Clinical Pharmacology Study Protocol

Drug Substance	Quetiapine Fumarate SR
Study Code	D1448C00017
Date	[redacted]

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D$_2$ to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

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**

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address and Telephone number
SDT Leader responsible for the protocol at central R&D site	[redacted]	[redacted]
SDT Physician responsible for the protocol at central R&D site	[redacted]	[redacted]

For further clarifications regarding:

Procedures in case of medical emergency see Section 8.2.

Procedures in case of overdose see Section 8.3.

PROTOCOL SYNOPSIS

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D$_2$ to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

Investigator

[redacted]

Study centre(s), type and number of subjects planned

[redacted] It is planned to include six to nine healthy male volunteers, aged 20-45 years.

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	Phase 1
Estimated date of last subject completed	[redacted]	

Objectives

The primary objectives are:

- to determine the occupancy of norepinephrine transporter (NET) induced by Seroquel (SQL) at doses of SEROQUEL SR™ currently evaluated in the clinical program for Major Depressive Disorder
- to determine the relationships: 1) between SQL dose at close to steady state condition and NET occupancy; 2) between plasma concentrations of quetiapine, its main active metabolite N-desalkyl-quetiapine (NDAQ) and NET occupancy

The secondary objectives of the study are:

1. to characterize the pharmacokinetics of quetiapine and its metabolite NDAQ in the subjects undergoing PET analysis

2. to assess adverse events (AEs), vital signs and changes in laboratory parameters and Bond- Lader VAS (Bond et al 1974)

Study design

This is an open-label, non-randomised, single centre study using positron emission tomography (PET) in six to nine healthy volunteers, aged 20-45 years, to determine central NET occupancy induced by SEROQUEL SR™ (SQL SR). For each healthy volunteer, titration and maintenance dosing of SQL SR will be used over four to eight days. The healthy volunteers will be confined to the CPU during titration and maintenance dosing of SQL SR. Each healthy volunteer will be examined by PET at two separate occasions, at baseline (no medication) and at close to steady state of chosen SQL SR dose. In the two PET examinations a tracer amount of the radioligand (S,S)[^{18}F]FMeNER-D_2 will be given. The study will be concluded by a follow-up visit at the CPU five to nine days after the last SQL SR dose.

Investigational product, dosage and mode of administration

For each healthy volunteer, titration and maintenance dosing of SQL SR will be used over four to eight days. SQL SR will be titrated increasingly from 50 mg per day and, if tolerated, to the target dose of 300 mg/day in Panel A. In Panel B the SQL SR maintenance dose will be selected to complete the information obtained in Panel A and may be chosen in the range from 50 to 300 mg/day. A third Panel may be added if judged necessary. The SQL SR dose will be administered orally, as a solid dosage form. Intact tablets will be swallowed with 240 mL of water.

Serial blood samples will be obtained from each healthy volunteer for 24 hours at the day for PET examination 2. The samples will be analysed for plasma concentrations of quetiapine and NDAQ.

In the present study (S,S)[^{18}F]FMeNER-D_2 will be synthesized by the radio chemists at the PET centre from a precursor immediately before intravenous administration. The total radioactivity will be maximum 375 MBq (approximately 185 MBq per injection), mass of radioligand injected will not exceed 5 micrograms per subject per injection (calculated from 0.07µg/kg body weight, 70 kg).

Duration of treatment

Each healthy volunteer in Panel A will receive eight doses of SQL SR and two single doses of the radioligand (S,S)[^{18}F]FMeNER-D_2.

Variables

- PET pharmacokinetics

The regional uptake and distribution of (S,S)[^{18}F]FMeNER-D_2 in regions of interest (ROI) in the brain, following a single intravenous dose will be assessed. Regional radioactivity uptake, presented as time-activity curves (TAC), and derived variable, binding potential (BP), will be used for the calculations of primary endpoints.

- SQL pharmacokinetics

The following steady-state pharmacokinetic variables will be determined for quetiapine, N-desalkyl-quetiapine; $C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss}, AUC (0-t) and $t_{½}$.

The following pharmacokinetic parameter will be determined for quetiapine alone: CL/F apparent oral clearance

- Safety

Adverse events, vital signs, ECG, clinical chemistry, haematology and urinalysis, Bond-Lader VAS.

- Statistical methods

The statistical analysis will be descriptive and exploratory. The safety, tolerability, and pharmacokinetic variables will be analysed using subject listings and summary statistics.

Exploratory analyses will be made of the relationships between dose, plasma concentration of quetiapine and NDAQ, and NET occupancy through nonlinear statistical modelling.

TABLE OF CONTENTS PAGE

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AUC_{PET}	Area under plasma concentration-time curve corresponding to the PET-assessment planned at 5 to 7 hr post-dose
BMI	Body mass index
BP	Binding potential
$C_{av,PET}$	Average plasma concentration during the PET-assessment planned at 5 to 7 hr post-dose.
C_{max}	Maximum (peak) plasma drug concentration
CRF	Case report form
CPU	Clinical Pharmacology Unit
DMP	Data Management Plan
EC_{50}	Plasma drug concentration corresponding to 50% occupancy of NET
ECG	Electrocardiogram
ED	Effective dose, parameter evaluation risk from radiation exposure
ED_{50}	Dose of drug inducing 50% occupancy of NET
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
Euratom	European Atomic Energy Community
FDA/RDRC	Federal Drug Agency: Radioactive Drug Research Committee
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
HBA	Human Brain Atlas
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
ICH	International Conference on Harmonisation
IR	Immediate release
IRB	Institutional Review Board
[redacted]	[redacted]

Abbreviation or special term	Explanation
[redacted]	[redacted]
LSD	Lysergic acid diethylamide
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
NET	Noradrenaline (norepinephrine) transporter
NDAQ	N-desalkyl-quetiapine (AZ10081909)
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.7.1.1).
PD	Pharmacodynamics
PET	Positron Emission Tomography
PK	Pharmacokinetics
Principal investigator	A person responsible for the conduct of a clinical study at a study site. Every study centre has a principal investigator.
ROI	Region of Interest
SAE	Serious adverse event
SQL	Seroquel
SR	Sustained release
(S,S)[^{18}F]FMeNER-D$_2$	(S, S)-2-(α-(2-methoxyphenoxy)benzyl)morpholine
SUV	Standard uptake values
TAC	Time-activity curve
T_{max}	Time to reach maximum drug plasma concentration
$T_{1/2}$	The terminal elimination half-life
VAS	Visual Analogue Scale
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

Quetiapine fumarate (SEROQUEL™) (SQL) is a benzodiazepine derivative that is designated clinically as 2-(2-[2-(4-dibenzo[b,f] [1,4]thiazepin-11-yl-1 piperazinyl)ethoxy]-ethanol] fumarate (2:1). This atypical antipsychotic was developed by AstraZeneca and was first licensed by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in July 1997 and by the US Food and Drug Administration (FDA) in September 1997 for the treatment of schizophrenia. Following this, SQL was approved in Europe in October 2003 and in the US in January 2004 for the treatment of bipolar mania and in November 2006 for the treatment of depression associated with bipolar disorder. Currently, SQL immediate-release (IR) tablets are administered 2 times daily and with a recommended 4-day treatment-initiation period to reach the target therapeutic dose.

[redacted] AstraZeneca has filed a new Submission for a sustained-release (SR) formulation, SEROQUEL SR™, in 2006 in several countries (including the US and Europe) for the management of the manifestations of schizophrenia. The dossier includes 20 completed studies: 7 biopharmaceutical (pharmacokinetic) studies, 6 clinical pharmacology (pharmacodynamic) studies, 5 efficacy and safety studies (covering 3 clinical settings: acute exacerbation of schizophrenia, relapse prevention, and switching from SQL IR to SQL SR under stable disease conditions) and 2 other studies. The efficacy and safety studies included more than 2400 patients with schizophrenia, more than 1500 of whom were treated with SQL SR. The biopharmaceutical and clinical pharmacology studies included approximately 300 additional patients with schizophrenia, schizoaffective disorder, or bipolar disorder who were treated with SQL SR. The submissions are currently under review.

SQL SR is [redacted] available as 50 mg, 200 mg, 300 mg, and 400 mg tablets, which have undergone a full program of pharmacokinetic evaluation (Investigator's Brochure, SEROQUEL™, 2007). SQL SR is a sustained-release formulation with a predictable and reproducible pharmacokinetic profile, designed to be administered once daily. Peak plasma quetiapine concentrations (C_{max}) occur approximately 6 hours after administration of quetiapine SR (t_{max}), compared with approximately 1 hour for the IR formulation. The elimination half-life of quetiapine is approximately 7 hours for both formulations. SQL SR displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. When compared directly to the same total daily dose of SQL IR administered in divided doses twice daily to steady state, SQL SR administered once daily displays the same area under the plasma concentration-time curve (AUC), and C_{max} for SQL SR is approximately 13% lower than that observed for the morning dose of SQL IR. A high-fat meal (approximately 800 to 1000 calories, with 50% derived from fat content) produced significant increases in C_{max} (44% to 52%) and AUC (20% to 22%). In comparison, a light meal (approximately 300 calories, with minimal fat content) had no significant effect on the C_{max} or AUC of SQL SR.

In an attempt to expand the treatment options currently available for the treatment of Major Depressive Disorder (MDD) and to build upon existing clinical data observed with SQL IR, AstraZeneca is exploring the use of SQL SR within the dose range 50 to 300 mg/day as a treatment of MDD in a number of clinical studies. AstraZeneca is conducting eight Phase III clinical studies to assess safety and efficacy of SQL SR in the treatment of MDD. The clinical development programme consist of four monotherapy studies, two adjunct studies, one study within the elderly population, and one study assessing the effectiveness of SQL SR in increasing the time to relapse of depression.

Both SQL IR and SQL SR have been studied in clinical programs directed at supporting clinical evaluation in man. The results of these studies may be found in the SEROQUEL™ Investigator's Brochure, 2007.

1.2 Rationale

Antidepressant activity of SQL IR has been suggested from anecdotal reports, case studies, and small published and unpublished studies in patients with MDD. In patients with schizophrenia, SQL IR has been shown to improve depressive symptoms independently of their effect on psychotic symptoms (Emsley et al 2003). Recent data, from two large randomized placebo-controlled studies utilizing SQL IR as monotherapy in the treatment of bipolar depression, showed SQL IR to be effective in treating depression associated with bipolar disorder (Calabrese et al 2005).

The neurochemical profile of SQL has been investigated in non-human primates and human PET experiments. It has been shown that active substance quetiapine and major metabolite N-desalkyl-quetiapine (NDAQ) has high to moderate affinity to several central neuroreceptors, including dopamine D2, D1, serotonin 5-HT1A, 5HT2 receptors, serotonin transporter, 5HTT (5077CN-0021, 2003, D2200C00011, 2006, Gefvert et al 1998). Based on the *in vitro* binding profile and initial Positron Emission Tomography (PET) study on non-human primates it is predicted that quetiapine/NDAQ may in addition have affinity to norepinephrine transporter (NET) *in vivo* in humans. Noradrenaline system is implicated in the pathophysiology of depression and anxiety disorders (Klimek et al 1997, Sullivan et al 1999).

In the present study relation between plasma concentrations of quetiapine and NDAQ and the occupancy of NET in male healthy volunteers will be investigated.

The selective radioligand (S,S)[^{18}F]FMeNER-D$_2$ will be used for PET measurements of NET occupancy (Seneca et al 2005, Seneca et al 2006). PET measurements will yield endpoint – binding potential (BP) and its change in response to treatment with clinically relevant SQL SR doses. BP will be derived from the regional time-activity curves in the target region - thalamus and caudate nucleus as a reference region (i.e. region with negligible NET expression) (Seneca et al 2006).

SQL binding to the norepinephirne transporter in the human brain will be examined and dose-dependent NET occupancy will be determined.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is:

- to determine the occupancy of NET induced by SQL at doses of SQL SR currently evaluated in the clinical program for MDD
- to determine the relationships: 1) between SQL dose at close to steady state condition and NET occupancy; 2) between plasma concentrations of quetiapine, its main active metabolite NDAQ and NET occupancy

2.2 Secondary objective(s)

1. to characterize the pharmacokinetics of quetiapine and its metabolite NDAQ in the subjects undergoing PET analysis
2. to assess adverse events (AEs), vital signs and changes in laboratory parameters and Bond- Lader VAS (Bond et al 1974)

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This is an open-label, non-randomised, single centre, exploratory PET study in six to nine healthy volunteers, aged 20-45 years, to determine central norepinephrine transporter occupancy of SQL SR.

The study will be conducted as a research collaboration between AstraZeneca Clinical Pharmacology Unit (CPU), [redacted]

The study will consist of two to three panels that are performed sequentially. Each panel will have 3 healthy volunteers. In the starting panel, Panel A, the SQL SR maintenance dose will be 300 mg. This will be followed by an interim analysis. In Panel B the SQL SR dose will be selected to complement the information obtained in Panel A. A third Panel (C) may be added if judged necessary.

In Panel A, the healthy volunteers will be administered with SQL SR 50 mg for 2 days beginning at Day 1. Beginning at Day 3, the healthy volunteers will be administered SQL SR 150 mg for 2 days and beginning at Day 5 the healthy volunteers will be administered 300 mg

SQL SR for 4 days (maintenance dose). See Figure 1 for a detailed presentation of SQL SR dosing and PET measurements in Panel A. In Panel B and C the titration period may be 0, 2 or 4 days depending on dose levels. Thus, depending on the panel, the total (titration and maintenance) dosing of SQL SR for an individual healthy volunteer may be from four to eight days. The healthy volunteers will be confined to the CPU during titration and maintenance dosing of SQL SR, with close monitoring of vital signs (pulse, systolic and diastolic blood pressure) and adverse events (see Table 1). The total length of participation for a healthy volunteer, including screening and follow-up procedures, is a max of 50 days.

Initially, healthy volunteers will undergo a medical examination (see section 4.1.1) at the CPU to determine eligibility criteria. Suitable healthy volunteers will be referred to the magnetic resonance imaging (MRI) centre at [redacted] to obtain MRI scans, that will verify absence of pathology in the brain and will be used in the analysis of PET data, for the detailed anatomical delineation of regions of interest (ROIs).

Thereafter, each healthy volunteer will undergo two PET examinations at two separate occasions at the [redacted] The first PET examination is a baseline assessment of the distribution and density of noradrenaline transporter in the brain. After that, healthy volunteers will be confined to the AstraZeneca CPU during all days of SQL SR dosing, one of the days will also include a second visit to the PET centre. The second PET examination will be performed under SQL SR dosing (maintenance dose). The study will be concluded by a follow-up visit at the CPU five to nine days after the last SQL SR dose.

On the PET 2 examination the timing of the PET examination will be matched with the known PK parameters, median T_{max} of quetiapine and NDAQ after oral administration of SQL SR at 6 hours post-dose. For this reason the radioligand will be administered tentatively 3 and a half hours after administration of SQL SR and PET scanning time will be at 5-7 hours post-dose. A light meal (breakfast) approximately 2 hours prior to SQL SR administration will be given and a light meal will be given at 4 hours post dose. Monitoring of vital signs will be performed, prior to SQL SR intake.

In the unexpected event of technical failure (camera breakdown or the radioligand synthesis fails), the PET examination has to be moved to the nearest working day. In this case the SQL SR maintenance dosing period will be prolonged by 1-3 days (three days if it is moved from Friday to Monday). If this occurs the time the healthy volunteer are confined to the CPU will be prolonged.

Twelve serial blood samples will be obtained from each healthy volunteer between 15 min before administration of SQL SR and up to 24 hr after drug administration, at the second PET examination. The samples will be analysed for plasma concentrations of quetiapine and NDAQ. The aim is to take one sample at the start of the PET examination, one in the middle and one at the end of the PET examination.

3.1.1 Stopping criteria for dose escalation

Daily doses of SQL SR, will be administered sequentially during the inpatient treatment portion of the study (Days 1 through 8 for Panel A). The titration scheme will progress to the next higher dose unless otherwise agreed by the Principal Investigator and sponsor to stop due to potentially clinically significant vital signs and safety laboratory measurements and/or clinically significant adverse events.

Table 1 Study plan

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4b**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Informed consent	X								
Demographic measurements	X								
Medical/surgical history	X								
Physical and neurological examination	X								X
Habits of nicotine, alcohol and caffeine	X								
Vital signs[d]	X				X[e]	X[e]	X	X	X
Electrocardiogram	X			X[f]		X[g]		X	
Inclusion/exclusion criteria	X								

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4b**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Clinical chemistry/Haematology	X			X[h]				X	
Urinalysis	X			X[h]					
Hepatitis B, C, and HIV	X								
Drugs of abuse screen	X								
Production of plaster helmet			X						
MRI		X							
PET after iv administration of (S,S)[18F]FMeNER-D2			X				X[i]		
Administration of SQL SR once daily in the morning					X	X	X		
Blood sampling for quetiapine PK							X[j]		

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4b**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Bond- Lader VAS[k]				X[l]	X	X	X	X	
Adverse events[m]				X	X	X	X	X	X

a) MRI and PET examination 1 cannot be done on the same day.
b) In panel B and C the titration period may be removed (i.e. if dose is set to 50 mg) or changed to two days (i.e. if dose is set to 150 mg). The range of total time at CPU may thus be from 6 to 10 days for panel B and C.
c) In the unexpected event of technical failure (camera breakdown or the radioligand synthesis fails), the PET examination has to be moved to the nearest working day. Then it is done during the nearest days. In this case the SQL SR maintenance dosing period will be prolonged by 1-3 days (three days if it is moved from Friday to Monday). If this occurs the time the healthy volunteers are confined to the CPU will be prolonged.
d) Vital signs includes pulse, systolic and diastolic blood pressure supine and again 2 min after standing.
e) Vital signs will be assessed pre-dose and 6 hours post-dose during SQL treatment days, except for the PET 2 examination day, when vital signs will be assessed only pre-dose.
f) ECG should be assessed prior to first titration dose, either day –1 or day 1.
g) ECG should be assessed 6 hours post-dose the third day of steady state (maintenance dose).
h) Blood sampling for a reduced Clinical chemistry/Haematology and Urinalysis should be repeated on the day of admission to the CPU if these samples were taken (at Enrolment visit) more than 1 week ago.
i) Radioligand (S,S) [^{18}F]F MeNER-D_2 to be injected 3.5 h (210 min) post-SRQ SR dose.
PET measurements to start approximately 5 h post-SQL SR dose.
j) Venous blood for PK analysis are to be taken 15 min pre-SQL SR dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h post-SQL SR dose.
k) Bond-Lader VAS should be in the morning pre-dose.
l) Training –Bond-Lader VAS
m) Adverse Events (AEs) must be recorded from the admission to the CPU and until the follow up visit. Serious Adverse Events (SAEs) must be recorded from the time when the informed consent is obtained until the follow-up visit.

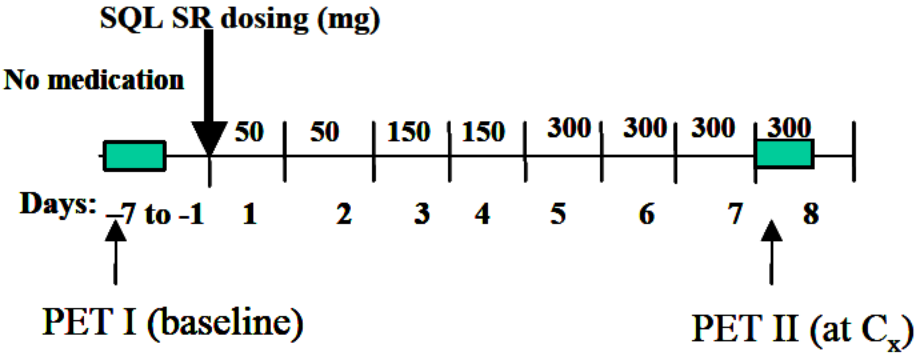
Table 2 Time schedule during confinement at PET centre/CPU (Visit 4, Day 8 (Panel A)

Protocol time (hh:mm)	Administration of SQL SR once daily in the morning	Adm of (S,S)[^{18}F]FMeNER-D_2 IV solution[a]	PET examination[a]	Blood sampling for quetiapine PK	Vital signs	Bond- Lader VAS	Other
Pre-dose				X[b]	X[c]	X[d]	Light breakfast (approx. 2 h before dose)
00:00 (~9am)	X						Transfer to PET centre
01:00				X			
02:00				X			
03:00				X			
03:30		X					
04:00				X			Light meal
05:00			↓	X			
06:00				X			
07:00				X			Transfer to CPU
08:00				X			Dinner
10:00				X			
12:00				X			
24:00				X			

a) Time of PET and administration of (S,S)[^{18}F]FMeNER-D_2 IV solution is tentative.
b) Blood sample for quetiapine PK analysis to be taken 15 min before administration of SQL SR.
c) Vital signs includes pulse, systolic and diastolic blood pressure supine and again 2 min after standing.
d) Bond-Lader VAS should be in the morning pre-dose.

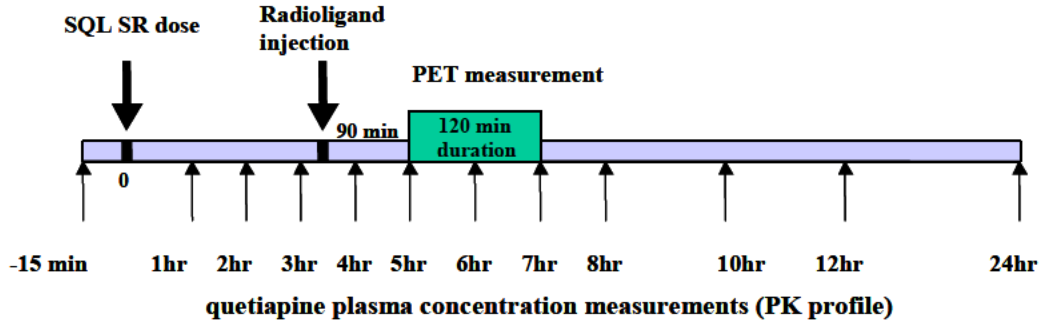
Figure 1 Study flow chart

Panel A: 300mg SQL SR



C_x is the quetiapine plasma concentration at the time of PET measurement. This will be assessed at the expected time of C_{max}.

During PET examination day



3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

In a study where the primary objective is to determine the occupancy of NET induced by quetiapine an open study is deemed sufficient.

The present study will be conducted in healthy male volunteers. The PET study requires to be performed in antipsychotic treatment-naïve subjects. Since patients requiring anti-psychotic therapy can rapidly destabilise and may have a relapse of symptoms when their anti-psychotic medication is stopped during the medication washout periods, it is considered inappropriate to

enrol such patients. Moreover it is also considered inappropriate to treat them with the SR doses proposed in this study, as they were not evaluated in the clinical program of SQL SR in patients with schizophrenia. Previous AstraZeneca studies have not shown any differences in pharmacokinetics of quetiapine between healthy and patient populations. Thus, it is presumed that NET occupancy of quetiapine in healthy volunteers will be representative of its binding to NET in human brain in vivo. Furthermore as many Central Nervous System (CNS) disease states to be studied with SQL SR will occur in antipsychotic treatment-naïve patients, healthy volunteers are thought to serve as an appropriate surrogate for the first study determining NET occupancy in man.

The doses that will be explored are those currently being evaluated in the MDD clinical program, 50 mg to 300 mg. The safety and tolerability of the doses selected in the present study and of a previous slightly quicker dose escalation scheme than currently proposed have been previously characterised in healthy volunteers and in patients with schizophrenia, schizoaffective disorder and bipolar disorder (Investigator's Brochure, SEROQUEL™, 2007). Necessary precaution to ensure the safety of the healthy volunteers will be taken (see 3.2.2). The PK characteristics of the doses chosen have also been characterized in healthy volunteers and/or in patients (Investigator's Brochure, SEROQUEL™, 2007): plasma quetiapine concentration time-profiles at oral doses of 50 mg, 150 mg and 300 mg: median time of C_{max}, T_{max} is 6 hours, $T_{1/2}$ is 6 hours post-dose. Plasma NDAQ concentration time-profiles: C_{max}, reaches T_{max} at 6 hours post-dose (Investigator's Brochure, SEROQUEL™, 2007).

The PET method is chosen for the study, as the molecular imaging method with highest image resolution (as compared to SPECT) and radioligand availability for the investigation of noradrenaline system. The radioligand (S,S)[^{18}F]FMeNER-D_2 will be used for the study, as it has the favourable pharmacokinetics (it reaches equilibrium) and shows high specific binding in thalamus, brainstem regions (locus coeruleus). These characteristics of the ligand enable application of quantitative methods that are needed to evaluate NET occupancy induced by quetiapine/NDAQ. Presently, it is the only radioligand available that provides such possibility.

3.2.2 Risk/benefit and ethical assessment

The aim of this study is to investigate if SQL SR at doses from 50 mg to 300 mg induces NET occupancy in healthy volunteers. Determining NET occupancy in vivo in human may reveal important mechanism of action for the antidepressant properties of SQL. Investigation of noradrenaline transporter as a target may also be important lead for the development of antidepressant drugs, beneficial for the patients and society at large.

The PET experimental procedures carry low risks. The administered maximum radioactivity is chosen as guided by the possibility to quantify the radioligand binding to NET (limited by the measurement signal-to-noise ratio). The total radioactivity will be maximum 375 MBq (approximately 185 MBq per injection) (following radiation safety requirements in EU (Annuals ICRP 1987), max 10 mSv per year).

Subjects who have previously been administered PET radioligands cannot participate in this study, in accordance with the routines established by the local radiation safety committee. The

risk posed by radioactivity exposure is considered acceptable in relation to the potential benefits. The procedure-related risks are few. The venipuncture may cause some pain. The PET procedure requires that subjects rest in the supine position with the head fixated inside the opening of the PET camera system. Possible physical discomfort due to restriction of movement or local pressure is usually alleviated by loosening and cushioning of the fixation system. The subjects are accompanied in the examination room throughout the procedure.

It is concluded that the exposure levels of (S,S)[^{18}F]FMeNER-D$_2$ micro dose and radioactivity as well as the study procedures defined in this protocol are not expected to pose any significant risks that cannot be monitored in the study.

The doses of SQL SR that will be administered have been previously evaluated in healthy volunteers (Investigator's Brochure, SEROQUEL™, 2007). In the studies the safety profile of SQL SR was acceptable and consistent with the known profile for SQL. There were no unexpected adverse events. Side effects are somnolence, dizziness and orthostatic hypotension. The side effects are reversible and do not put the subject to a serious risk. The escalated dosing of the SQL SR will be slightly slower than previously studied. Healthy volunteers will remain hospitalized and monitored throughout the period of treatment. In order to further ensure the safety of the healthy volunteers and avoid orthostatic hypotension related side effects, healthy volunteers will be instructed to be cautious when standing up and close medical monitoring will be observed when orthostatic blood pressure will be assessed. In addition a nurse from the CPU will accompany and monitor/assist the subjects during transportation between the CPU and the PET centre and at the PET centre.

The MRI investigations are clinical routine investigations with strict safety protocols to assure that subjects do not have any contraindications for the procedure such as magnetic metallic implants. The MRI staffs are specifically trained and there are specific routines to handle these types of unusual complications. Overall, the MRI investigations involve very low risk and the results of the investigations are crucial for the study, both for ensuring inclusion criteria and to correctly analyse the PET-data.

There are no direct benefits for healthy volunteers participating in the study. The risk is judged to be minor, all investigational procedures are otherwise routinely used in clinical medical investigations. The ethical assessment is of course also dependent on provision of informed consent and reviews by local ethical committee as well as local radiation protection committee.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of subjects who were considered for enrolment but never enrolled e.g., subject screening log, according to local procedures. This information is necessary to establish that the subject population was selected without bias.

Subjects will be enrolled and undergo a screening visit at AstraZeneca CPU within the 30 days preceding the first PET examination.

3.3.2 Inclusion criteria

For inclusion in the study subjects must fulfil all of the following criteria:

1. Provision of a signed written informed consent.

2. Male healthy volunteers, aged 20 to 45 years inclusive, and judged to be healthy by the investigator on the basis of medical history, physical examination, ECG, vital signs, and laboratory tests (clinical chemistry, haematology, and urinalysis) at enrolment.

3. Weight of at least 50 kg and maximum 100 kg; Body Mass Index (BMI) of ≥ 19 to ≤ 30 kg/m^2.

4. Subjects are able to communicate with the investigator and to understand and comply with all requirements of study participation.

5. Negative results of the urine drug screen (amphetamines/ecstasy, benzodiazepines, cannabinoids, cocaine, opiates, and LSD).

6. Normal MRI scan at Visit 2.

3.3.3 Exclusion criteria

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

1. A history or presence of neurological, haematological, psychiatric, gastrointestinal, hepatic, pulmonary, renal disease or other condition as judged by the investigator.

2. Trauma or sickness 2 weeks before the first PET examination, as judged by the investigator.

3. Intake of any prescribed medicine and over-the-counter (OTC) drugs (including herbals, vitamins and minerals), except for occasional paracetamol or adrenergic nasal spray, within 7 days before the first PET examination.

4. Use of drugs that induce the liver drug metabolising enzymes (including carbamazepine, phenytoin, barbiturates) or use of potent drugs that inhibit the cytochrome metabolising enzymes (e.g. Ketoconacole, itroconazole) within 4 weeks before first PET examination.

5. Consumption of liquorice or grapefruit-containing products within 7 days prior to Day 1.

6. Excessive use of caffeine (more than 5 cups of coffee or equivalent per day) within 7 days before first PET examination.

7. Habitual smoker (>5 cigarettes or snuff or other nicotine products per day).

8. Past or present drug or alcohol abuse, positive test results for drugs of abuse.

9. Positive test results for human immunodeficiency virus (HIV), hepatitis B (HBV) surface antigen (HBsAg), or hepatitis C antibody (HCV).

10. Donation of more than 400 mL of blood within 3 months prior to enrolment and 1200 mL 12 months prior to enrolment.

11. Plasma donation within two weeks prior to enrolment.

12. Participation in another study within 3 months before the start of the present study (or within 1 month for methodology studies in which no drugs were administered).

13. History of significant allergy.

14. Previous participation in a PET study (as required by the Radiation Ethics Committee).

15. Have had exposure to ionizing radiation that, in combination with the study, will exceed the ED limits.

16. Exposure to radioligand(s), which would result in a cumulative exposure that exceeds recommended EU exposure limits.

17. Subject suffer from claustrophobia.

18. Subject has implanted or embedded metal objects or fragments in the head or body.

19. Previous participation in and AstraZeneca Seroquel study.

20. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational site).

3.3.4 Restrictions

Subjects will be required to:

1. On PET II examination day, subjects will be served breakfast approximately 2 hours prior to SQL SR intake, and will have light meal 4 hours after SQL SR intake, prior to PET-scanning procedure.

2. Refrain from the use of drugs that induce the liver drug metabolising enzymes (including carbamazepine, phenytoin, barbiturates) or use of potent drugs that inhibit the cytochrome metabolising enzymes (e.g. Ketoconacole, itroconazole) from enrolment and through the study period.

3. Refrain from consumption of liquorice and grapefruit containing products from 7 days prior to Day 1 through the study period.

4. Refrain from the use of any prescribed medicine and over-the-counter (OTC) drugs (including herbals, vitamins and minerals), except for occasional paracetamol or adrenergic nasal spray, from 7 days prior to PET (baseline) measurement and through the study period.

5. Abstain from drinking alcohol from 7 days prior to PET (baseline) measurement and through the study period.

6. On the PET examination days no caffeine or other stimulant drink intake is allowed until end of PET experiment. From 7 days prior to PET (baseline) measurement and through the rest of the study period the subject should abstain from excessive use of caffeine (more than 5 cups of coffee or equivalent per day).

7. Abstain from consumption of energy drinks containing taurine or glucuronolactone from enrolment and through the study period.

8. Refrain from the use of tobacco or other nicotine-containing products from enrolment through completion of the last PET examination.

9. Abstain from blood and plasma donation during the study and up to 3 months after completion of the study.

10. Refrain from strenuous physical exercise within 48 hours from PET (baseline) measurement and through the study period.

11. Subjects are to eat standardised meals during the residential period.

12. From first SQL SR dose and through the treatment period the subject will be instructed to be and should be cautious when standing up.

13. Subjects should on a daily basis drink at least a liter of water or other fluids in addition to what they drink with meals.

14. Male volunteers must refrain from fathering a child during the study and for three months following the study. Hence, they should not donate sperm and should ensure that their partners of child bearing potential use reliable method of contraception, as well as themselves using a barrier-method for this period.

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment

- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.
- Incorrect enrolment ie, the subject does not to meet the required inclusion/exclusion criteria for the study
- Subject lost to follow-up
- Development of exclusion criteria
- Protocol non-compliance, which in the judgment of the investigator and AstraZeneca, has the potential to significantly affect the integrity of the data.

3.3.5.2 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up until resolution or until the investigator(s) decides that no further follow-up is necessary.

If a subject is being withdrawn due to a suspected infection in WHO risk categories 2, 3, and 4, no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

3.3.5.3 Procedures for handling incorrect enrolled subjects

The following applies to incorrectly enrolled subjects or subjects fulfilling discontinuation criteria but not discontinued:

- The subject should not receive any further investigational product
- If the subjects has received investigational product, the follow-up visits should be performed
- If the subjects has received investigational product, the subject will be included in the safety analysis

3.4 Treatment(s)

3.4.1 Investigational product(s)

3.4.1.1 Identity of investigational product

AstraZeneca will manufacture and supply the investigational products to the investigator. The investigational products will be supplied as tablets for oral use as specified in Table 3.

The PET ligand (S,S)[^{18}F]FMeNER-D_2 will be manufactured by the PET centre [redacted] from a precursor supplied by AstraZeneca. After synthesis, the ligand will be dissolved in a sterile buffer solution and filtered before administration.

Table 3 Identity of investigational product

Investigational product	Manufacturer	Strengths	Presentation	Formulation number
Quetiapine SR	AstraZeneca	50 mg	Peach oval tablet	F13219
Quetiapine SR	AstraZeneca	200 mg	Yellow capsule shaped tablet	F12840
Quetiapine SR	AstraZeneca	300 mg	Light yellow oval tablet	F12527
(S,S)[^{18}F]FMeNER-D_2	PET centre, [redacted]		Solution for intravenous injection	Not applicable

3.4.1.2 Labelling

SQL SR

The clinical study drug, SQL SR tablets will be supplied by Investigational Products (IPS [A]) at AstraZeneca, Macclesfield, UK as a bulk supply. The SQL SR will be dispensed into individual dosing containers by staff at the Pharmacy Huddinge Hospital. Individual dosing containers will be labelled with a detachable tear-off label. The study drug label will include:

Sponsor name and address
The phrase 'keep out of reach of children'
The phrase 'for clinical trial use only'
Study number
Subject number
Description of contents
Dosing / dispensing instructions
Date of dispensing
Batch number
Expiry date
Storage conditions
Any local regulatory requirements

(S,S)[^{18}F]FMeNER-D_2

The prepared (S,S)[^{18}F]FMeNER-D_2 will be labelled with the following information:

- Name of the radioligand; (S,S)[^{18}F]FMeNER-D_2,

- Total radioactivity (in MBq),
- Total volume (in mL),
- Radioactivity per mL,
- Date and time of injection,

In addition, the vial will be marked "For injection", "Radioactive", the symbol for radioactivity, and "[redacted]"

3.4.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. SQL SR must be stored at controlled room temperature below 30°C. A description of the appropriate storage and shipment conditions are specified on the investigational product pack label and investigator brochure.

All PET ligands must be kept in a secure place under appropriate storage conditions.

3.4.1.4 Accountability

The investigator is responsible for maintaining study drug accountability at the site.

The investigational product and PET ligand provided for this study is for use only as directed in this Clinical Pharmacology Study Protocol. All dispensed and unused drug will be accounted for by the investigational site personnel. Any unused PET ligand will be destroyed by the investigational site personnel. Unused SQL SR tablets will be destroyed at [redacted]. Any discrepancies between dispensed and returned or accidentally destroyed drug must be explained. Certificates of delivery, return, and destruction must be signed.

3.4.2 Doses and treatment regimens

SQL SR will be titrated increasingly from 50 mg per day and, if tolerated, to the target dose. The SQL SR dose range will be 50 mg up to 300 mg. Stepwise dose increase will be used together with monitoring of vital signs, namely pulse and blood pressure.

Maintenance doses will be followed for 4 days to achieve steady state drug plasma concentration of SQL SR before the start of PET-measurements. The plasma concentration range expected is 70-500 ng/ml.

In Panel A the SQL SR maintenance dose will be 300 mg. This will be followed by an interim analysis (section 6.4). In Panel B the SQL SR dose will be selected to complement the information obtained in Panel A. A third Panel, Panel C, may be added if judged necessary, please see section 6.4.

Subjects in Panel A

The healthy volunteers will be administered with SQL SR 50 mg tablets once daily in the morning at the same time point for 2 days beginning at Day 1. Beginning at Day 3, the subjects will be administered SQL SR 3 x 50 mg tablets once daily in the morning (150 mg) for 2 days. At Day 5, SQL SR 300 mg tablets once daily in the morning will be administered for 4 days.

Subjects in Panel B and C

For panel B and C the SQL SR maintenance dose may be between 50 mg and 300 mg (maintenance dose of 50 mg, 100 mg, 150 mg, 200 mg, 250 mg or 300 mg). In Panel B and C the titration period may be 0, 2 or 4 days depending on dose levels.

For Panel A and B (and Panel C, if necessary)

On the second PET examination the subjects starts the served light meal breakfast 2 hours prior to administration of the study drug product. The meal must be finished within 30 minutes. The study drug product is administered 2 hours after start of the meal. The SQL SR tablet is administered together with 240 mL of water. Water is allowed as desired except for one hour before and after drug administration. On the day of the second PET examination, subject should remain in an upright position (sitting or standing) for at least 1 hour after dose administration.

In the unexpected event of technical failure (camera breakdown or radioligand synthesis fails), the PET examination has to be moved the nearest working day. Then it is done during the nearest days. In this case the SQL SR maintenance dosing period will be prolonged by 1-3 days (three days if it is moved from Friday to Monday). If this occurs the time the subjects are confined to the CPU will be prolonged

(S,S)[^{18}F]FMeNER-D$_2$

Total maximum 375 MBq, (S,S)[^{18}F]FMeNER-D$_2$ in an aqueous solution will be administered in two intravenous bolus injections (approximately 185 MBq per injection). The radiation protection committee (Karolinska University Hospital, Solna) will decide the maximum allowed radioactivity. The injected radioligand will have high specific radioactivity and the total mass administrated will be less than 0.07 µg/kg body weight (approximately 185 MBq and 5 µg per injection, counted as average 70 kg body weight).

3.4.2.1 Light meal

The light meal for breakfast and the light meal at 4 hours after SQL SR administration should have a similar composition as the following example: 2 slices of toast, 2 teaspoons (10 g) of jelly (jam), 180 mL (6 fluids ounces) of orange juice, 2 tablespoons (30.6 g) of 0.1% (skim) milk and 2 teaspoons (10 g) of sugar, thus a total of 292 kcal according to (Yeh et al 1998). Please note that this is an example and guidance for the light meal breakfast and light meal.

3.4.2.2 Other meals

Other meals during the study will be served on a regular basis during the study days according to the CPU routines.

3.4.3 Method of assigning subjects to treatment groups

Written informed consent will be obtained before enrolment and the subjects identified with an enrolment number starting with E0001001. Subjects fulfilling the eligibility criteria will at Day 1 be assigned a subject number (randomisation code) starting with number 101 for Panel A, 201 for Panel B and 301 for Panel C.

In total six to nine healthy volunteers will be enrolled in the study. If there are subjects not completing the study, additional subjects may be included to have the required number of evaluable subjects at the end of the study. A decision on the need to recruit additional subjects will be taken by the investigator after consulting with the AstraZeneca co-ordinator and medically responsible person at AstraZeneca R&D Södertälje.

If a subject discontinues from the study the subject number will not be re-used and the subject will not be allowed to re-enter the study.

3.4.4 Concomitant medication

No concomitant medication or therapy will be allowed except paracetamol and nasal spray for nasal congestion, without prior consent of the investigator. The subjects must be instructed that no additional medication will be allowed without the prior consent of the investigator.

Any medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the case report form (CRF).

3.4.5 Treatment compliance

Treatment compliance will be ensured by supervised administration of the investigational product and by intravenous administration of the radioligand by the investigator or his/her designee.

4. MEASUREMENT OF STUDY VARIABLES

4.1 Medical examination and demographic measurements

4.1.1 Enrolment medical examination and demographic measurements

Each subject will undergo an enrolment medical examination within 30 days (1 month) prior to Day 1. This will consist of

- Recording of demographic data - date of birth, sex, height, weight, race

- A standard medical history and a physical examination including the cardiovascular and respiratory systems and neurological examination
- Blood samples for standard clinical chemistry and haematology assessments and a mid-stream urine sample for urinalysis and drug abuse screen
- Blood pressure (supine and orthostatic) and pulse rate
- Normal resting 12 lead ECG
- A blood sample for serology tests (Hepatitis B and C, and HIV)
- Habits of nicotine, alcohol, and caffeine use

The physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, and throat), lymph nodes, thyroid, musculoskeletal system/extremities (including spine), cardiovascular system, lungs, peripheral oedema assessment, abdomen, and neurological system.

4.1.2 Post-study medical examination

A similar post-study physical examination will be performed and vital signs taken at the follow-up visit 5-9 days after last SQL SR dose.

4.2 Pharmacokinetic measurements

For sampling time points refer to the study plan (Table 1) and time schedule during confinement at PET centre/CPU (Table 2). Time points in the protocol may be adjusted if found impracticable.

4.2.1 Determination of drug concentration in biological samples

Samples for the determination of quetiapine and NDAQ will be analysed by [redacted] The method used will be documented in the clinical study report.

4.2.2 Collection of biological samples

Blood samples (5 mL) for the determination of quetiapine and NDAQ in plasma will be taken at the times presented in Table 1 and Table 2. Using aseptic technique, a blood sample will be collected from a forearm vein into a 5 mL EDTA-Monovette tube at each collection time. The use of an indwelling catheter with a mandrin is permitted.

Each blood sample should be immediately gently inverted to thoroughly mix the blood and then placed on ice until centrifugation. All samples should be centrifuged within 15 minutes of collection for approximately 10 minutes at 2-4°C at a relative centrifugal force of 1500 x *g*. The resulting plasma should be transferred to an appropriately labelled polypropylene tube (approximately 1.0 mL of plasma sample per tube) and frozen immediately in dry ice or in a

-20°C freezer (may also use a -70°C freezer). The plasma sample tubes to be used are 1.8 mL screw-cap microcentrifuge, conical, upright polypropylene tubes. The samples should be arranged in boxes ordered by subject and sampling time. The tubes should be stored and shipped in the labelled mailing boxes provided by AstraZeneca. If these boxes are not available, substitute only vial boxes that fit the tube height and contain inserts that separate and secure each vial. The vials must not contact each other during shipping. The plasma samples must be maintained at -20°C or colder until analysed.

The date and time of collection will be recorded on the appropriate CRF. Samples should be stored at -20°C and analysed within the timeframe after collection for which the stability in plasma has been validated and found acceptable. Results from samples stored longer than the validated period will not be reported.

Samples will be disposed of after the clinical study report has been finalized. Samples will be coded for importance to maintain subject confidentiality. Access to the code list will require authorization from the Investigator. The samples will only be used in accordance with the study protocol and Ethics Committee approval is required if the samples are to be used for another purpose. The samples are to be destroyed upon request of the subject.

See Table 4 for the total amount of blood to be drawn from each subject throughout the study, including routine clinical laboratory.

4.2.3 Labeling of plasma samples

Labels will be prepared and supplied by AstraZeneca for all tubes and containers used to collect blood, and to store and ship plasma samples for analysis of quetiapine and NDAQ. The labels for the polypropylene tubes should be waterproof or wrapped with freezer safe transparent tape (or laminate supplied with label) to ensure that the labels remain attached to tubes during processing and shipment. The labels must be able to maintain their integrity even if they come into contact with moisture. The labels should not be obscured or extend over the tube, and no additional label should be attached to the sample tube. Each label will include the following information:

Study number: D1448C00017
Subject number:
Panel A, B or C
Study day:
Analyte: quetiapine, NDAQ
Sampling (nominal) time:
Matrix: PLASMA

4.2.3.1 Shipment of SQL SR plasma samples

Any sample from a subject who is withdrawn from the study due to a serious intercurrent illness not related to drug therapy will not be transmitted to AstraZeneca or [redacted]. Such samples should be destroyed according to local, state, and national laws, regulations, and ordinances.

The plasma samples are to be shipped to [redacted]. The investigator will arrange the transportation of the frozen plasma samples for the analysis of quetiapine and NDAQ to: [redacted]

A Specimen Shipment Form must be completed and sent to [redacted] with each set of samples, detailing the following information:

Study number
Subject number
Cohort
Study day
Sampling (nominal) time
Sampling date
Matrix (plasma)
Sample comment (to be entered if collection of sample deviates from protocol in any way)

All shipments of diagnostic or potentially infectious substances should be made in accordance with all applicable regulations. It is the responsibility of the investigational site to ensure that each specimen is classified, packaged, labelled, marked, and documented in compliance with all applicable regulations. The samples must be kept frozen at a temperature of -20°C or colder until analysed. The shipping container should be packed with sufficient dry ice to prevent thawing for at least 72 hours. For samples shipped on Monday or Tuesday, overnight delivery must be used in order to avoid possible arrival at BASi on weekends.

[redacted] must be notified by telephone or fax as samples are shipped. Additionally, AstraZeneca [redacted] must be notified by fax or email of sample shipment to BASi.

4.2.3.2 MRI examination

MRI scans will be performed on a 1.5 Tesla unit (General Electric, Signa), at the MRI center [redacted]. The standard protocol, developed by the MRI center and concordant with the needs of PET imaging will be used, with no specific additions, as it is a group of typical healthy volunteers.

4.2.3.3 PET examination

The PET system ECAT EXACT HR follow radioactivity in 47 sections of the brain with three-dimensional acquisition. PET examinations may also be performed with the PET system (HRRT (Siemens/CTI)) using standard data acquisition protocol. The spatial resolution in the reconstructed section is 3.5 mm. All subjects participate in two PET examinations with (S,S)[^{18}F]FMeNER-D_2 of high specific radioactivity, one at baseline and one after oral pre-treatment with SQL SR.

In each PET measurement the subject is placed supine and the head is fixed to the positron camera with head fixation system that uses the plastic individual helmet. Approximately 185 MBq (per single injection) of the radioligand is injected intravenously as a bolus during three seconds. The PET examination comprises a series of sequential measurements. The study protocol is adjusted to the pharmacokinetics of radioligand (S,S)[^{18}F]FMeNER-D$_2$, showing late equilibrium. The PET- data sampling will start at 90 min post-injection time and will continue over 120 min.

4.3 Pharmacodynamic measurements (Not applicable)

4.4 Safety measurements

4.4.1 Laboratory safety measurements

Blood and urine samples for determination of laboratory variables will be taken at the times given in the Study Plan (Table 1) and the time schedule during confinement at CPU/PET centre (Table 2). The date and time of collection will be recorded on the appropriate CRF.

Samples will be collected in tubes according to standard routines. Blood volumes to be taken are described in Table 4.

The following laboratory variables will be measured:

Clinical chemistry	**Haematology**
P-Albumin	Complete blood count (CBC)
P-Fasting glucose	B-Haemoglobin
P-Total bilirubin	B-Haematocrit
P-Alkaline phosphatase (P-ALP)	B-Red blood cell count and absolute neutrophil count
P-Alanine aminotransferase (P-ALT)	B-Leukocyte count including differential count (lymphocytes, monocytes, neotrophils, eosinophils, basophils and granulocytes)
P-Aspartate aminotransferase (P-AST)	B-Platelet count
P-Calcium, total	
P-Chloride	
P-CRP	
B-Standard bicarbonate	

Clinical chemistry

P-Creatinine

P-Gamma-Glutamyl-Transferase

P-Glucose

P-Lactate dehydrogenase

P-Potassium

P-Sodium

S-Thyroxine (S-T4)

S-Triglycerides

P-Total cholesterol

P-HDL-Cholesterol

P-LDL-Cholesterol

P-Urea

S-Thyroid-stimulating hormone (S-TSH)

Haematology

Urinalysis

Protein Dipstick

Glucose Dipstick

The samples for clinical chemistry, haematology, coagulation, and urinalysis will be analysed with routine methods at the Department of Clinical Chemistry [redacted].

The serology test will be analysed at the Department of Clinical Virology at [redacted]

Urine will be tested for the following drugs of abuse: opiates, bensodiazepines, cocaine, cannabis/cannabinol, amphetamines, ecstacy, and LSD. The samples will be analysed at the Department of Clinical Pharmacology at [redacted].

If any laboratory values outside the reference limits are suspected to be of clinical significance, judged by the principal investigator and/or AstraZeneca, the sampling will be repeated. Subjects in whom the suspected clinical significance is confirmed at repeated sampling will either not be included or, if already included (started treatment), the deviating

values will be monitored until normalisation or for as long as the investigator considers necessary.

If a subject tests positive for drugs of abuse they will be excluded from entering, or continuing the study. For subjects, if the drug is illegal, advice will be offered and the healthy volunteers will be removed from the AstraZeneca Volunteer Panel.

All routine blood and urine samples will be disposed of immediately after they have been analysed.

Management of neutropenia

Complete blood count (CBC) including white blood cell count (WBC) differential count will be performed for all healthy volunteers. CBC with a WBC differential should also be performed at any time a healthy volunteer presents with a fever, pharyngitis (sore throat), or other signs and symptoms of infection. Healthy volunteers should be instructed to seek medical care (refer to the CPU physician during the residential period at the CPU and between discharge from the CPU and the follow up visit, to contact the CPU physician or their usual physician) if they develop symptoms of infection such as fever and/or pharyngitis and mucous membrane ulceration. If signs and symptoms of the low neutrophil count are present, e.g., infection, these should be recorded as an AE. If a healthy volunteer has a neutrophil count of $<1.0 \times 10^9$/L, the test should be repeated within 24 hours after the result of the first test has become available to the investigator. If the second neutrophil count remains $<1.0 \times 10^9$/L, the healthy volunteer should be discontinued from treatment with the investigational product due to AE. The AE should be recorded as "Neutrophil count decreased". These healthy volunteers should be monitored weekly with a CBC and a WBC differential until their counts recover. While experiencing neutropenia, healthy volunteers should avoid invasive procedures such as dental work, rectal exams or enemas, exposure to people who are obviously ill, and exposure to fresh fruits, vegetables, or flowers. If a healthy volunteer develops fever or symptoms of infection, he/she should contact the CPU physician or their usual physician and acquire a CBC with differential immediately.

4.4.2 Electrocardiographic measurements

For timing of individual measurements refer to study plan (Table 1).

4.4.2.1 Resting 12-lead ECG

Twelve-lead ECGs with a paper speed 50 mm/second will be obtained after the subject has been lying down for 10 minutes.

The following data will be collected: heart rate, rhythm, extra systoles, conduction and ST-T changes, including specification, PR intervals, (ms), QRS duration (ms), QT interval (ms), RR interval (ms), overall evaluation, normal/abnormal.

QT corrected (ms) will be calculated according to Fridericia's formulae.

ECGs will be recorded and evaluated by the investigator. If indicated, additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment on the CRF.

4.4.3 Vital signs

4.4.3.1 Blood pressure and heart rate

Pulse rate, supine and orthostatic (2 min) systolic and diastolic blood pressure will be measured at time points specified in the study plan (Table 1) and time schedule during confinement at PET centre/CPU.

Orthostatic vital signs will include supine blood pressure and pulse rate (obtained after at least 10 minutes in a supine position) and standing blood pressure and pulse rate (obtained after 2 minutes in the standing position).

Vital sign assessments and pulse rates will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size.

If possible, for each subject throughout the study, blood pressure will be measured using the same arm and blood pressure cuff.

4.4.4 Bond-Lader Visual Analog Scale (VAS)

This psychometric test will be collected at the times given in Table 1 to assess self-rated feelings. The first assessment upon admission to the CPU will be a training session to overcome practice effects and ensure optimal performance for the following assessments, which will take place pre-dose on the days of dosing of SQL SR and the day of discharge from the CPU. The second assessment on Day 1 (pre-dose) will be the baseline assessment.

The test being used for this study consists of a total of 16 100-mm lines anchored at either end by antonyms (Bond et al 1974). Participants mark their current subjective state between the antonyms on the line. Each line is scored as millimetres to the mark from the negative antonym.

The scale has a set of opposing adjectives at either end, as listed below:

alert – drowsy, calm–excited, strong–feeble, muzzy–clear headed, well-coordinated–clumsy, lethargic–energetic, contented–discontented, troubled–tranquil, mentally slow–quick witted, tense–relaxed, attentive–dreamy, incompetent–proficient, happy–sad, antagonistic–amicable interested–bored, withdrawn–gregarious

At the specified time points during the study, subjects are asked to record how they feel at that time by making a vertical mark on the lines. Standardized instructions will be given to each subject before he completes the questionnaire. Study site personnel will check that the scale has been completed by the subject when collecting the questionnaire. The questionnaires will be evaluated using the same ruler for each subject. Date and time of collection and the distance from beginning of the line and the mark made by the subject on the VAS scale will

be recorded in mm in the CRF. If the mark occurs in between two hash marks on the ruler, the more conservative distance, ie, the longer distance will be recorded in the CRF.

4.5 Genetic measurements and co-variables (Not applicable)

4.6 Volume of blood sampling

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 4 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	n of samples	Total volume (mL)
Quetiapine plasma concentration		5	12	60
Safety	Clinical chemistry	11	2x2	44
	Haematology	4	2	8
Serology		10	1	10
(Additional unforeseeable samples)				(50)
Total (approximately)				**122** (172)

Depending on whether any extra blood samples will be drawn e.g., for safety reason or to clear the indwelling catheter from saline, it is assumed that the total amount of blood taken will not exceed 172 mL.

4.7 Adverse Events

The methods for collecting adverse events are described below.

4.7.1 Adverse Events

4.7.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?". For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Pharmacology Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of adverse events

AEs will be collected and recorded from Visit 4 (admission to the CPU) and until the follow-up visit (Visit 5). SAEs must be recorded from the time when the informed consent is obtained at Visit 1 until the follow-up visit.

The following variables will be recorded for each AE: AE description, start date and time, stop date and time, maximum intensity, outcome, causality rating (yes or no), and whether it constitutes an SAE or not

The following definitions for intensity rating should be applied:

mild (awareness of sign or symptom, but easily tolerated)

moderate (discomfort sufficient to cause interference with normal activities)

severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problem during the study day?"/"Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom should be recorded separately.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and other safety variables need not be reported as AEs. They will be evaluated in the overall safety analysis. Such deteriorations are only to be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment should be reported as an AE.

However, all deteriorations should be followed up by the investigator for as long as medically indicated.

Should AEs occur, therapeutic procedures according to standard medical practice will be followed as needed. All AEs should be followed up by the investigator for as long as medically indicated.

Any AEs that are unresolved at the subject's last AE assessment in the study (ie, at the follow-up visit) are to be followed up by the investigator for as long as medically indicated,

but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 8.3, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

All Serious Adverse Events (SAE) must be reported to Clinical Drug Safety, AstraZeneca Marketing Company Sweden, within one day (that is immediately but not later than the end of the next business day) by fax [redacted]. Clinical Drug Safety will forward the SAE report to the applicable AstraZeneca R&D. The monitor should also be informed when an SAE has occurred.

For any product provided by AstraZeneca, the Investigator's responsibility of safety reporting to the Medical Products Agency and Ethics Committee is delegated to AstraZeneca.

For any concomitant product, i.e., products not provided by AstraZeneca, it is the responsibility of the investigator to report to the Medical Products Agency any SAE with a causality related to the concomitant medication.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. . For a non-serious AE that become serious but which is not fatal or life-threatening a report should be received within 5 days.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the Case Report Form. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

AstraZeneca is responsible for informing the Ethics Committee and the Regulatory Authority of the SAE as per local requirements.

5. STUDY MANAGEMENT

5.1 Monitoring

5.1.1 Study monitoring

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonisation (ICH) document "Good Clinical Practice: Consolidated Guideline".

5.1.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the subject's medical notes (permission from the subject will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

For this study original data regarded as source data are defined by a source data verification plan.

Monitoring including source data verification should routinely be performed prior to the transfer of data to Data Management.

5.1.3 Archiving of study documents

The Investigator Study File (ISF) must be archived for at least 10 years after the study report is finalized.

5.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority or an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

5.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

5.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the principal investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by each Ethics Committee, and in many countries also the local regulatory authority, before implementation. Local requirements must be followed.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s) who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

5.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

5.6 Study timetable and end of study

The study is expected to start in May 2007 and to be completed by September 2007. End of study is defined as database lock (estimated to September 2007), which is the time point after which no subject will be exposed to study-related activities

5.7 Data management

5.7.1 Case report forms

Paper CRFs (pCRFs) will be used to record all data not captured electronically. Data should be recorded legibly onto the pCRFs in blue or black ballpoint pen. Correction fluid or covering labels must not be used.

The AstraZeneca Monitor will check data at the monitoring visits to the study site. The Investigator will ensure that the data in the pCRFs are accurate, complete and legible.

Data from the completed pCRFs will be entered onto AstraZeneca's clinical study database and validated as described in the data management plan. Any missing, impossible or inconsistent recordings in the pCRFs will be referred back to the Investigator using a data query form and be documented for each individual subject before clean file status is declared.

The data management plan (DMP) will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Further, the DMP will also describe the data flow and timelines within the study. For more information, see the DMP.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

6.1 Pharmacokinetic / pharmacodynamic evaluation

6.1.1 Calculation or derivation of pharmacokinetic variables

The PET- pharmacokinetic analyses will be performed at AZ, by joint work of PET-pharmacokineticist and pharmacokineticists from Dept. of Clinical Pharmacology, AstraZeneca.

6.1.2 Regions of interest (ROIs) in the PET measurement

Before delineation of region of interests (ROIs) the orientation of the brain is spatially normalised by having the high resolution T1-images reoriented according to the line defined by the anterior and posterior commissures (ac-pc line) being parallel to the horizontal plane and the inter-hemispheric plane parallel to the sagittal plane. The PET images are co-registered to the high-resolution T1-weighted MRI into the same space using Statistical Parametric Mapping 2 (SPM2) (Wellcome Department of Cognitive Neurology, UK). The delineations of anatomical brain regions are made manually on the co-registered MRI images using in-house image analysis software, Human Brain Atlas (Hba). The main target ROI for NET measurements will be thalamus. If possible (due to relatively low signal-noise ratio), ROI of the midbrain, or even more precisely - locus coeruleus- will be investigated. The reference region for NET binding will be caudate nucleus, presumed to have low NET density (less than 10%). In addition, other regions may be outlined based on the observed distribution of radioactivity in the brain. The ROIs will be displayed on the corresponding PET images and pooled for each anatomical region.

6.1.3 Pharmacokinetic evaluation of PET data

The radioactivity concentration in each ROI is calculated for each sequential frame, corrected for ^{18}F decay, and plotted versus time (CROI). The results will be presented as time-activity (TACT) data for brain tissue, given as radioactive concentration (nCi/mL).

6.1.3.1 Occupancy and the relationship to plasma exposure

An index of NET density, binding potential (BP) will be calculated using ratio method (Farde et al 1989), a graphical linear analysis (Logan et al 1990). The most appropriate method(s) for the calculation of BP will be then used for further calculation of occupancy.

The occupancy will be calculated according to the equation:

$$Occupancy(\%) = \frac{BP_{Baseline} - BP_{drug}}{BP_{baseline}} \cdot 100$$

The relationship between exposure and NET occupancy will be evaluated using PK/PD modelling procedures, based on the equations:

$$Occupancy(\%) = \frac{Occ_{\max} \cdot Dose}{ED_{50} + Dose}$$

$$Occupancy(\%) = \frac{Occ_{\max} \cdot C_{av,PET}}{EC_{50} + C_{av,PET}}$$

where ED_{50} represents the SQL SR dose corresponding to a 50% occupancy and EC_{50} represents the plasma concentration of quetiapine or its major active metabolite NDAQ corresponding to 50% occupancy. Occ_{max} is the maximum achievable occupancy and $C_{av,PET}$ is the average plasma concentration during the PET experiment.

6.1.4 Quetiapine pharmacokinetics

Pharmacokinetic variables for quetiapine and NDAQ will be derived from concentration-versus-time data obtained over a 24-hour pharmacokinetic sampling interval following SQL SR administration.

The following steady-state pharmacokinetic parameters will be determined:

AUC_{ss}	area under plasma concentration-time curve during any dosing interval at steady state (from 0 to 24 hours), calculated using the trapezoidal rule
AUC(0-t)	area under plasma concentration-time curve from time 0 until the last quantifiable plasma concentration up to 24 hours post-dose, calculated using the trapezoidal rule
AUC_{PET}	area under plasma concentration-time curve from start to stop of PET-assessment (planed at 5-7 hours post dose)
$C_{ss,max}$	maximum (peak) steady state drug concentration in plasma during dosing interval
$C_{ss,min}$	minimum (trough) steady state drug concentration in plasma during dosing interval
$C_{av,PET}$	average drug concentration in plasma during the PET-assessment, calculated as AUC_{PET}/duration of PET-assessment
t_{max}	time to reach peak or maximum concentration or maximum response following drug administration
$t_{½}$	the terminal elimination half-life (where calculable), where $t_{½} = \ln 2/\lambda_z$, where λ_z is the terminal slope of the regression of ln concentration versus time curve

The following pharmacokinetic parameter will be determined for quetiapine alone:

CL/F apparent oral clearance, where CL/F= Dose/AUC_{ss}

6.2 Safety evaluation

6.2.1 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, vital signs, ECG, clinical chemistry, haematology, urinalysis, Bond-Lader VAS and pharmacokinetic variables.

6.3 Statistical methods and determination of sample size

6.3.1 Statistical evaluation

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before database lock. The final version of the SAP will be attached as an appendix to the study report.

6.3.2 Description of analysis sets

Subjects will be included in the statistical analysis of the pharmacokinetic data, if they provide sufficient pharmacokinetic data as judged by the pharmacokineticist and the principal investigator.

All subjects who receive study medication, and for whom at least one measure of safety has been collected, will be evaluated for safety.

6.3.3 Methods of statistical analyses

The statistical analysis will be descriptive and exploratory. The safety, tolerability, and pharmacokinetic variables will be analysed using subject listings and, if applicable, summary statistics comprising mean, median, standard deviation, min, and max in the case of continuous variables and frequency distributions in the case of categorical variables. Graphical analysis may also be used for further description of the results.

Exploratory analyses of the relationships between dose, plasma concentration of quetiapine and NDAQ, and NET occupancy will be made by fitting nonlinear models reflecting the theoretical relationships described in Section 6.1.3.1.

Details will be given in the SAP.

6.3.4 Determination of sample size

This is an exploratory study and the sample size has not been calculated on any statistical criteria. Thus, the sample size chosen is based on previous experience with PET studies.

The number of subjects in each group (n=3) is based on the experience in calculating drug occupancy using PET measurements. No power calculations are used.

6.4 Interim analyses

An interim analysis will be performed by the study team, to decide if panel C will be needed and to decide on doses to use in panel B and C. If a Panel C is needed, Panel B and Panel C may be run in parallel.

The dose for Panel B (and C) will be determined based on the evaluation of relationship between the dose of 300 mg of SQL SR and NET occupancy as well as the relationship between plasma concentration of quetiapine/NDAQ and NET occupancy. The interim analysis may also be performed without PK-data if judged appropriate based on the results from panel A. Decision can be taken to decrease the dose to 50 mg, introduce intermediate doses between 100-250 mg or repeat panel A - a 300 mg dose.

6.5 Data presentation

The details of data presentation will be provided in the Statistical analysis plan (SAP), which will be included in the final Clinical Study Report.

6.6 Data monitoring committee (Not applicable)

7. ETHICS

7.1 Ethics review

AstraZeneca will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any subject into the study.

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

7.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

7.3 Informed Consent

The principal investigator at each centre will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Informed Consent Form. A copy of the Informed Consent Form must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

7.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by subject number/study code.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority or an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

The medical records for each subject should contain information which is important for the subject's safety and continued care and to fulfil the requirement that critical study data should be verifiable. To achieve this, the medical records of each subject should clearly describe at least:

- That the subject is participating in the study, e.g., by including Enrolment and/or Randomisation Code and Study Code or other study identification
- Date when Informed Consent was obtained
- Diseases (past and current; both the disease studied and others, as relevant)
- Treatments withdrawn/withheld due to participation in the study
- Treatments given, including Study Drugs, changes in treatments during the study, and the time points for the changes (e.g., "The subject is receiving either rosuvastatin 10 mg o.d. or placebo 16 January, 2004").

- Visits to the clinic during the study, including those for study purposes only
- Serious Adverse Events
- Date of and reason for discontinuation.

8. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

8.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact AstraZeneca personnel shown below.

- [redacted]
- [redacted]

For Serious Adverse event reporting

- [redacted]

8.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.3.**

8.3 Procedures in case of overdose

During the study, an overdose is defined as an ingestion of investigational product exceeding the dosage specified for each day in the protocol.

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRF as an AE of 'Overdose' unless there are associated symptoms or signs
- An Overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRF as the associated SAE symptoms. If symptoms meeting the criteria for an SAE have occurred in association with the overdose, the case must be reported immediately, within 1 day to the AstraZeneca representative

- An Overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF. In addition, the Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form" and forwarded to AstraZeneca Drug Safety within 30 days

- An Overdose without associated symptoms should not be recorded as an AE in the CRF. The Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form" within 30 days from notification of the overdose to AstraZeneca Drug Safety

In all instances, the overdose substance must be stated and an assessment whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide attempt, this fact should be clearly stated.

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone.

In postmarketing experience with SEROQUEL (quetiapine IR) , there have been very rare reports of overdose of quetiapine alone resulting in death or coma.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (Investigator's Brochure, SEROQUEL™, 2007).

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension.

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Close medical supervision and monitoring should be continued until the healthy volunteer/patient recovers.

9. REFERENCES

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Clinical Pharmacology Study Protocol: Appendix A	
Drug Substance	Quetiapine Fumarate SR
Study Code	D1448C00017
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D_2 to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

---

This Clinical Study 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]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D_2 to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

This Clinical Study 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]

SIGNATURE OF PRINCIPAL INVESTIGATOR

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D_2 to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

---

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.:

Signature: [redacted]

Clinical Pharmacology Study Protocol: Appendix B	
Drug Substance	Quetiapine Fumarate SR
Study Code	D1448C00017
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- *Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment*
- *Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine*
- *Intensive treatment in an emergency room or at home for allergic bronchospasm*
- *Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation*
- *Development of drug dependency or drug abuse.*

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Pharmacology Study Protocol: Appendix C

Drug Substance	Quetiapine Fumarate SR
Study Code	D1448C00017
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix C
WHO Risk Categories

Risk group	Shipping Requirement	Pathogen	Risk to individuals	Risk to the community	Examples of Pathogens and their Risk groups
1	Standard Diagnostic (IATA PI650)	A micro-organism that is unlikely to cause human disease.	NONE OR VERY LOW	NONE OR VERY LOW	Most bacteria, fungi and viruses
2	Standard Diagnostic (IATA PI650)	A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.	MODERATE	LOW	Legionella pneumophila E. Coli 0157
3	Standard Diagnostic (IATA PI650)	A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.	HIGH	LOW	HIV Hepatitis B Hepatitis C
4	High risk(IATA PI602)	A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.	HIGH	HIGH	Lassa Fever Ebola Virus

If a subject is being withdrawn due to a suspected infection in WHO risk categories 2, 3 and 4 no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

Clinical Pharmacology Study Protocol: Appendix D	
Drug Substance	Quetiapine Fumarate SR
Study Code	D1448C00017
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix D
Insurance and Indemnity

INSURANCE AND INDEMNITY

AstraZeneca's liability is covered by a liability insurance policy with AstraZeneca Reinsurance Limited, policy No.: [redacted]

With respect to any directly or indirectly caused by the investigational products in connection with this Clinical Study, AstraZeneca assumes liability by law on behalf of the investigator(s)/ delegate (and his assistants) for possible injury to the patient (subject) provided the investigator(s) /delegate (and his assistants) have followed the instructions of AstraZeneca in accordance with this protocol and any amendments thereto, that the investigational products administered to the subject in this Clinical Study have been supplied by AstraZeneca and that the investigator /delegate (and his assistants) have general performed this Clinical Study in accordance with scientific practice and currently acceptable techniques and know-how.

AstraZeneca agrees to indemnify the investigator/delegate and institution and hold them harmless from liability in the event of any claim or legal proceedings arising from the study, with the following conditions:

1. The investigator must have complied with the Protocol and conducted the Study to the accepted medical and ethical standards.

2. The investigator must notify AstraZeneca immediately on receipt of any claim or legal proceedings and AstraZeneca shall have full control of the management and defence of any such claim or legal proceedings.

3. The investigator must not make any offer to compromise or settle any claim or legal proceedings without the written agreement of AstraZeneca.

4. AstraZeneca will not provide an indemnity in respect of any claim or legal proceedings caused by the negligence of the investigator.

Compensation in the event of study-related injury

The Informed Consent Form should include information regarding compensation in the event of study-related injury. In clinical studies carried out in Sweden, this is covered by "Läkemedelsförsäkringen" and "Patientförsäkringen" (only by "Patientförsäkringen" for studies where no drugs are used).

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Quetiapine Fumarate SR
Study Code	D1448C00017
Date	[redacted]

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D$_2$ to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Secondary objectives, Protocol synopsis Page 4 and CSP Section 2.2 Page 14, 3rd secondary objective added

Previous text:

1. to characterize the pharmacokinetics of quetiapine and its metabolite NDAQ in the subjects undergoing PET analysis

2. to assess adverse events (AEs), vital signs and changes in laboratory parameters and Bond- Lader VAS (Bond et al 1974)

Revised text:

1. to characterize the pharmacokinetics of quetiapine and its metabolite NDAQ in the subjects undergoing PET analysis

2. to assess adverse events (AEs), vital signs and changes in laboratory parameters and Bond- Lader VAS (Bond et al 1974)

3. to collect serum samples for *in vitro* determination of NET inhibition to determine the relationship to NET occupancy at the time of PET examination

Section of protocol affected:

Section 1.2 Rationale, Page 13, a paragraph added at the end of the rationale section

Previous text:

SQL binding to the norepinephirne transporter in the human brain will be examined and dose-dependent NET occupancy will be determined.

Revised text:

SQL binding to the norepinephrine transporter in the human brain will be examined and dose-dependent NET occupancy will be determined.

In vitro determination of NET inhibition at the time of PET examination will be investigated (Gilmor et al 2002). The relationship between central NET occupancy measured by PET, and *in vitro* NET inhibition, will also be evaluated.

Section of protocol affected:

Section 3.1 Overall study design, Page 15, a paragraph added at the end of the overall study design section

Previous text:

-

Revised text:

Two serum samples will be collected from each healthy volunteer. At Day 1 at CPU, before SQL SR dose is administered, a baseline sample will be collected, the second sample to be collected during PET Examination 2, in the middle of the PET examination. The samples will be analysed for *in vitro* determination of NET inhibition.

Section of protocol affected:

Section Table 1, Study plan, Page 17-19, a new raw to the table and a footnote has been added

Previous text:

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period[b]					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4[b]**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Informed consent	X								
Demographic measurements	X								
Medical/surgical history	X								
Physical and neurological examination	X								X
Habits of nicotine, alcohol and caffeine	X								
Vital signs[d]	X				X[e]	X[e]	X	X	X
Electrocardiogram	X			X[f]		X[g]		X	
Inclusion/exclusion criteria	X								

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period[b]					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4[b]**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Clinical chemistry/Haematology	X				X[h]			X[h]	
Urinalysis	X				X[h]				
Hepatitis B, C, and HIV	X								
Drugs of abuse screen	X								
Production of plaster helmet			X						
MRI		X							
PET after iv administration of (S,S)[18F]FMeNER-D2			X				X[i]		
Administration of SQL SR once daily in the morning					X	X	X		
Blood sampling for quetiapine PK							X[j]		

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period[b]					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4[b]**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Bond- Lader VAS[k]				X[l]	X	X	X	X	
Adverse events[m]				X	X	X	X	X	X

a) MRI and PET examination 1 cannot be done on the same day.
b) In panel B and C the titration period may be removed (i.e. if dose is set to 50 mg) or changed to two days (i.e. if dose is set to 150 mg). The range of total time at CPU may thus be from 6 to 10 days for panel B and C.
c) In the unexpected event of technical failure (camera breakdown or the radioligand synthesis fails), the PET examination has to be moved to the nearest working day. Then it is done during the nearest days. In this case the SQL SR maintenance dosing period will be prolonged by 1-3 days (three days if it is moved from Friday to Monday). If this occurs the time the healthy volunteers are confined to the CPU will be prolonged.
d) Vital signs includes pulse, systolic and diastolic blood pressure supine and again 2 min after standing.
e) Vital signs will be assessed pre-dose and 6 hours post-dose during SQL treatment days, except for the PET 2 examination day, when vital signs will be assessed only pre-dose.
f) ECG should be assessed prior to first titration dose, either day –1 or day 1.
g) ECG should be assessed 6 hours post-dose the third day of steady state (maintenance dose).
h) Blood sampling for Clinical chemistry/Haematology and Urinalysis - As no fasting samples will be collected at the enrolment visit, fasting glucose and lipids should be performed on Day 1 of admission to the CPU. If the samples taken at the Enrolment visit are more than 1 week old, all samples have to be repeated. At Day -1 and Day 8 the healthy volunteers will be fasting from 22.00, water is allowed, sample collection should take place in the morning before administration of SQL dose.
i) Radioligand (S,S) [^{18}F]F MeNER-D_2 to be injected 3.5 h (210 min) post-SRQ SR dose.
PET measurements to start approximately 5 h post-SQL SR dose.
j) Venous blood for PK analysis are to be taken 15 min pre-SQL SR dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h post-SQL SR dose.
k) Bond-Lader VAS should be in the morning pre-dose.
l) Training –Bond-Lader VAS
m) Adverse Events (AEs) must be recorded from the admission to the CPU and until the follow up visit. Serious Adverse Events (SAEs) must be recorded from the time when the informed consent is obtained until the follow-up visit.

Revised text:

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period[b]					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4[b]**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Informed consent	X								
Demographic measurements	X								
Medical/surgical history	X								
Physical and neurological examination	X								X
Habits of nicotine, alcohol and caffeine	X								
Vital signs[d]	X				X[e]	X[e]	X	X	X
Electrocardiogram	X			X[f]		X[g]		X	
Inclusion/exclusion criteria	X								
Clinical chemistry/Haematology	X				X[h]			X[h]	
Urinalysis	X				X[h]				

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period[b]					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4[b]**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Hepatitis B, C, and HIV	X								
Drugs of abuse screen	X								
Production of plaster helmet			X						
MRI		X							
PET after iv administration of (S,S)[18F]FMeNER-D2			X				X[i]		
Administration of SQL SR once daily in the morning					X	X	X		
Blood sampling for quetiapine PK							X[j]		
Blood sampling for NET inhibition (*in vitro*)					X[n]		X[n]		
Bond- Lader VAS[k]				X[l]	X	X	X	X	

Visit	**1**	**2**	**3**	**4**					**5**
				Residential period[b]					
Visit Description	**Enrolment**	**MRI Scan[a]**	**PET Exam1a**	**Admission to CPU**	**SQL SR titration**	**SQL SR maintenance**	**PET Exam 2 after SQL SR dose**	**Discharge**	**Follow-up**
Visit Window (Day)	**Within −30 to -4 days**	**Within −29 to -1 days**	**Within -7 to – 1 days**	**Day -1**	**Day 1-4[b]**	**Day 5-7[b,c]**	**Day 8**	**Day 9**	**5-9 days after last dose**
Adverse events[m]				X	X	X	X	X	X

a) MRI and PET examination 1 cannot be done on the same day.
b) In panel B and C the titration period may be removed (i.e. if dose is set to 50 mg) or changed to two days (i.e. if dose is set to 150 mg). The range of total time at CPU may thus be from 6 to 10 days for panel B and C.
c) In the unexpected event of technical failure (camera breakdown or the radioligand synthesis fails), the PET examination has to be moved to the nearest working day. Then it is done during the nearest days. In this case the SQL SR maintenance dosing period will be prolonged by 1-3 days (three days if it is moved from Friday to Monday). If this occurs the time the healthy volunteers are confined to the CPU will be prolonged.
d) Vital signs include pulse, systolic and diastolic blood pressure supine and again 2 min after standing.
e) Vital signs will be assessed pre-dose and 6 hours post-dose during SQL treatment days, except for the PET 2 examination day, when vital signs will be assessed only pre-dose.
f) ECG should be assessed prior to first titration dose, either day –1 or day 1.
g) ECG should be assessed 6 hours post-dose the third day of steady state (maintenance dose).
h) Blood sampling for Clinical chemistry/Haematology and Urinalysis - As no fasting samples will be collected at the enrolment visit, fasting glucose and lipids should be performed on Day 1 of admission to the CPU. If the samples taken at the Enrolment visit are more than 1 week old, all samples have to be repeated. At Day -1 and Day 8 the healthy volunteers will be fasting from 22.00, water is allowed, sample collection should take place in the morning before administration of SQL dose.
i) Radioligand (S,S) [^{18}F]F MeNER-D_2 to be injected 3.5 h (210 min) post-SRQ SR dose.
PET measurements to start approximately 5 h post-SQL SR dose.
j) Venous blood for PK analysis are to be taken 15 min pre-SQL SR dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h post-SQL SR dose.
k) Bond-Lader VAS should be in the morning pre-dose.
l) Training –Bond-Lader VAS
m) Adverse Events (AEs) must be recorded from the admission to the CPU and until the follow up visit. Serious Adverse Events (SAEs) must be recorded from the time when the informed consent is obtained until the follow-up visit.
n) Serum sample will be collected before SQL SR dose Day 1 at CPU; the second sample will be collected when at PET Examination 2, at the same time as the middle PK sample during PET examination.

Section of protocol affected:

Section Table 2, Time schedule during confinement at PET centre/CPU (Visit 4, Day 8 (Panel A), Page 20, a new column and a footnote has been added

Previous text:

Protocol time (hh:mm)	Administration of SQL SR once daily in the morning	Adm of (S,S)[^{18}F]FMeNER-D_2 IV solution[a]	PET examination[a]	Blood sampling for quetiapine PK	Vital signs	Bond- Lader VAS	Other
Pre-dose				X[b]	X[c]	X[d]	Light breakfast (approx. 2 h before dose)
00:00 (~9am)	X						Transfer to PET centre
01:00				X			
02:00				X			
03:00				X			
03:30		X					
04:00				X			Light meal
05:00			↓	X			
06:00				X			
07:00				X			Transfer to CPU
08:00				X			Dinner
10:00				X			
12:00				X			
24:00				X			

a) Time of PET and administration of (S,S)[^{18}F]FMeNER-D_2 IV solution is tentative.
b) Blood sample for quetiapine PK analysis to be taken 15 min before administration of SQL SR.
c) Vital signs includes pulse, systolic and diastolic blood pressure supine and again 2 min after standing.
d) Bond-Lader VAS should be in the morning pre-dose

Revised text:

Protocol time (hh:mm)	Administration of SQL SR once daily in the morning	Adm of (S,S)[^{18}F]FMeNER-D_2 IV solution[a]	PET examination[a]	Blood sampling for quetiapine PK	Blood sampling for NET inhibition (*in vitro*)	Vital signs	Bond-Lader VAS	Other
Pre-dose				X[b]		X[c]	X[d]	Light breakfast (approx. 2 h before dose)
00:00 (~9am)	X							Transfer to PET centre
01:00				X				
02:00				X				
03:00				X				
03:30		X						
04:00				X				Light meal
05:00			↓	X				
06:00				X	X[e]			
07:00				X				Transfer to CPU
08:00				X				Dinner
10:00				X				
12:00				X				
24:00				X				

a) Time of PET and administration of (S,S)[^{18}F]FMeNER-D_2 IV solution is tentative.
b) Blood sample for quetiapine PK analysis to be taken 15 min before administration of SQL SR.
c) Vital signs include pulse, systolic and diastolic blood pressure supine and again 2 min after standing.
d) Bond-Lader VAS should be in the morning pre-dose
e) The blood sample should be collected in the middle of the PET examination

Section of protocol affected:

Section 4.3 Pharmacodynamic measurements, Page 35, a new section has been added

Previous text:

4.3 Pharmacodynamic measurements (Not applicable)

Revised text:

4.3 Pharmacodynamic measurements

For sampling time points refer to the study plan (Table 1) and time schedule during confinement at PET centre/CPU (Table 2).

4.3.1 Determination of serum levels of NET

Samples for *in vitro* determination of NET inhibition will be analysed by [redacted] The methods used and the results may be presented in a separate report outside the clinical study report.

4.3.2 Collection of blood samples

Blood samples (5ml x 2) will be collected for the *in vitro* determination of NET inhibition. The serum collected from the whole blood sample should be separated into 1-2 ml aliquots into polypropylene tubes and stored at -80C (-20C is acceptable as long as it is not a frost-free freezer). Using aseptic technique, a blood sample will be collected from a forearm, the use of an indwelling catheter with a mandrin is permitted.

The date and time of collection will be recorded on the appropriate CRF.

Samples will be disposed of after the clinical study report has been finalized. Samples will be coded in order to maintain subject confidentiality. Access to the code list will require authorization from the Investigator. The samples will only be used in accordance with the study protocol and Ethics Committee approval is required if the samples are to be used for another purpose. The samples are to be destroyed upon request of the subject.

See Table 4 for the total amount of blood to be drawn from each subject throughout the study.

The handling, labelling and shipment of the serum samples will be described in a separate document, outside the CSP.

Section of protocol affected:

Section 4.6 Volume of blood sampling, Page 39, a new raw has been added

Previous text:

Table 4 Volume of blood to be drawn from each subject

Assessment		**Sample volume (mL)**	**n of samples**	**Total volume (mL)**
Quetiapine plasma concentration		5	12	60
Safety	Clinical chemistry	11	2x2	44
	Haematology	4	2	8
Serology		10	1	10
(Additional unforeseeable samples)				(50)
Total (approximately)				**122** (172)

Depending on whether any extra blood samples will be drawn e.g., for safety reason or to clear the indwelling catheter from saline, it is assumed that the total amount of blood taken will not exceed 172 mL

Revised text:

Table 4 Volume of blood to be drawn from each subject

Assessment		**Sample volume (mL)**	**n of samples**	**Total volume (mL)**
Quetiapine plasma concentration		5	12	60
Blood sampling for NET inhibition (*in vitro*)		5	2	10
Safety	Clinical chemistry	11	2x2	44
	Haematology	4	2	8
Serology		10	1	10
(Additional unforeseeable samples)				(50)
Total (approximately)				**132** (182)

Depending on whether any extra blood samples will be drawn e.g., for safety reason or to clear the indwelling catheter from saline, it is assumed that the total amount of blood taken will not exceed 182mL

Section of protocol affected:

Section 9, References, addition of one more reference

Previous text:

-

Revised text:

Gilmor et al 2002
Gilmor M, Owens MJ, Nemeroff CB. Inhibition of the norepinephrine transporter in depressed patients treated with paroxetine. Am J Psychiatry 2002;159:1702-1710

Reason for Amendment:

In the study, the aim is to determine the occupancy of norepinephrine transporter (NET) induced by Seroquel (SQL) using the PET method. Emerging data indicates that the NET occupancy may be measured in serum samples by an *in vitro* method. The reason for the amendment is to add this in vitro analysis of NET inhibition and to correlate this peripheral measure to the PET determined central NET occupancy data. The aim is to find a widely applicable biomarker in blood that correlates to the NET occupancy measured by PET.

Informed consent

Revised informed consent form will be written in accordance with the changes in this protocol amendment.

Persons who initiated the Amendment:

This change was initiated by the Clinical Project Team (CPT).

Section of protocol affected:

Section 4.1.1 Enrolment medical examination and demographic measurements, 1st bullet point, Page 31

Previous text:

- Recording of demographic data - date of birth, sex, height, weight, race

Revised text:

- Recording of demographic data - date of birth, sex, height, weight, race and ethnicity

Reason for Amendment:

A slight inconsistency between the Master Informed Consent (MICF) and the Clinical Study Protocol (CSP) has been identified. In the MICF we are writing that we will collect ethnicity, which is not mentioned in the protocol, the CSP is updated to reflect the inconsistency.

Persons who initiated the Amendment:

This change was initiated by the Study Delivery Team (SDT).

Study Protocol Amendment 1 Appendix A	
Drug Substance	Quetiapine Fumarate SR
Study Code	D1448C00017
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D$_2$ to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

---

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

AstraZeneca Research and Development site representative

[redacted]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D_2 to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

---

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

AstraZeneca Research and Development site representative

[redacted]

SIGNATURE OF PRINCIPAL INVESTIGATOR

An open label Positron Emission Tomography (PET) study with (S,S)[^{18}F]FMeNER-D_2 to determine central norepinephrine transporter occupancy of quetiapine (SEROQUEL SR™) in healthy male volunteers

---

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.:

Signature: [redacted]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.