Retrospective Observational Database Study Protocol

Drug Substance	Quetiapine fumarate
Study Code	D1443C00128
Edition	1
Date	[redacted]

Objective assessment of metabolic monitoring in patients treated with Seroquel® or Seroquel® XR/quetiapine fumarate: use of *IMS Disease Analyzer* to assess physician behaviour in the UK and Germany

Requesting AZ department: [redacted]
Therapeutic area: [redacted]
Name of Requester: [redacted]

Sponsor:
AstraZeneca AB, 151 85 Södertälje, Sweden

[redacted]

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

Amendment No.	**Date of Amendment**		

Administrative Change No.	**Date of Administrative Change**		

PROTOCOL SYNOPSIS

Objective assessment of metabolic monitoring in patients treated with Seroquel® or Seroquel® XR/quetiapine fumarate: use of *IMS Disease Analyzer* to assess physician behaviour in the UK and Germany

Principal Investigators:

[redacted]

[redacted]

Co-Investigator:

[redacted]

Objectives

Primary Objective: Determine whether physicians in the UK and Germany perform monitoring of patients treated with Seroquel® and Seroquel® XR (using lab tests, measurements and counselling as described below) during encounters with patients and document the proportion of physician encounters within the study sample where the following patient monitoring is performed:

- counseling patients on healthy eating, exercise and healthy lifestyle improvements
- recording patient weight at initiation of treatment
- monitoring of weight of patients receiving on-going treatment
- monitoring of hyperlipidemia
- monitoring for signs and symptoms of hyperglycemia
- monitoring of blood glucose in patients with diabetes mellitus
- monitoring of blood glucose in patients with risk factors for diabetes mellitus for worsening of glycemic control

Study design

This is a quasi experimental design that includes cross sectional assessment of physician behaviours during encounters with patients in two countries following the distribution of metabolic educational materials on Seroquel® and Seroquel® XR.

Databases to be used

IMS Disease Analyzer

Target subject population

The study population includes all patients with a diagnosis of schizophrenia, bipolar disorder or major depressive disorder treated with Seroquel® or Seroquel® XR/quetiapine fumarate seen by

- general practitioners and psychiatrists in Germany based upon patient encounters recorded in IMS Disease Analyzer during the calendar period [redacted], and
- general practitioners in the United Kingdom based upon patient encounters recorded in IMS Disease Analyzer during the calendar period from [redacted].

Key Inclusion criteria:

Electronic medical records of patients age 18 and over with diagnoses of schizophrenia, bipolar disorder or major depressive disorder treated with Seroquel® or Seroquel® XR/quetiapine fumarate during the calendar periods [redacted] seen by general practitioners or psychiatrists in Germany and patients seen by general practitioners in the UK during the period [redacted].

Key Exclusion Criteria:

Patients with diagnoses of schizophrenia, bipolar disorder or major depressive disorder treated with Seroquel® or Seroquel® XR/quetiapine fumarate not having any medical encounters during the time periods: [redacted] in Germany and during the period [redacted] in the UK.

Exposures of Interest

Treatment with Seroquel® or Seroquel® XR/quetiapine fumarate

Outcomes of Interest

The proportion of physician encounters where the following are performed:

- counseling patients on healthy eating, exercise and healthy lifestyle improvements,
- patient weight at initiation of treatment,
- monitoring weight of patients receiving on-going treatment
- monitoring of hyperlipidemia for patients,
- monitoring for signs and symptoms of hyperglycemia,
- monitoring blood glucose in patients with diabetes mellitus,
- monitoring of blood glucose in patients with risk factors for diabetes mellitus for worsening of glycemic control

Statistical Methods

Age and risk factor adjusted proportion of patients receiving metabolic monitoring tests/assessments summarized by physician specialty: general practitioners and psychiatrists in Germany and general practitioners in the UK including confidence intervals associated with the proportions observed.

Adjustment is performed on the following potential risk factors for which there is relatively complete ascertainment (> 60%): use of other antipsychotics in addition to Seroquel® or Seroquel® XR/quetiapine fumarate in past 12 months, BMI > 25, age (50+), female gender, relevant family history, high blood pressure, high cholesterol, and history of cardiovascular disease (in past 12 months).

Limitations

- The degree of ascertainment of these monitoring measures in the IMS Disease Analyzer database in each country is not known
- Recording of lifestyle factors and weight may be limited

- Ability of text mining to ascertain outcomes (i.e. counseling of patients regarding healthy lifestyle choices) is unknown

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1. INTRODUCTION

1.1 Background

The MEB, as the Reference Member State (RMS) for SEROQUEL and SEROQUEL XR, requested AstraZeneca to update the education materials in scope of the EU Risk Management Plan (RMP) and Summary of Product Characteristics (SmPC) changes with respect to hyperglycaemia and metabolic monitoring. The content and the messages for these educational materials have been agreed and distribution in the individual member states is ongoing.

AstraZeneca was also requested to provide a plan for assessing the effectiveness of these educational materials. During discussion with the MEB, it was communicated that there are 2 components to the assessment of effectiveness: process indicators (receipt and understanding of materials) and outcome indicators (changes in behaviour and effect on patients). To realize these 2 indicators, AstraZeneca is proposing 2 components for the evaluation of the effectiveness of the metabolic education: an easy to understand and complete healthcare provider survey and the evaluation of Electronic Medical Record (EMR) data, as a means to have an objective assessment of the monitoring of patients.

A companion proposal describes the evaluation of the effectiveness of the distribution of metabolic educational materials using a healthcare provider survey to assess the receipt of the educational material, whether the material was read, and to assess healthcare provider behaviour regarding the conduct of monitoring of metabolic parameters for patients treated with SEROQUEL and SEROQUEL XR.

This protocol describes the objective assessment of metabolic monitoring in patients treated with quetiapine through the evaluation of electronic medical record (EMR) data including details on objectives, the source of data, and the target physician-base for the database assessment. An assessment of healthcare provider behaviour in the UK and Germany will be accomplished by use of EMR data from the IMS Disease Analyzer database.

1.2 Scientific and Business Rationale and Significance

Electronic Medical Records are a source of data that include documentation of evaluation and management activities of physicians in the performance of routine practice including subjective evaluations, objective testing, assessment, and planning as part of the general medical care and specialized care provided to patients. EMR data can been used to provide insight into the counselling and medical tests that patients receive during interactions with health care providers and for this reason it is a source for objective assessment of the type of medical monitoring that patients receive.

An evaluation of EMR data is proposed to be used to provide a more objective assessment of the medical monitoring of physician records during encounters with patients with schizophrenia, bipolar disorder or major depressive disorder who were treated with Seroquel® or Seroquel® XR/quetiapine fumarate. The assessment of this data in a retrospective manner

is expected to be more objective than information obtained via surveying physicians who have treated patients with Seroquel® or Seroquel® XR/quetiapine fumarate.

2. STUDY OBJECTIVES

2.1 Primary objective

Determine whether physicians in the UK and Germany perform monitoring of patients treated with Seroquel® or Seroquel® XR/quetiapine fumarate (using lab tests, measurements and counselling as described below) and to document the frequency range among physicians within the study sample on the following:

- counseling patients on healthy eating, exercise and healthy lifestyle improvements,
- recording patient weight at initiation of treatment,
- monitoring of weight of patients receiving on-going treatment,
- monitoring for hyperlipidemia,
- monitoring for signs and symptoms of hyperglycemia,
- monitoring of blood glucose in patients with diabetes mellitus, and
- monitoring of blood glucose in patients with risk factors for diabetes mellitus for worsening of glycemic control.

3. STUDY DESIGN SELECTION AND RATIONALE

3.1 Rationale for study design

This is a quasi experimental design that includes cross-sectional assessment of physician behaviours during encounters with patients in two countries following the distribution of metabolic educational materials on Seroquel. The proposed design provides a pragmatic approach to document the monitoring of patients around the following key metabolic monitoring messages communicated through educational materials that were previously distributed: monitoring of weight, lipids, metabolic risk concerning signs of hyperglycaemia and changes in glucose for patients with diabetes mellitus or with risk factors for diabetes mellitus, and counselling for exercise, nutrition, and maintenance of a healthy lifestyle.

4. DATABASE(S) TO BE USED

IMS's LifeLink Electronic Medical Record (EMR)-EU resource comprises longitudinal patient-level databases from physician-practice data systems of office-based physicians in

France, Germany, and the United Kingdom (UK). For this study, we will focus on Germany and the UK. The database includes up to 18 years of data drawn from EMR, offering excellent long-term disease tracking on more than 19 million patients. The magnitude of the LifeLink EMR-EU data available for each country of interest is summarized in the following table:

	UK	Germany
Total population	60M	82.5M
Patient Records	4.2M	15.5M
Physicians	1,151	3,002
Practices	218	2,357
Prescriptions	206M	150M

There are several EMR software partners within each country from which IMS derives relationships with physician practices to participate in the LifeLink EMR-EU panel. As with any EMR software, there are fixed-format data collection fields as well as some free text, note fields. Standard practice of what information, how much, and in what format (fixed vs. free text) is collected may vary by physician practice, EMR software used, and country. The basis of the data collection within an EMR is encounter-based, indicating that all recorded data revolves around an interaction with the practice, which may include an office visit, referral, telephone call, or laboratory/test results sent to the practice.

In Germany, LifeLink EMR-EU data are collected from participating specialists as well as primary care physicians including specialists such as psychiatrists and neurologists. German patients may receive care from any physician specialty. More frequently, physician practices in Germany consist of a single practitioner, so EMR encounters are often linkable to the specific physician. UK patients are assigned to a particular PCP who coordinates all of the patient's care. Traditionally, UK PCP practices are composed of several physicians, making it difficult to link specific EMR encounters to a specific physician within the practice. Therefore, within the UK, physician behaviour may need to be viewed at the practice-level.

Data include basic demographics (gender and age) and medical diagnoses, recorded in ICD-10 (and READ codes in the UK) and linked to physician-written prescriptions and the date of the visit during which the diagnosis was made and/or the prescription was written. Details regarding physician-written prescriptions include the specific medication (only generic name in the UK), form, strength, and the European Pharmaceutical Market Research Association (EphMRA) drug classification ATC code. The total units prescribed and the prescribed units per day (daily dose) may be available. In the UK, the specific quantity of medication supplied is an individual unit count.

The EMR encounter data contain notes on actions taken and the health status recorded during the patient's visit; these notes may be entered by a nurse, physician, or other staff with whom

the patient had contact. Notes and entry into fixed fields are based on discussion with the patient as well as the healthcare professional's impressions. Data may include referrals and hospitalizations (although limited); the specialty of the physician to which the patient is referred is also available.

In addition, EMR encounter data may include the patient's height, weight, and smoking status. The German data also include the patient's obesity status and insurance status.

EMR encounter data include:

- ICD-10 diagnosis codes with dates of diagnoses or resolution of condition – to help identify CNS diagnosis as well as risk factors (e.g., high cholesterol, cardiovascular diseases), prior conditions, and relevant family history as well as hyperglycemia
- Vital and biometric measurements (e.g., blood pressure, weight, height), as recorded per visit
- Lipid panel (includes cholesterol and triglyceride) lab results, as recorded by practice
- Other lab results, such as blood glucose, as recorded by practice
- Treatments – prescription orders: date, EphMRA's ATC classification code, dose, form, pack, reason for any switch or stoppage of prior medication; as recorded by the physician practice
- e.g., prescriptions for self monitoring blood glucose strips, other antipsychotics, cholesterol medications, and blood pressure medication can be identified
- Notes containing references to diet/exercise counseling or ICD-10 diagnoses/READ codes corresponding to the provision of patient counseling for nutrition, exercise, or maintenance of healthy lifestyle
- Referrals to hospitals or another physician, often noting specialty of "referred to" physician

5. SELECTION OF STUDY POPULATION

5.1 Population to be studied

The study population includes all patients with a diagnosis of schizophrenia, bipolar disorder or major depressive disorder treated with Seroquel® or Seroquel® XR/quetiapine fumarate by

- general practitioners and psychiatrists in Germany based upon patient encounters recorded in IMS Disease Analyzer during the calendar period [redacted] and

- for patients in the United Kingdom with the same diagnoses who were treated with Seroquel® or Seroquel® XR/quetiapine fumarate by general practitioners based upon patient encounters recorded in IMS Disease Analyzer during the calendar period from [redacted].

5.2 Participant eligibility

5.2.1 Inclusion criteria

Patients must fulfil all of the following criteria:

1. Aged ≥ 18 years as of [redacted]

2. Have active diagnosis of one or more of these conditions based on ICD-10 diagnosis or READ codes: Schizophrenia, Bipolar Disorder, or Major Depressive Disorder between [redacted] in Germany or between [redacted] in the UK, or within the respective 12 month look-back. Record earliest date associated with condition as diagnosis-index

3. Treated with Seroquel® or Seroquel® XR/quetiapine fumarate between [redacted] in Germany or between [redacted] in the UK

4. Be considered an "active" patient within the EMR as of [redacted] in Germany and as of [redacted] in the UK

5. Have available history of at least 12 prior months to their respective country study start

6. Have at least one medical encounter (i.e., office visit, telephone call) during the study period of [redacted] in Germany or [redacted] in UK

7. If a German patient, must be under the care of a physician with a specialty of psychiatry, neurology, or general practice medicine

5.2.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Patients who are treated outside of the target timeframe

2. Patients who are not treated with Seroquel® or Seroquel® XR/quetiapine fumarate inside the target timeframe

6. DEFINITIONS OF OUTCOME VARIABLES

6.1 Primary outcome variables

Diagnostic codes, biometric assessments, blood tests, signs and symptoms recorded and other notes recorded regarding physician evaluation and management performed during a medical encounter and notation of new and continuing prescriptions are sources which will be used to define whether metabolic monitoring was performed during the physician encounters for the population of interest.

The following operational definitions will define outcomes during patient encounters reflecting the performance of metabolic monitoring:

- recording patient weight at initiation of Seroquel® is derived by the date of the encounter for recording of weight which corresponds to date of first prescription order for Seroquel® or Seroquel® XR/quetiapine fumarate (with first treatment established based upon 12 month history),

- monitoring of weight of patients receiving on-going treatment with Seroquel® is derived by the date of the encounter for recording of weight which corresponds to dates of continuing prescription orders for Seroquel® or Seroquel® XR/quetiapine fumarate,

- monitoring for hyperlipidemia is derived by the date of an encounter in which a lipid panel test is ordered or test results reviewed which correspond to dates of continuing prescription orders for Seroquel® or Seroquel® XR/quetiapine fumarate. In addition, lipid panel tests ordered/ test results reviewed for patients with a diagnosis of hyperlipidemia is evaluated,

- monitoring for signs and symptoms of hyperglycemia is derived by the date of an encounter in which signs or symptoms for hyperglycaemia or blood glucose testing is ordered or test results are reviewed which correspond to dates of prescription orders for Seroquel® or Seroquel® XR/quetiapine fumarate,

- monitoring of blood glucose in patients with diabetes mellitus is derived by the date of an encounter in which blood glucose tests are ordered/test results reviewed which correspond to dates of prescription orders for Seroquel® or Seroquel® XR/quetiapine fumarate in patients with either a diagnosis of diabetes mellitus or patients' prescription orders for an anti-diabetic drug ,

- monitoring of blood glucose in patients with risk factors for diabetes mellitus for worsening of glycemic control is derived by the date of an encounter in which blood glucose tests are ordered/test results reviewed or dates for prescriptions for self monitoring blood glucose strips correspond to dates of treatment with Seroquel® or Seroquel® XR/quetiapine fumarate in patients with the following risk factors for diabetes mellitus: obesity (BMI >25), pre-diabetes mellitus, history of previous

coronary heart disease, whether derived from biometric measurements, from diagnoses assigned in encounters during the previous 12 months, or through physician notes.

6.2 Data limitations

The LifeLink™ EMR-EU databases have limitations consistent with other EMR databases. Patients and physicians included in the database may not be fully representative of all patients and physicians in their respective countries, as data is collected only from physicians who have agreed to participate in the EMR-EU panel. Additional limitations of the dataset include (1) the inability to see data for patients who seek care outside the EMR practice setting; (2) the inability to link data if a patient visits multiple physician practices within the EMR-EU panel, as the patient will be assigned different identification numbers by each physician practice; and (3) the inability to track actual medication fills, as the prescription information only highlights those prescriptions written by the participating physician, (4) depending on the standards of the physician practice, tests or actions may be performed but not recorded.

7. DEFINITIONS OF OTHER VARIABLES

7.1 Demographic variables

Practice - Germany:

- Age and gender of physician leader in practice
- Specialty of physician leader in practice
- Years qualified of physician leader in practice
- Practice specialty (e.g., general practice, neurology)
- Practice type (i.e., single, group, community)
- Number of physicians in practice
- Practice region

Practice - UK:

- No physician-level characteristics available

Patient – Germany & UK:

- Age (based on year of birth and increments each first of new year)
- Gender

- Smoking status (e.g., non-smoker, former smoker, heavy smoker)
- Insurance status (Germany only)

7.2 Potential confounders and risk factors

The following factors are considered potential confounders or variables that are risk factors and which may influence the performance of metabolic monitoring:

use of other antipsychotics, obesity (BMI $\geq$25), increased age, female gender, sedentary lifestyle, family history of lipid abnormalities / diabetes mellitus, high blood pressure, elevated cholesterol, previous lipid panel testing (in past year), high cholesterol/high fat diet, history of cardiovascular disease, pre-diabetes mellitus or previous testing of blood glucose (in past year).

8. DATA MANAGEMENT

The databases utilised for current analyses will be the IMS Lifelink Electronic Medical Record (EMR)-EU IMS Disease Analyzer in the UK and Germany, which is comprised of longitudinal patient-level data from primary care physicians and specialists (in the case of Germany). All research undertaken using data obtained from IMS DA is approved by a Scientific and Confidentiality Committee.

IMS database researchers do not have access to patient identifiable details (e.g. names, addresses, post codes or date of birth) and have detailed procedures in place with each data source/data controller, to protect both patient and healthcare professional confidentiality. Methods of anonymisation are used at more than one point in the process of making data available for a research project. When sent from the clinical dataset to the research dataset, data is always split in a way to maximise data confidentiality. Researchers can only access key datasets via the use of robust, industry standard security systems.

The acquisition of the data follows a predefined statistical data-collection design/plan. Once the data is acquired, the data is checked for compliance and completeness of data requested. Data may be bridged to internal reference files. Data is checked by data provider to ensure consistency of total data volume as well as completeness of parameters over time. Additionally, data volume is checked across analysis units, such as regions.

Standard company IMS operating procedures are in place and will be followed to ensure data quality management. Quality management includes the validation of data and the quality assurance of construct of indicators. All data manipulation will be subject to quality assurance, with results being checked for internal consistency following standard company IMS operating procedures. The IMS specific, internal QA processes cover the whole data lifecycle from the receipt of source data to their deployment within analyses.

9. STATISTICAL METHODS AND SAMPLE SIZE

9.1 Statistical evaluation – general aspects

Age and risk factor adjusted proportion of patients receiving each metabolic monitoring test/ assessment in each country UK and Germany is derived including confidence intervals (95%) associated with the proportions observed. In evaluating patient encounters meeting certain monitoring characteristics, physician or physician practice is considered.

- A determination is made as to whether adjustment for any of the following factors is required (for factors with relatively complete ascertainment, > 60%): use of other antipsychotics in addition to Seroquel® in past 6 months, overweight (from physician record or based upon BMI $\geq$ 25), age (50+), female gender, relevant family history, high blood pressure, high cholesterol, and history of cardiovascular disease (in past 12 months), previous lipid panel or blood glucose testing (in the past 12 months).

9.2 Sample size

Germany, between [redacted]: 6,400 patients within the IMS Disease Analyzer database with at least one Seroquel® or Seroquel® XR/quetiapine fumarate prescription and at least one diagnosis of Schizophrenia, Bipolar Disorder, or Major Depressive Disorder

- 1,100 patients from GP practices
- 5,300 patients from psychiatrist practices

The UK, Between [redacted]: there are 111 patients diagnosed with schizophrenia, 182 diagnosed with bipolar disorder and 37 with major depressive disorder within the IMS Disease Analyzer database with at least one Seroquel® or Seroquel® XR/quetiapine fumarate prescription.

Based upon the anticipated number of patient encounters by country, a minimum sample size of 300 encounters will allow estimation of the outcome measures with a moderate-high degree of precision (within 5 percentage points regardless of the actual frequency of the outcome measure). The table below shows the precision of the estimates for outcome measures of effective monitoring behaviour using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 patient encounters. The noted CIs are used to indicate that for any database-estimated level of effectiveness of risk minimization, the true population level of effective monitoring behaviour is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI. Since the number of patient encounters is expected to be larger, greater precision in estimates of effective monitoring behaviour are anticipated.

Table 1: Precision of estimated rates of effective metabolic monitoring behaviour during patient encounters (as Outcome measure) with a Sample Size of 300 (Two-sided 95% Confidence Interval)

Estimated Rate	95% Confidence Interval Lower Limit	95% Confidence Interval Upper Limit
1%	0.0%	2.1%
6%	3.3%	8.7%
11%	7.5%	14.5%
16%	11.9%	20.1%
21%	16.4%	25.6%
26%	21%	31%
31%	25.8%	36.2%
36%	30.6%	41.4%
41%	35.4%	46.6%
46%	40.4%	51.6%
51%	45.3%	56.7%
56%	50.4%	61.6%
61%	55.5%	66.5%
66%	60.6%	71.4%
71%	65.9%	76.1%
76%	71.2%	80.8%
81%	76.6 %	85.4%

10. ADVERSE EVENT REPORTING

Due to the non-interventional design of this database evaluation, adverse event (AE), serious adverse event (SAE) and other safety data are not proactively collected.

11. CHANGES TO THE PROTOCOL

Study procedures will not be changed without the agreement of AstraZeneca.

Any amendments, new versions, or administrative changes will be reviewed with Regulatory authorities.

AstraZeneca

Retrospective Observational Database Study Protocol

Drug Substance	Quetiapine fumarate
Study Code	D1443C000128
Edition Number	1
Date	[redacted]
Protocol Dated	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

Objective assessment of metabolic monitoring in patients treated with Seroquel® or Seroquel® XR/quetiapine fumarate: use of IMS Disease Analyzer to assess physician behaviour in the UK and Germany

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This Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

[redacted]

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