Data Base Audit (DBA) Protocol

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An epidemiological registry study to evaluate clinical practice treatment in patients with Bipolar Disorder treated with quetiapine XR and/or quetiapine IR

Sponsor:

AstraZeneca Nordic
151 85 Södertälje
Sweden

The following Amendment(s) have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

National Co-ordinating Investigator of the Non-Interventional Study

[redacted]

Project group

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this NIS Protocol.

Abbreviation or special term	Explanation
APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical classification system
AZ	AstraZeneca
BD	Bipolar Disorder
DBA	Data Base Audit
DDD	Defined Daily Dose
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
National Coordinator	The National Coordinator is the main line of contact to coordinate the submissions and responses of the Ethics Committee.
NPR	National Patient Register
NBHW	National Board of Health and Welfare
OTC	Over-the-counter drugs, medicines sold without a prescription
PDR	Prescribed Drug Register
PIN	Personal Identification Number
Quetiapine IR	Immediate Release quetiapine
Quetiapine XR	Extended Release quetiapine
SCB	Statistics Sweden
Variable	A characteristic of a property of a an item that may vary eg, from time to time between items

1. INTRODUCTION

1.1 Background

Psychiatric disorders account for a large part of the global burden of disease (Prince et al 2007). Bipolar disorder (BD) is a lifelong illness characterized by one or more episodes of mania or hypomania usually alternating with recurring major depressive episodes, which is an important contributor to this disease burden (Prince et al. 2007, APA 2002). The estimated lifetime prevalence of bipolar I and II disorder is affecting an estimated 0.5–5% of adults and characterized by a heterogeneous course, including: hypo manic, manic, or depressed episodes; slow or incomplete recovery from acute episodes; risk of recurrence; and sustained morbidity over time (Kupfer 2004, Pini 2005, Merikangas et al. 2007). BD cause substantial loss of function for many patients, and place high financial and social burdens on caregivers, the health care system and society as a whole. The economic implications of these disorders may have been previously underestimated (Grant et al. 2005).

BD is a progressive illness that requires long-term treatment. Individualizing drug treatments in BD is crucial for treatment success, with respect to side effects, adherence challenges and patient preferences (Altamura et al. 2008, Parks et al. 2009). Different patient and drug characteristics therefore determine the psychiatrist's drug choice. Adherence is a major problem and a range of treatment options are needed.

Immediate-release quetiapine (quetiapine IR) and extended-release quetiapine (quetiapine XR) are both indicated in Europe for the treatment of bipolar I and II disorder. The two formulations of quetiapine have different characteristics. Quetiapine XR is characterized by once-daily dosing, faster dose titration and different pharmacological profile with different occupancy on dopamine D2 receptors and has different tolerability profiles compared to quetiapine IR (Datto et al. 2009, Figueroa et al. 2009, Meulien et al. 2010, Peuskens et al. 2007, Nord et al. 2011). The differences between the two formulations of quetiapine may potentially result in differential use in clinical practice in BD. [redacted]

Differential use of quetiapine IR and quetiapine XR has been documented in schizophrenia in Sweden and Finland. In Sweden, "A retrospective, naturalistic study evaluating the use of quetiapine XR and quetiapine IR in the clinical practice of inpatients in schizophrenia in Sweden" documented differences between the two quetiapine formulations in mean doses, number of add-on medications, disease severity and reasons for treatment in 178 inpatients with schizophrenia across 14 psychiatric clinics (Eriksson et al. 2011). A Finnish study (Hallinen et al. 2011, "the Lappeenranta study") documented a similar differential use of quetiapine XR and IR in 156 inpatients at the South Karelia Central Hospital in Lappeenranta. A small sample with BP mania was included in the in the Finnish study (The Lappeenranta study) and differential use was documented.

We aim to investigate the clinical practice treatment in BD in Sweden, with particular focus on the use of quetiapine XR and quetiapine IR.

1.2 Rationale for conducting this DBA

Quetiapine IR and quetiapine XR are both indicated in Europe for the treatment of BD. The target dose depends on if the episode is depression or mania. In treatment of bipolar depression the target dose is 300 mg and in the treatment of mania the target dose is 600-800 mg. In maintenance treatment the dosing is 300-800 mg with quetiapine XR and 300-750 mg with quetiapine IR, depending on if the patient needs protection for depression or protection for both depression and mania.

It has been shown differences between quetiapine XR and quetiapine IR in plasma concentration profile, occupancy in D2 receptors and tolerability profile according to sedation. Fast titration is an advantage in treatment with quetiapine XR. Results of two studies (Datto et al. 2009) and study code D1443C00040 (Reported 2010, data on file) supported a different tolerability profile in quetiapine XR and quetiapine IR, with different sedation profile. Nord et al. 2011 have shown different D2 occupancy profile for quetiapine XR and quetiapine IR.

Psychiatrists have discussed that, due to the different characteristics, quetiapine XR and quetiapine IR are used differently in the clinical practice of patients with BD. Quetiapine XR, [redacted] is believed to be primarily used as foundation treatment, whilst quetiapine IR is believed to be more commonly used in lower doses as add-on to other treatments. In the treatment of schizophrenia two non-interventional (NIS) studies in Finland (Hallinen et al. 2011, "the Lappeenranta study") and in Sweden (Eriksson et al. 2011) have shown differential use with quetiapine XR and quetiapine IR. Many patients were treated with higher doses of quetiapine XR compared to when treated with quetiapine IR and patients were frequently treated with both formulations at the same time. In Lappeenranta, only few patients with BD mania were investigated.

The aim of this study is to describe the treatment pattern and describe patient characteristics in real life setting in patients with BD treated with quetiapine XR and/or quetiapine IR in Sweden. No outcome analysis will be performed between the formulations due to the high amount of confounding factors.

The clinical everyday use of quetiapine XR and quetiapine IR, when treating patients with BD, is unknown and explorative assessment of patient and drug treatment characteristics will be performed.

2. DBA OBJECTIVES

2.1 Primary objective

The primary objective of the study is to describe the detailed clinical treatment (including duration of treatment, doses, drug switches, and add-on therapy), in patients with BD and on treatment with quetiapine XR and/or quetiapine IR before, at and after the index date.

2.2 Secondary objectives

1. To describe co-morbidity, demographics, sick leave, early retirement and socioeconomic factors in patients with BD and on treatment with quetiapine XR and/or quetiapine IR before and at the index date.
2. To describe the detailed clinical treatment (including duration of treatment, doses, drug switches, and add-on therapy) in patients with BD, including all drug treatment after the index date.
3. To describe co-morbidity, demographics, sick leave, early retirement and socioeconomic factors in patients with BD, including all drug treatment before and at the index date.

3. STUDY PLAN AND PROCEDURES

This DBA Study Protocol has been subject to an internal review according to AstraZeneca standard procedures.

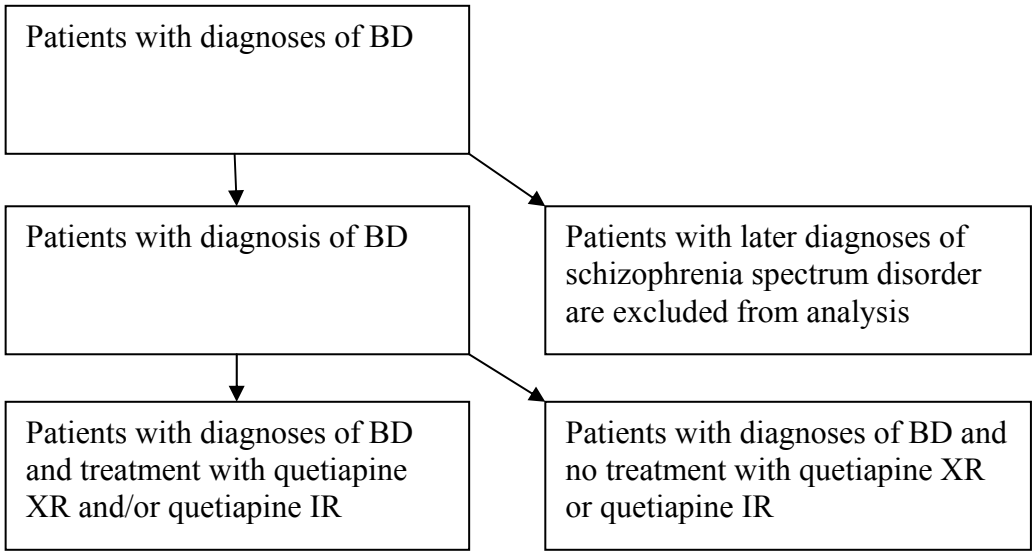
3.1 Study Design

This is an epidemiological registry study on all patients who have been hospitalised in Sweden at least once since 1987 with a diagnosis during hospitalisation of BD and/or schizophrenia spectrum disorder. Index visit (baseline) is defined as the date when a patient dispensed their first prescription of quetiapine XR and/or quetiapine IR. Patients with index visit between 1st of January 2009 and 31st of December 2010 will be more detailed described, and data will be collected six months prior to the first dispensed prescription of quetiapine XR and/or quetiapine IR. Patients started their treatment with quetiapine XR and/or quetiapine IR before 1st of January 2009 will have 1st of January 2009 as index visit.

May 2008 quetiapine XR was launched for the indications schizophrenia and bipolar mania in Sweden and March 2009 quetiapine XR and IR was launched in bipolar depression.

Data on patients with schizophrenia spectrum disorder will be collected in order to allow us to exclude patients who have been re-diagnosed to or from bipolar disorder. The latest diagnose is defined as the patients diagnose, i.e. if a patient gets a schizophrenia spectrum disorder diagnose after diagnose of bipolar disorder, the patient will not be included in the study.

Figure 1 Patient flow



3.2 Data collection method

This is an epidemiological registry study to evaluate clinical practice treatment in patients with BD. Data will be extracted from the National Patient Register (NPR) and merged with the National Prescribed Drug Register (PDR), and the Population Register. These data will also be matched with data on socioeconomic factors in order to describe the patients. The data will be obtained from various national registers in the LISA database maintained by Statistics Sweden (SCB).

Data will be collected for all patients who have been hospitalised in Sweden at least once since 1987 with a diagnosis during hospitalisation of BD and/or schizophrenia spectrum disorder.

All the registers include the Personal Identification Numbers (PIN) assigned to each resident in Sweden, enabling identification and linkage of records (Ludvigsson et al. 2009). The merging of the data from registers will be performed by National Board of Health and Welfare (Socialstyrelsen) who will replace the PIN of anonymous serial number before delivery of the database. No identification of patients will be possible elsewhere.

3.3 Data sources

3.3.1 National Patient Register

NPR includes all in-patient care in Sweden from 1987. From 2001 the register also contains information on outpatient visits at hospitals, including day surgery carried out by both private

and public caregivers. Information on primary care visits or open care visit outside hospital are not included in the NPR. The information in NPR can be divided into four different groups

1. Patient data (personal registration number (PIN), sex, age, place of residence)
2. Geographic data (county council, hospital/clinic, department)
3. Administrative data (dates of admission and discharge, length of stay for inpatients, acute/planned admission, admitted from, discharged to) and
4. Medical data (the main diagnosis, secondary diagnoses, external cause of injury and poisoning, procedures and surgery).

Before 1997 the register contained a total of six diagnoses per admission, increasing to eight in 1997 and since 2009 an unlimited number of secondary diagnoses can be recorded.

At present, the NPR is updated once a year and normally available in September-October for the preceding year. The missing data on PIN for 2007 has been estimated to less than one percent.

3.3.2 Prescription Drug Register

The Prescribed Drug Register was started July 1, 2005 and is updated each month. The register comprises national coverage of dispensed drugs, pharmacies (dispensed drugs), not including OTC and in-patient care.

The variables include the patient's ID-number (PIN) and place of residence. Also registered is information about dispensed drugs (by ATC code), dates, dosages and for an unknown proportion indication in free text, DDDs, and expenditure. Information on the prescriber's profession (physician or other) and specialist code are registered.

PDR can be linked to other national registers by the unique patients PIN. Limitations include the lack of in-patient drug use and the lack of specific coding of the indication and prescribed dose. Information on indication and prescribed dose may in many cases be retrievable by text search procedures.

3.3.3 Population Register

To ascertain a correct population at risk time in the data analysis, information on dates of emigration and death for all patients will be retrieved from the Register of Population at Statistics Sweden.

3.3.4 Socioeconomic factors

Data on socioeconomic factors will be obtained from various national registers available in the LISA database maintained by SCB. In LISA information is available for all people, aged 16 or older, who have been a resident in Sweden by the end of the year. Data is available at least from 1990.

4. SUBJECT POPULATION

The patient population will consist of all patients who have been hospitalised in Sweden at least once since 1987 with a diagnosis during hospitalisation of BD. Patients with a later diagnosis of schizophrenia spectrum disorder will be excluded.

4.1 Inclusion criteria

1. Patients with a diagnosis of BD, see Appendix B Table 1 for the ICD10 and ICD9 diagnosis.

4.2 Exclusion criteria

1. Patients with a diagnosis of any schizophrenia spectrum disorder after the diagnosis of bipolar disorder, see Appendix B, Table 2 for the ICD10 and ICD9 diagnosis.

5. STUDY VARIABLES

5.1 Study variables from different registers

Data on patients with a diagnosis of BD and/or schizophrenia spectrum disorder who have been hospitalized due to this disease (the latest diagnose will be valid for inclusion) at any time since 1987 will be extracted from following registers.

5.1.1 National Patient Register

- Date of admission and length of stay
- Main diagnosis
- Secondary diagnosis
- DRG codes set by the discharge hospital

5.1.2 Prescription Drug Register (see attachment 1)

- Dispatching pharmacy (council code for the dispatching pharmacy)
- Dispensed prescribed medications
- Patients information (Personal code number, age and gender, place for national registration)
- Prescriber information (occupation, education code, specialist code)
- Place of work information (County, working place code, ownership, health care, activity direction)
- Prescription information (Prescription date, type of ordination, type of benefit, category of execution, start package, permitted exchange, exchange code, prescribed identity of goods (connected to the register of goods with access to ATC-

code, name of prescribed drug, DDD per package etc.), number of prescribed packages, dispatched identity of goods, type of goods, number of complete packages, dosage instruction)

- Cost (price each, total cost, patient cost, county cost, VAT, surplus cost)

5.1.3 Population Register

- Dates of emigration
- Date of death

5.1.4 Socioeconomic Data

- Educational level
- Marital status
- Living situation
- Occupation status
- Sick leave
- Income level
- Income source (salary/sick pension)
- Country of birth

5.2 Other variables

co-morbidities of special interest at index visit, before treatment with quetiapine XR and/or quetiapine IR and co-medications of special interest at the index visit and afterwards.

5.2.1 Co-morbidities

- Ischemic heart disease
  - ICD-9: 413
  - ICD-10: I 20.9, I 25.1
- Peripheral arterial disease including extra cerebral, non-coronary arterial thrombo-embolism
  - ICD-9: 440,441,444
  - ICD-10: I70- I79
- Chronic obstructive pulmonary disease (COPD)

  - ICD-9: 496
  - ICD-10: J44.9

- Psychiatric admission history including number of previous admissions.
  All F psychiatric (diagnosis) will be collected, with special interest of diagnoses specified see Table 3-4. All V, X and Y diagnosis (External causes of morbidity and mortality) are included, see appendix B, Translator ICD10 to ICD9.
- Drug and alcohol abuse
  - ICD-9; 305.0, 291.89, 292, 305.00-305.93, 304.00-304.93
  - ICD-10: F10-F19
- Cancer
  - ICD-9: 140-209
  - ICD-10: C00-C99
- Endocrine disease
  - ICD-9: 240-246
  - ICD-10: E16-E99
- Diabetes mellitus
  - ICD-9: 250
  - ICD-10: E10-E11
- Neurological
  - ICD-9.: 320-389
  - ICD-10: G00-G99 (excluding G45)
- Heart failure
  - ICD-9: 428
  - ICD-10: I 50
- Myocardial Infarction
  - ICD-9. 410, 429
  - ICD-10: I 21-22

- Stroke and TIA
  - ICD-9: 430-438
  - ICD-10: I 60-69
- Hypertension
  - ICD-9: 401
  - ICD-10: I 10
- Renal failure
  - ICD-9: 586, 403, 404, 639.3
  - ICD-10: N 17-19
- Intoxication
  - ICD9: 960-979
  - ICD10: T4n

5.2.2 Co-medications

- Anti-depressant: N06A;
  - N06AA, N06AB, N06AC, N06AD, N06AE, N06AF, N06AG, N06AX
- Benzodiazepine-derivates: N05BA;
  - NO5BA01, NO5BA02, NO5BA03, NO5BA04, NO5BA05, NO5BA06,
  - NO5BA07, NO5BA08, NO5BA09, NO5BA10, NO5BA11, NO5BA12,
  - NO5BA13, NO5BA14, NO5BA15, NO5BA16, NO5BA17, NO5BA18, NO5BA22
- Narcoleptics: N05A;
  - N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AK,
  - N05AL, N05AN, N05AX
- Quetiapine IR: N05AH04
- Quetiapine XR: N05AH04
- Anti-epileptics: N03A;
  - N03AA, N03AB, N03AC, N03AD, N03AE, N03AF, N03AG
    - NO3AG01, NO3AG02, NO3AG03, NO3AG04, NO3AG06
  - NO3AX

- Valproate: N03AG01
- Sulfonylurea: A10BB
- Metformin: A10Ba
- Insulin: A10A
- Broncho dilatating drugs: R03
- Betablockers: C07
- ARB: C09C, C09D
- ACE: C09A, C09B
- Ca-antagonists: C08C, C08D
- Thiazides: C03A
- Loop diuretics: C03C
- Statins: C10AA
- Lamotrigine: N03AX09
- Lithium: N05AN01

5.2.3 Socioeconomic variables

- Educational level
- Marital status
- Living situation
- Occupation status
- Sick leave
- Income level
- Income source (salary/sick pension)
- Country of birth

6. ETHICAL CONDUCT OF THE NON-INTERVENTIONAL STUDY

The DBA will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs and the applicable legislation on Non-Interventional Studies.

6.1 Ethics review

The final protocol of the DBA must be approved or given a favourable opinion in writing by the Ethics Committee. The Ethics Committee must also approve any amendment to the protocol, according to local regulations.

After an approval from the Ethics committee, the NBHW and SCB also make an independent evaluation of the data request.

6.2 Subject Informed consent

Normally, informed consent is needed when either the research imposes a risk for patients or the study requires data containing personal identifiers. Studies conducted entirely using administrative databases and which do not use any personal identifiers may require only abbreviated review or may not require formal review at the discretion of the Ethics Committee.

6.3 Subject data protection

The merging of data from the registers will be performed by the NBHW. No identification of patients will be possible elsewhere.

7. STUDY MANAGEMENT

7.1 DBA timetable and end of study

Before any data retrieval is initiated the following should be fulfilled

- Written approval of the DBA by the Ethics Committee, according to local regulations
- Proper agreements between AstraZeneca and National Board of Health and Welfare (Socialstyrelsen) are signed

The planned timetable for the DBA is estimated to be as follows:

- First data collection: Q4 2011

- Last data collection: Q4 2011
- Data Base Audit report: Q1 2012

Should AstraZeneca decide to discontinue the study prior to what was established in this protocol, the investigator, and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date.

8. DATA MANAGEMENT

8.1 Collection, monitoring, processing of data and archiving

Please see section 3.2 for details regarding data collection.

The anonymous databases with the merged data will be hosted at Psykiatri Nordväst, Karolinska sjukhuset and by the institution doing the statistical analysis. Data Management and statistical analysis of data will be managed by AstraZeneca (or external service provider contracted by AstraZeneca).

8.2 Reporting and publication of data

AstraZeneca will ensure analysis and aim to publish the results in a scientific paper and/or scientific congress. Authorship will be according to the principal criteria for eligibility that are detailed in the Uniform Requirements for Submission of Manuscripts to Biomedical Journals (ICMJE, 5th Edition, 1997).

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

9.1 Statistical evaluation – general aspects

A DBA is a study in which epidemiological methods including other methods that can be used to analyse human population health data.

The principal features of the planned statistical evaluation will involve descriptive statistics analysis the different populations.

The descriptive analysis (both for the primary and secondary objectives) will for the continuous variables be done by calculating mean, standard deviation, 95% CI, number of observations, minimum, maximum, median and number of missing observation and for categorical variables number of observations, frequencies and percentage.

The analysed variables at the index date will be age, gender, educational level, marital status, living situation, occupation status, sick leave, income level, income source (salary/sick pension), country of birth, co-morbidities (as specified in section 5), co-medications (as specified in section 5).

The prescribers occupation, education and specialist code will be analysed, ownership (private/public) and country divided in quetiapine IR and quetiapine XR.

The variables analysed before the index date will be; number of hospital stays and sum of length of hospital stays.

The treatments after the index date will be analysed for the following variables: duration, dosage, drugs switches, DDD per package, number of prescribed packages for quetiapine IR/XR and co-medications including dosage and duration of these co-medications.

Attempts will be made to find the prescribed dose and the diagnosis from the free text on the prescription label on the drug for quetiapine IR and quetiapine XR either by text mining or by manually go through the different prescription labels.

9.2 Determination of sample size

This is an epidemiological registry analysis and no formal sample size calculation has been made. The population in Sweden is 9 300 000. We estimate a sample size of 14-16 000 patients with BD treated with quetiapine XR and quetiapine IR.

10. REFERENCES

Al Jurdi RK, Dixit LA, Sajatovic M. Role of extended release quetiapine in the management of bipolar disorders. Neuropsychiatr Dis Treat 2010;6:29-35.

Altamura AC, Armadoros D, Jaeger M, Kernish R, Locklear J, Volz HP. Importance of open access to atypical antipsychotics for the treatment of schizophrenia and bipolar disorder: a European perspective. Curr Med Res Opin 2008; 8:2271-82.

American Psychiatric Association. Practice Guidelines for the treatment of patients with Bipolar disorder. Am J Psychiatry 2002;159(suppl.):S2-S50.

Datto C, Berggren L, Patel JB, Eriksson H. Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release quetiapine fumarate during dose initiation: a randomized, double-blind, crossover study in healthy adult subjects. Clinical Therapeutics 2009;31(3):492-502.

Eriksson L, Hallerbäck T, Jörgensen L, Carlborg A. Use of quetiapine XR and quetiapine IR in clinical practice for hospitalized schizophrenic patients – a retrospective study. (Data on file).

Figueroa C, Brecher M, Hamer-Maansson JE, Winter H. Pharmacokinetic profiles of extended release quetiapine fumarate compared with quetiapine immediate release. Prog Neuropsychopharmacol Biol Psychiatry 2009;33(2):199-204.

Gaudiano BA, Weinstock LM, Miller IV. Improving treatment adherence in bipolar disorder. A review of current psychosocial treatment efficacy and recommendations for future treatment development. Behaviour Modification 2008;32(3):267-301.

Grant BF, Stinson FS, Hasin DS et al. Prevalence, correlates, and co morbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and related conditions. J Clin Psychiatry 2005;66 (10):1205-1215.

Hallinen T, Ovaskainen Y, Granström O. Differential use of extended and instant release quetiapine: A naturalistic register study of Finnish in-patients with schizophrenia spectrum and bipolar disorder ("The Lappeenranta study", data on file). Abstract submitted, ISPOR 2011.

Hardeman SM, Harding RK, Narasimhan M. Simplifying adherence in schizophrenia. Psychiatr Serv 2010;61(4):405-8.

Hassan M, Pelletier E et al. Comparison of hospitalizations and costs among bipolar patients who switched to extended release quetiapine from immediate release quetiapine. 2010 Abstract. NR 4-47.

Kupfer DJ (Ed.), Montvale NJ. Epidemiology and clinical course of bipolar disorder. In: Bipolar Depression. The Clinician's Reference Guide (BD-CRG). Current Psychiatry, LLC, 2004.

Ludvigsson, Otterblad-Olausson P, Petersson BU, Ekbom A. Eur J Epidemiol. The Swedish personal identify number: possibilities and pitfalls in healthcare and medical research. 2009; 24:659-667.

Merikangas KR, Akiskal HS, Angst J et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Co morbidity Survey replication. Arch Gen Psychiatry 2007;64(5):543-552.

Meulien D, Huizar K, Brecher M. Safety and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: pooled data from randomised, double-blind, placebo-controlled studies. Hum Psychopharmacol 2010;25(2):103-15.

Nord M, Nyberg S et al. Comparison of D2 dopamine receptor occupancy after oral administration of quetiapine fumarate immediate-release and extended release formulations in healthy subjects. International J of Neuropsychopharmacology 2011; 1-0.

Parks J, Radke A, Parker G, Foti ME, Eilers R, Diamond M et al. Principles of antipsychotic prescribing for policy makers, circa 2008. Translating knowledge to promote individualized treatment. Schizophr Bull 2009;35(5):931-36.

Peuskens J, Trivedi J, Malyarov S, Brecher M, Svensson O, Miller F, et al. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: a randomized, placebo-controlled trial in clinically stable patients. Psychiatry (Edgmont) 2007;4(11):34-50.

Pini S et al. Eur Neuropsychopharmacol. 2005;15(4):425–434.

Prince M, Patel V, Saxena et al. No health without mental health. Lancet 2007;370(9590):859-877.

Study code D1443C00040. A phase IV, multi-centre, double-blind, double-dummy, randomized parallel-group study to compare the tolerability of quetiapine fumarate immediate release (SEROQUEL®) with quetiapine fumarate extended release (SEROQUEL XR®) during initial dose escalation in patients with bipolar depression. (Reported 2010, data on file).

Thieda P, Beard S, Richter A, Kane J. An economic review of compliance with medication therapy in the treatment of schizophrenia. Psychiatr Serv 2003;54(4):508-16.