall aim:

To monitor the short-term (12 weeks) use and safety of asenapine prescribed to asenapine naïve (new user) patients for the treatment of moderate to severe manic episodes associated with bipolar I disorder, and other psychiatric disorders by psychiatrists under normal conditions of use in the mental health care setting.

2.2 Specific objectives:

2.2.1 The primary objectives

These are given below. Their purpose is to provide timely information on:

(i) Accrual of psychiatrists based within mental health care

(ii) Cohort accrual, the type of clinician responsible for, and the setting of initiation of treatment.

(iii) To quantify the incidence rate of selected important identified and potential risks which are:

1. Somnolence and sedation
2. Weight gain
3. Oral hypoaesthesia
4. Swelling of the tongue and throat
5. 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:

(i) To provide timely information on the baseline health profile of patients prescribed treatment with asenapine in the mental health care in-patient and out-patient 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 week observation period 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 weeks 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 iii) 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

All studies conducted at the DSRU will be conducted in accordance with national and international guidelines.[13-15] For this open cohort study, ethics approval via IRAS (integrated research application system) in the UK will be required. Participating psychiatrists will be asked to provide patients with documentation (with a unique registry reference code) including a consent form so that the patients can consider and give their consent for their participation within this project and for access to secondary care medical charts (other than psychiatrists case notes). For those patients who wish to have a further opportunity to reflect on their participation, the psychiatrist or designated member of clinical care team will ask the patient to complete a 'consent to contact' form, which will enable DSRU study research staff to contact the patient by telephone after a period of at least 48 hours to obtain consent. This will be the only point at which DSRU research staff will contact the eligible patients directly. If the patient agrees to participate, they will sign the consent form, retain a copy and send the original

and one further copy via surface mail to the DSRU, or, if preferred, return it to the clinical care team (who will then submit the original form to the DSRU). Access to secondary care medical charts for additional information may be required on any relevant outcomes which may be collected after the patient's 12 week observation period has ended, but within time-frame of active study data collection.[‡] The consent form will stress confidentiality and that no specific details of their treatment will be released to external parties. The patient/guardian will receive a copy, the original returned to the DSRU and a third copy will be kept in the patients notes, if required. For patients who cannot give capacity reference will be made to The Medicines for Human Use (Clinical Trials) Regulations 2004- Statutory Instrument 2004 No. 1031. London Stationary Office (www.opsi.gov.uk/si/si2004/20041031.htm)

4.0 METHODS

4.1 Study Design & Time frame

This study will use an observational, population-based cohort design based on cohort event monitoring to study the short-term (up to 12 weeks) safety and use of asenapine initiated by psychiatrists in the mental health care setting in the immediate post-marketing period. Randomisation will not be required. The cohort will reflect naturalistic patterns in order to reduce any selection bias (i.e., no selection for inclusion by the psychiatrist based on the preparation type).

Patient recruitment into the study is anticipated to start in Q4 2012 and continue for a maximum of 47 months, 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 psychiatrists (see section 4.2). Cohort recruitment rate for this study is based on prescribing data, incidence and prevalence statistics. Data collected during later time periods can be compared with earlier periods to identify any trends that may be emerging. 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 Project Steering Committee (See section 4.9.1) in order to monitor and agree upon any appropriate remedial actions.

[‡] The exception will be if a female patient becomes pregnant, the outcome of the birth will be requested.

Patients will be observed from start of treatment with asenapine (index date) and for 12 weeks (or less if patient discontinues to be under the care of the psychiatrist; to be established via the 12 week end of observation questionnaire) in order to allow for detection of outcomes associated with treatment initiation.

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 SCEM study, a sample size of 1000 evaluable patients is desirable to detect an effect size (relative incidence rate) of at least 2.0 with power of 80 % 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.

As sample size calculations are based on overall cohorts, further sub-groups or stratification of the data in this study would underpower subsequent analyses.

Table 1. Sample sizes 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); * Such effect sizes with assumed background rate will not be detected with the proposed cohort sample of 1000 patients.

Reference: Machin D, Campbell M, Fayers P, Pinol A. 1997. *Sample Size Tables for Clinical Studies*, 2nd edn, Blackwell Science: Oxford, pp. 144. [16]

4.2.2 Sample size for general safety surveillance of events where background 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 (i.e. those prescribed asenapine according to labelled indication), 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. [18]For this study, a sample size of 1000 evaluable patients (see section 4.3.2.3) should allow for the detection of at least three cases of an adverse event with 85% probability, if the event occurs at a rate of at least one in 200, whilst a sample size of 500 should allow for the detection of at least three cases with a rate of at least one in 100 at 85% probability. [18]

4.2.3 Sample size for self-controlled case-series analysis.

For exploratory objective (iv) section 2.2.3, 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

– [§] 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. [17]

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comprised of 1000 patients (- section 4.3.2.3) , from which 50 cases of oral events would be expected. [**] Such a study would have 80% power to detect a relative incidence of 4.2 (or greater). [Personal Communication P Farrington 28/10/2010]

4.3 Study Population

4.3.1 Selection of psychiatrists

This study has been adopted by the UK Mental Health Research Network (MHRN). Psychiatrists will be invited to participate in the study prior to study start. Psychiatrists will be informed that they will be participating in a study which will monitor the use of a new entity oral atypical antipsychotic (asenapine), in accordance with requirements within the Risk Management Plan. Using a bespoke website, psychiatrists will be required to register online with the study co-ordinating centre (DSRU) in order to receive access to relevant study documentation. Each participating psychiatrist will be instructed to make treatment decisions independent of the study and then to evaluate whether a patient is eligible for inclusion based on entry criteria (see below).

Remuneration, in line with the standard British Medical Association (BMA) rate will be paid to the investigator's employer to cover time and administration costs incurred (either by psychiatrists or associated staff) assist with consent, complete questionnaires and monitor the patients.

4.3.2 Selection of patients

Patients will be those who present to psychiatrists within the standard course of care as in- or out-patients for treatment of a clinical diagnosis of a mental health disorder which requires pharmacological treatment with an atypical antipsychotic. Once the pharmacotherapeutic treatment decision has been made, and asenapine prescribed as the most appropriate treatment, the patient will be invited to participate in the study and consent obtained for access to information from secondary care hospital records, and general practice primary care records, as appropriate (if required for follow up). In some cases, potential participants may be identified by members of the care team by checking the medical notes of selected patients in order to confirm whether they have just been prescribed asenapine. For patients treated with asenapine by a specialist in a community setting, community pharmacists may be used to notify potential

[**] 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 1000 evaluable patients followed-up over 3 month study duration, the expectation is that 5.1% of these would be cases which is effectively equivalent of 50 cases over that time, or 4 cases per week.

and existing participating prescribers regarding the potential for these patients to participate in the study (Appendix 3). Once consent has been received, relevant (routinely collected) demographic and clinical information on patients general health at the start of asenapine treatment (index date), past and current medical history plus drug exposure, and patient compliance as available from psychiatrists' medical records will be collected. The patient will not be asked to attend the psychiatrist more than usual or undergo any additional treatment. However, number or visits to the psychiatrist in the observation period will be recorded as a further surrogate of disease severity.

At least 12 weeks post index date, additional information on exposure, including details of changes to treatment programme, and information on common outcomes as reported by the patient and recorded in the medical charts since treatment initiation will be collected. These data will be submitted to the DSRU. If outcomes of interest (see section 2.2) are reported, additional information will be requested, where necessary. Remuneration will cover administration costs incurred to complete questionnaires

4.3.2.1 Patient Inclusion Criteria

The intention as per study aim is to recruit adult patients newly initiated on 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.

4.3.2.2 Patient Exclusion Criteria

Patients who do not provide consent will be excluded from the study. Patients within selected institutions (for example prisons) will also be excluded.

Enrolled patients will also be excluded if both the baseline and 12-week questionnaires are returned blank (contain no clinical information), if the psychiatrist, designated member of clinical care team, or study facilitator from the DSRU reports that the patient did not take or was never prescribed asenapine, if there is evidence to suggest duplication of patients.

Patients will be automatically withdrawn if the patient or psychiatrist, designated member of clinical care team, or study facilitator from the DSRU provides informed written or verbal notification that they no longer wish to participate at any stage of the study.

With regard to patients aged ≤ 17 years, it is acknowledged that such patients fall outside the terms of license and we are unlikely to obtain ethical approval to include them in this study and thus for this reason they will not be included in the hospital specialist study which requires patient consent.

4.3.2.3 Post inclusion Exclusion Criteria.

Evaluable patients for secondary objective (i) will not include those where the 12-week 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 neither the baseline or 12-week questionnaires were returned blank (contain no clinical information) or had not been returned.

4.4 Data Collection

Records-based data collection in this study will be conducted in various phases; relevant documentation (such as information leaflets, questionnaire, consent forms, etc) will be available both as hard copies and electronically for download by the participating psychiatrists.

4.4.1 Data Collection Methods

4.4.1.1 Recruitment

The first phase will have two parts.

Part 1: Recruitment of eligible psychiatrists/designated member of clinical care team: demographic data on these individuals will be collected upon registration with the DSRU. The DSRU will allocate a unique study reference number to each participant psychiatrist/ designated member of clinical care team for study audit and data management processes.

Part 2: Recruitment of consenting patients initiated with the study drug under clinical care of participating psychiatrists/ designated member of clinical care team;; date of recruitment into the study will be recorded and the index date will be the date of starting the relevant treatment. The DSRU will allocate a unique study reference number to each participating patient for study audit and data management processes.

4.4.1.2 Exposure/outcome data collection

The second phase will also have two parts.

Part 1: Data relevant to index date contained within the patients medical charts will be abstracted onto a baseline questionnaire (capturing past medical and drug history of relevant

conditions that are recorded within time period parameters if appropriate), by the psychiatrist, designated member of clinical care team, or study facilitator from the DSRU Note that undertaking laboratory tests and ECG monitoring are not current standard practice in psychiatry; therefore such information will not be collected. These questionnaires will be submitted to the DSRU. A proportion of psychiatrists or designated members of clinical care team are likely to fail to submit these questionnaires, so they will be sent a reminder request.

Post end of twelve weeks observation (from index date), the psychiatrist, designated member of clinical care team, or study facilitator from the DSRU will be prompted to complete a second questionnaire which will gather information on clinical events of medical interest and serious adverse event reports [classified using the International Conference on Harmonisation definitions. [19] Events of interest will undergo further evaluation, which may include follow-up using event-specific questionnaires sent to the psychiatrist (see 4.4.2.3). These events will be assessed for drug-relatedness by DSRU staff. [20]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.

4.4.2 Data Collection

4.4.2.1 Psychiatrists

The following data will be collected for psychiatrists or designated member of clinical care team upon recruitment into the study:

1. Demographic characteristics;
2. Practice type (setting- inpatient, outpatient);
3. Practice location (hospital ward, community outreach hospice etc);
4. Participation response/non response rates of prescribers.

4.4.2.2 Patients

As part of the consent procedure, participating psychiatrists / designated members of clinical care team will invite patients to provide the following information:

The data will include:

- ethnicity
- current marital status,
- current employment status,
- category of residential setting,
- smoking and alcohol consumption

Since it is important to examine the representativeness of the evaluable study population, audit information obtained retrospectively from eligible but non-participating patients will be utilised:

These data will include:

- sex, year of birth
- Proposed clinical condition requiring asenapine treatment and start date

Once consent has been obtained for eligible patients, the following information as relevant to the index date will be captured from medical charts via questionnaires. NB. socioeconomic status will be derived from patient postcode given on consent form.

1. *Psychiatric history and indication (clinical conditions which require asenapine treatment)-related variables:* ICD-10 diagnostic criterion for bipolar I disorder and other relevant psychiatric illness, age at first diagnosis of indication for asenapine, disease severity (using Clinical Global Impression Scale of Severity),[21]history of antipsychotic medication adherence using a subjective ordered categorical scale based on a Visual Analogue Scale, [22] history of tolerability and/or response to past/current treatment

2. *Clinical and general health status:* co-morbidities at treatment initiation, body mass index (BMI), weight and height (most recent measurements prior to index date); relevant risk factors for selected events of interest (not all collected for all patients – some at follow-up).

3. *Exposure variables:* Asenapine treatment initiation details (start date, dose, frequency) and reasons for prescribing; use of atypical antipsychotics within 6 months prior to index date (e.g. past users of an antipsychotic drug and antipsychotic); other concurrent drugs (including other psychoactive medications)/herbal/non-prescription medications used within the four weeks prior to and including the date of treatment initiation; new additions or changes in other antipsychotic medication as part of treatment combination(including start and stop dates); stop dates of antipsychotic treatments (if stopped); alternative antipsychotic medications substituted (if stopped).

For evaluable patients providing consent and for whom a completed index date questionnaire has been received by the DSRU, after at least 12 weeks of observation, a second questionnaire will be systematically generated to collect information the following outcome variables:

1. alterations in diagnosis

2. significant health-related events (excluding those considered to be indication-related) recorded in the patient's psychiatrists medical notes as **occurring during the first 12 weeks of treatment** with the study drug;
3. date of stopping asenapine and reasons for stopping treatment (if therapy stopped);
4. date of restarting asenapine and reasons for restarting (if treatment break occurred)
5. any other alterations in treatment regimen (other drugs stopped/started plus dates)
6. events (e.g. acute withdrawal symptoms) occurring in the thirty days after stopping (if therapy stopped);
7. the psychiatrist's opinion on effectiveness.

4.4.2.3 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). [20]

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 4.9.2 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 events 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: For patients taking lithium or valproate, number of prescriptions (date dose and frequency), - for lithium only TSH, renal function (eGFR) and lithium plasma levels at baseline and 12 weeks post index (date of measurement nearest to these dates)

4. Prescribing: For patients 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 may be followed-up for additional information on relevant risk factors.

6. Events: Psychiatrist awareness of poor 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.

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 (not patient self-reported)
Increased exposure in patients with severe hepatic impairment	Targeted outcome question	Data on CYP 450 Drug-drug interactions and special at risk groups (elderly and patients with severe hepatic or renal disorder) will be collected
Oral hypoaesthesia	Targeted outcome question	
Swelling of the tongue and throat	Targeted outcome question	
Increased liver transaminases and Gamma-Glutamyl Transferase (GGT); Bilirubun	Targeted outcome question	Data on diagnosis of hepatic failure and where abnormal laboratory results indicate 3 X ULN relevant parameters will be collected.
Orthostatic hypotension	Targeted outcome question	Data on orthostatic hypotension and hypotension, syncope and falls will be collected
Neuroleptic Malignant Syndrome (NMS)	Targeted outcome question	
Rhabdomyolysis		Free text reports
Seizures	Targeted outcome question	
Hyperprolactinaemia	Targeted outcome question	
Cardiovascular effects: QT prolongation	Targeted outcome question	Data on arrhythmias (inc syncope) will be collected and follow-up for ECG confirmation
Neutropenia	Targeted outcome question	
Metabolic effects other than weight gain: dyslipidemias , diabetes mellitus	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	Targeted outcome question	Data on allergic reactions including hypersensitivity will be collected since possible 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 indicators of substance misuse at baseline, aberrant behaviour during treatment and GP awareness of unsanctioned diversion will be collected

4.4.3 Methods to Maximise Questionnaire Response Rate

4.4.3.1 End of (12 weeks) observation period

A proportion of psychiatrists are likely to fail to respond to these questionnaires at this monitoring stage. Methods to maximise the psychiatrist response rates will include prompts from study facilitators by phone, email and personal contact and reminder questionnaires targeted at those psychiatrists who have not responded within one month of the date the initial questionnaire was sent.

4.4.3.2 Specific event follow-up questionnaires

A duplicate event follow-up questionnaire will be sent to psychiatrists 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. Psychiatrists will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

4.5 Data processing

Psychiatrist/ patient identifiable information will be stored within a unique 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 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 targeted closed format questions on the questionnaire (which reference Medical Dictionary for Regulatory Activities (MedDRA) terminology) and coded onto the bespoke study database. Other events reported on the questionnaires as free text will be coded onto this database using a synonym list that is mapped to MedDRA, in order to enable consistent reporting to be provided using MedDRA terminology.

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific SCEM database 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 personal 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 at an appropriate time point (provisionally this is at datalock or earlier if patients have provided informed notification that they wish to withdraw from the study, but the DSRU will request an extension to this to comply with CHMP requirements). 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 questionnaires), error reporting and correction of discrepancies between the entries by quality assurance staff
- Coding of 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 To describe psychiatric and patient recruitment

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

Psychiatrist responders and non-responders will be compared in terms of demographic variables to assess potential for selection bias through non-participation, as will patients who provide consent to participate compared to those who decline or are not eligible.

4.7.2 To quantify the incidence rate of selected events considered to be important identified and potential risks and to explore the hazard rates of these events over time

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

The incidence rate 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

**e.g when the shape parameter (p) for the Weibull model is equal to one, the hazard is estimated to be constant over time, if p is greater than one the hazard is increasing,, if p is 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 the mental health care in-patient and out-patient 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 objective (i). Valid cohort demography (age and gender) will be presented, as reported at baseline. Carstairs Deprivation Score [23] will be determined for patients and used as surrogate marker of patient socioeconomic status. Other baseline general health factors [BMI and 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 or any other condition that required referral to psychiatrist, relevant number of hospitalisations and Clinical Global Impression Scale as indicators of disease severity]; general pattern of treatment adherence of the patient [psychiatrist impression using a subjective ordered categorical scale based on a Visual Analogue Scale [22;24] measure since first ever referral and first referral for current proposed clinical diagnosis]; treatment initiation programme (asenapine starting dose and frequency, treatment as mono- or combination therapy, drugs given as combination therapy) and prescribing reasons will be described.

A synopsis of prior and baseline relevant morbidities and medication use will also be provided. Patient 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
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 5 indicators)*
History of NMS
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 week observation period 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). Event monitoring 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 for this study will be performed using 'Higher-level' MedDRA event terms. The risk profile of the overall cohort and each sub-group of interest defined at baseline 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 for specific time periods in order to quantify rates of events. IDs will be calculated, for a 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. 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 event, 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.For this study, IDs will be calculated for each event as for each week as follows:

$$ID_t = \frac{\text{Number of first reports of an event during treatment for period t} \times 1000}{\text{Number of patient-weeks of treatment for period t}}$$

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 = $\frac{\text{Number of patient-days of treatment for period t}}{7}$

IDs will also be calculated for all 12 weeks during treatment combined (ID_A), and the first thirty days 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-week 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 weeks 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 psychiatrist visits post index date, Clinical Global Impression Scale) and pattern of adherence at the end of 12 week observation period (psychiatrist impression and subjective ordered categorical scale based on VAS) [‡‡]plus Medication Possession Ratio derived from prescription data[§§]) will 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

[††] 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.

[‡‡] This is a subjective measure; this study can only examine what is reported in the study forms by doctors.

[§§] For this study, MPR will be defined as: $\frac{\text{No. days supply held during treatment}}{\text{No. days supply expected during treatment}} \times 100$

Where no. days held will be calculated from information derived from 12 week 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)

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, indication-related characteristics and treatment details will be examined by comparing values at baseline and at 12 weeks 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 consultant psychiatrist 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 and symptoms of withdrawal during treatment or after stopping, asenapine restarted after stopping for reasons other than clinical need or physician direction); and prescriber awareness of unsanctioned diversion/ accidental exposure to third parties, formulation tampering and alteration in route of administration (i.e not sublingual – chewed or swallowed).

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 iii) 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 within the cohort 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 (12 weeks) 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 (first four weeks) is significantly greater than the rate of events in months two to three (subsequent eight weeks) combined. This result is considered to be a signal for an event occurring shortly after starting treatment with asenapine, which then requires further evaluation and signal strengthening(with the exception of some indication related events). 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, which then requires further evaluation and signal strengthening.

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 and previous/baseline use of selected medications) 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 ≥ 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 oral events (Oral hypoaesthesia, Oropharyngeal swelling) 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 end of data collection (12 week end of study 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, the other period (weeks 3-12) 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 end of treatment 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 (weeks 1 and 2) relative to low risk period (weeks 3-12 inclusive). 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 4.4.2.3) selected events of interest (Table 2) that require further characterisation and evaluation may 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). The aim of the drug-relatedness assessment, which will be done collectively for groups of events during the analysis of the interim and final reports, is to put events in context regarding temporality co-morbidity, pre-existing disease and concomitant medications. 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 (see Box 1) . [33] The relatedness of selected events to asenapine will be assessed as the following four categories: 1) probable, 2) possible, 3) unlikely, and 4) not assessable. This assessment

will take account of time to onset of event, whether the event was the reason for stopping therapy, concurrent medication, concurrent disorders, positive or negative dechallenge (resolution or not of symptoms after withdrawal of asenapine, with or without specific treatment of such symptoms), rechallenge if applicable (recurrence or absence of symptoms after re-exposure to the medicine), previous history of similar problems, or another specified cause. [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 have been 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 has been 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 Project Steering Committee

A Project Steering Committee (PSC) will be set up to be comprised of the study investigators and collaborators, and may include a patient representative. The role of the PSC will be to oversee the smooth running of the project and provide scientific and technical advice when needed and will liaise biannually (either in person or by teleconference). The PSC is broadly analogous to a Safety Monitoring Committee or Review Board, but the purpose may be slightly different such that the PSC includes investigators and also oversees the effective progress of the study.

The first PSC meeting will orientate the project team members and establish the logistics for psychiatrist and patient recruitment and confirm patient inclusion criteria. Subsequent PSC meetings will clarify the understanding of the ongoing project requirements, monitor progress through assessment of data within the interim reports [psychiatrist/cohort accrual rates, preliminary analyses of individual variable responses on questionnaires], consider any additional proposed inclusion criteria, and act as a forum to review and discuss any queries.

4.9.2 Communications

Progress reports (relevant to psychiatrist and patient cohort accrual) 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 an interim report on a study cohort of 500 valid patients or on the valid cohort achieved at approximately 18 months, a second interim report on the valid cohort achieved at approximately 29 months, a third interim report on the valid cohort achieved at approximately 41 months and

a detailed final report based on the valid cohort achieved at approximately 47 months (unless an extension to study period is required).

4.9.3 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 according to applicable regulatory requirements and legislation including 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 AND POSSIBLE SOURCES OF BIAS

5.1. Strengths

- The observational and inclusive design allows for the surveillance of a diverse patient population under the care of specialist psychiatrist, particularly those that are more complex in terms of underlying disease, co-morbidities and concomitant medications that would not have been included in clinical trials, and also would not be comparable to the general disease population. Thus error introduced through selection based on

[***] **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.

disease severity or type will be minimised; there are no specific exclusion criteria. The approach also allows for effective surveillance of asenapine when used off-label.

- The prescribing of relevant pharmacological therapy should not be affected because of participation in this study therefore the observational non-interventional nature of the study design is maintained.
- 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. This method will enable more reliable examination of exposures in relation to outcomes.
- By obtaining patient consent, additional information from medical records from other clinical specialities may be examined for selected outcomes.
- Extension to monitor long-term safety is possible.
- The DSRU has established a network of psychiatrists in the UK to conduct such study.

5.2 Limitations

- Possible delay in new user cohort accrual if adoption by mental health care settings and psychiatrists is low.
- There is no comparator cohort, however where appropriate, within cohort comparisons will be considered.

5. 3 Potential for bias

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

- The most important is selection bias and the possibility that the cohorts will not be representative of the general population with these mental health disorders. Because of the nature of patient recruitment, bias in recruitment may be introduced by some participating psychiatrists through awareness of some form of remuneration (regardless of how and when payment is made). This study does not look at the comparative early safety of asenapine in the context of initiations of other atypical antipsychotics, therefore the extent of selection bias cannot be established. Since there is no comparator cohort, within cohort comparisons are considered the practical most appropriate approach.

- Knowledge of which patients will be participating may affect the non-interventional nature of observational research. Exclusion of patients initiated on treatment between date of market launch and study start may also add to selection bias. Nevertheless patient identification (case ascertainment) is likely to be more complete than through retrospective methodology; this may also minimise bias introduced by non-participation of patients. It is also possible that psychiatrists who participate in the study will be self-selected group, but we do not believe that this selection bias will affect the types or number of events experienced and reported by a patient after treatment has been initiated.
- Under- and mis- reporting of outcomes is possible; psychiatrists notes may be incomplete with regard to medical history and non-psychiatric related outcomes associated with current treatment. The two-phase data capture approach could facilitate compliance with data reporting as well as spreading workload for psychiatrists. Obtaining patient consent at the start of treatment will facilitate access to secondary and primary medical records. Confounding by indication is possible since data abstracted from psychiatrists' notes are likely to be biased towards recording psychiatric events. Overreporting and overrecording of health related events in the period following the administration of the baseline questionnaire are possible due to increased physician attention to specific events and conditions detailed in the questionnaire (e.g. somnolence).
- 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, however, the relatively short period of observation should mitigate this possibility at least to some extent.
- 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. 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 since starting treatment is required for study participation.
- 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). [35]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. For this study, the DSRU (the academic sponsor) receives an unconditional grant from Merck (the funder).

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

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

Appendix 3. Using community pharmacy to notify the prescriber regarding potential study participants

Introduction:

Community pharmacists will also be used to notify potential and existing participating specialist prescribers about patients who may potentially be suitable for inclusion in the study. This approach aims to facilitate recruitment of patients initiated on asenapine by a specialist providing treatment within a community setting. It will involve the issue of a study introduction letter from the pharmacy about the OBSERVA study, to the specialist prescriber. The letter will also notify the prescriber about an eligible patient that has received treatment with asenapine. A unique patient identifier will be used in this notification letter, accompanied by the prescription details (prescription issue date, dose, frequency and quantity). No patient identifiable information will be provided. The local OBSERVA study facilitator will also be notified and they will contact the prescriber who will then be able to consider their participation within the study (if new). Prescribers may then contact the pharmacy to request de-anonymised details about the patient under their care from the participating pharmacist.

Methods:

1. If a community pharmacy receives a prescription for asenapine, it will be dispensed as normal, in line with current best practice and standard operating procedures
2. If the community pharmacist identifies the patient as potentially being appropriate for inclusion in the study[†††], a study introduction letter will be sent to the prescriber, a copy to the OBSERVA study facilitator and a copy of the letter retained in the pharmacy
3. The community pharmacist will maintain their own log of eligible patients with unique patient identifier to whom the prescriber may subsequently be signposted in order to avoid duplication of referrals. This log will be securely stored in pharmacy safe and maintained by the responsible pharmacist.

Considerations:

- The community pharmacist's involvement will be to flag potential prescribers to the OBSERVA study facilitators. Only after the prescriber has agreed to participate in the OBSERVA study and has made a request to the pharmacy for details of eligible patients, will potential study participants be signposted to the prescriber. No further involvement in the study process will be required
- **The community pharmacist will not approach the patient about involvement in the study, will not take consent from the patient and will not be required to access patients' medical notes**

[†††] Criteria for inclusion in the study:

- Prescription is written by a specialist prescriber on a prescription form suitable for dispensing in a community pharmacy
- The medication prescribed is asenapine, and has been prescribed in line with the inclusion criteria detailed in the study protocol
- The prescriber has not already been signposted to this patient by the community pharmacy on a previous occasion
-

- The study introduction letter sent by the community pharmacist will not share patient-identifiable information
- The community pharmacies are not considered to be research sites, as the role being undertaken will only involve the identification of prescribers and participants

Appendix 4. Summary of Amendments and Updates

Amendment	Ref	Summary	Submission to Res Ethics Committee	Response from Res Ethics Committee
Substantial Amendment 1	**SA01**	• Amendment to allow members of the care team and Mental Health Research Network (MHRN) Clinical Study Officers (CSOs) to check the medical notes to identify potential patients • Additional question added to the consent form	Submitted 17.09.2012	Unfavourable opinion received 24.10.2012
Substantial Amendment 2	**SA02**	• Modification of SA01 removing role of CSOs in reviewing or screening identifiable personal information of patients	Submitted 06.11.2012	Favourable opinion received 09.11.2012
Non-substantial Amendment 3	**NA03**	• Administrative and minor operational amendments to protocol and questionnaires	Submitted 17.09.2012	Acknowledgement received 15.11.2012
Non-substantial Amendment 4	**NA04**	• Typographical corrections and minor amendments to forms and questionnaires	Submitted 06.12.2012	Acknowledgement received 15.01.2013
Non-substantial Amendment 5	**NA05**	• Typographical corrections and minor documentation amendments predominantly aimed at increasing potential recruitment sites	Submitted 15.01.2013	Withdrawn
Substantial Amendment 6	**SA06**	• Slight protocol amendments and additional documents prepared, predominantly aimed at increasing potential recruitment sites and consenting participants	Submitted 04.02.2013	Unfavourable opinion received 15.02.2013
Non-substantial Amendment 7	**NA07**	• As NA05, includes Welsh sites and non-NHS sites and typographical corrections	Submitted 14.03.2013	Acknowledgement requested
Substantial Amendment 8	**SA08**	• Modification of SA06 providing requested clarification	Submitted 05.04.2013	Favourable opinion 15.04.2013
Substantial Amendment 9	**SA09**	• Allows for retrospective recruitment and includes front reporter page for both baseline and 12 week questionnaires	Submitted 26.07.2013	Favourable opinion 03.09.2013
Non-substantial Amendment 10	**NA10**	• Remove named manager from staff and patient info sheets, replaces with generic 'study manager' and team email address.	Submitted 17.09.2013	Acknowledgement received 03.01.2014
Substantial Amendment 11	**SA11**	• Submission of 12 bespoke follow up event questionnaires, as per mention in Protocols already approved.	Submitted 14.04.2014	Favourable opinion 22.05.2014
Non-substantial Amendment 12	**NA12**	• Patient Consent Form bullet 3 of page 2. To comply with NRES request, the sentence closes " … for this study" rather than " … for research purposes".	Submitted 14.07.2014	Acknowledgement received 18.07.2014
Non-substantial Amendment 13	**NA13**	• Study recruitment extension from 24 to 36 months.	Submitted 17.09.2014	Acknowledgement received 25.09.2014
Non-substantial Amendment 14	**NA14**	• To reflect participation of Scotland (in addition to England and Wales), Protocol, Staff Info/Patient Info and Consent to Contact amended	Submitted 30.06.2015	Acknowledgement received 10.07.2015
Non-substantial Amendment 15	**NA15**	• Study recruitment extension from 36 to 47months.	Submitted 21.09.2015	