AstraZeneca

Revised Clinical Study Protocol 1

Drug Substance	Quetiapine fumarate
Study Code	D144AC00001
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Date	[redacted]

An 8-week, Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Extended-release in Children and Adolescent Subjects with Bipolar Depression

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Quintiles representative

[redacted]

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	[redacted]		

AstraZeneca

PROTOCOL SYNOPSIS

An 8-week, Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Extended-release in Children and Adolescent Subjects with Bipolar Depression

International Co-ordinating Investigator

[redacted]

Study centers and number of subjects planned

This study will be conducted at approximately 75 study centers globally. Approximately 194 subjects will be randomized to obtain approximately 184 evaluable subjects (92 per treatment arm).

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

Objectives

The primary objective is to evaluate whether quetiapine XR formulation at a dose of 150 to 300 mg/day demonstrates superior efficacy compared to placebo in children and adolescents 10 to 17 years of age with bipolar depression after 8 weeks of treatment, as assessed by change in the Children's Depression Rating Scale-Revised (CDRS-R) total score from baseline to final assessment (Day 57).

The secondary objectives are:

1. To evaluate whether quetiapine XR is superior to placebo in achieving remission in bipolar depression in children and adolescents.

2. To evaluate whether quetiapine XR is superior to placebo in achieving depressive symptom response in bipolar depression in children and adolescents.

3. To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in both rapid and non-rapid cyclers.

4. To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in children and adolescents with bipolar I or bipolar II disorder.

5. To evaluate whether quetiapine XR is significantly more effective than placebo in the treatment of a broad range of bipolar depression symptoms in children and adolescents.

6. To evaluate the safety and tolerability of quetiapine XR 150 to 300 mg once daily in the treatment of bipolar depression in children and adolescents.

7. To compare the effects of quetiapine XR with that of placebo in younger (10-12 years) and older (13-17 years) age groups as assessed by primary efficacy and safety variables.

8. To collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety and tolerability of quetiapine XR in subjects with bipolar I or bipolar II disorder.

Study design

This is an 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled, study of the efficacy and safety of quetiapine XR 150 to 300 mg/day in the treatment of children and adolescents with bipolar I or bipolar II disorder with current (or most recent) episode depressed. This study consists of an up to 35-day enrollment period, an 8-week treatment period with 1 of 2 treatment regimens (quetiapine XR 150 to 300 mg/day or placebo), and a 1-week safety follow-up assessment. If the subject has increased sitting systolic or diastolic blood pressure (BP) >95th percentile based on the mean measurement on the final study visit (or at study discontinuation), a follow-up visit for BP measurement will be arranged 2-4 weeks after the final study visit or after study discontinuation. Subjects will be randomly assigned to blinded study treatment in a 1:1 ratio within age strata (10 to 12 years and 13 to 17 years) and treated as outpatients. Double-blind treatment will be preceded by a medication washout period lasting 7 to 28 days (depending on the medications involved and at the discretion of the investigator) before randomization.

Target subject population

The study will enroll male and female outpatient children and adolescent subjects (aged 10 to 17 years inclusive), with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) diagnosis of bipolar I or bipolar II disorder with the current episode depressed (296.50-296.54 and 296.89, respectively), as confirmed by the Kiddie

Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL). A CDRS-R total score of ≥45 and Young Mania Rating Scale (YMRS) ≤16 are required at both screening and at time of evaluation after washout of current medications and prior to randomization. Subjects with psychotic features will be allowed in the study.

Investigational product, dosage and mode of administration

Quetiapine XR will be administered orally, once daily, in the evening. Quetiapine XR will be titrated up to 150 mg/day over 3 days: the initial dose will be 50 mg (1 tablet) on Day 1, 100 mg (2 tablets) on Day 2, and 150 mg (3 tablets) on Day 3. If during the study treatment period, there is deterioration or no improvement, then the dose of quetiapine XR or placebo must be increased to 300 mg in a step-wise manner as follows: the dose is to be increased to 200 mg (4 tablets) of quetiapine XR or placebo, then increased to 250 mg (5 tablets) of quetiapine XR or placebo 1 day later, and again to 300 mg (6 tablets) of quetiapine XR or placebo 1 day later until symptom control is achieved.

Comparator, dosage and mode of administration

The comparator in this study is placebo. Placebo to match 50 mg quetiapine XR tablets will be administered orally, once daily in the evening, in blinded fashion according to randomized treatment assignment. The placebo will be titrated up and down in the same manner as described above for quetiapine XR.

Duration of treatment

Eligible subjects will have a screening period of up to 35 days, including a washout of all psychotropic medications lasting at least 7 days and up to an additional 28 days (depending on type of medication taken) before randomization. Afterwards, subjects will enter an 8-week (56 days) double-blind treatment period. After 56 days of treatment, subjects will enter a 7-day follow-up post-treatment period.

Outcome variables:

- **Efficacy**:
  - **Primary outcome variable**: Change in the CDRS-R total score from baseline to final assessment (Day 57)
  - **Secondary outcome variables**:
  - Proportion of subjects with response (ie, subjects with ≥50% reduction from baseline to final assessment [Day 57] in CDRS-R total score)
  - Proportion of subjects with remission (ie, subjects with a CDRS-R total score ≤28 at final assessment [Day 57])

- Change in the CDRS-R total score in both rapid and non-rapid cyclers from baseline to final assessment (Day 57)

- Change in the CDRS-R total score in both bipolar I and bipolar II disorder from baseline to final assessment (Day 57)

- Change from baseline to final assessment (Day 57) in the CGI-BP-S

- CGI-BP-C score at final assessment (Day 57)

- Proportion of subjects at final assessment (Day 57) with a CGI-BP-C of "Much" or "Very much" improved in overall bipolar illness assessment

- Change in the CDRS-R total score in both younger (10-12 years) and older (13-17 years) subjects from baseline to final assessment (Day 57)

- **Safety**:

  - incidence of AEs, discontinuation due to AEs, serious adverse events (SAEs), death

  - incidence of AEs of extrapyramidal symptoms (EPS) and other specific safety areas, including somnolence, suicidality, neutropenia/agranulocytosis, and thyroid function

  - incidence of AEs of mania or hypomania and/or YMRS total score ≥16 on 2 consecutive assessments or at final visit

  - change from baseline to each visit, when measured, in clinical laboratory test results (ie, clinical chemistry and hematology), electrocardiogram (ECG) results including QTc prolongation, vital signs and weight

  - shift from baseline to final visit in physical examination

  - categorized change from baseline in Simpson-Angus Scale (SAS) total score, in Barnes Akathisia Rating Scale (BARS) global score, and in Abnormal Involuntary Movement Scale (AIMS) total score: improved versus no change/worse for each post randomized assessment visit

  - proportions of subjects with suicidal behavior and suicidal ideation occurrences after baseline up to final assessment (Day 57) as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

- **Pharmacogenetics**:

  - Genetic analysis may be performed to test for association between genetic polymorphisms and drug response (ie, the above efficacy and safety endpoints) and/or susceptibility to bipolar I or bipolar II disorder.

Statistical methods

Efficacy analyses will be based on the modified intent-to-treat (mITT) population, which will comprise all randomized subjects who received at least one dose of study treatment and who have baseline assessments and at least one post-baseline efficacy assessment for the CDRS-R. Safety analyses will include all randomized subjects who took at least one dose of study treatment.

The primary outcome variable, change from baseline to final assessment (Day 57) in CDRS-R total score, will be analyzed using mixed model for repeated-measurements (MMRM) analysis. The contrast of interest will be the quetiapine XR 150 to 300 mg/day treatment group versus the placebo treatment group at final assessment (Day 57).

The secondary outcome variables, changes from baseline to final assessment (Day 57) in CDRS-R total score among rapid and non-rapid cycler subjects, among subjects with bipolar I and bipolar II disorder, and among younger and older subjects, as well as the change from baseline to final assessment (Day 57) in CGI-BP-S and the CGI-BP-C score at final assessment (Day 57) will also be analyzed using MMRM analyses. Logistic regression will be used to assess the differences between quetiapine XR and placebo in the rates of CDRS-R response and CDRS-R remission, in the proportion of subjects with CGI-BP-C of "Much" or "Very much" improved in overall bipolar illness assessment at Day 57, in the incidence of treatment-emergent adverse event (TEAE) of EPS and treatment-emergent mania or hypomania, and the proportion of subjects who improved in SAS total score, BARS global score, and AIMS total score assessment at Day 57, and the proportions of subjects with of suicidal behavior and suicidal ideation occurrence after baseline up to final assessment (Day 57).

All laboratory test results, ECG results, vital signs, weight and waist circumference measurements, and the changes from baseline in these variables will be summarized using descriptive statistics for each visit (when available).

All statistical comparisons will use 2-sided tests with a significance level of 0.050, unless otherwise specified. Secondary analyses will report nominal 5% levels of significance, with no additional correction. Where appropriate, 95% confidence intervals (CI) will be reported.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADHD	Attention-Deficit Hyperactivity Disorder
AE	Adverse event (see definition in Section 7.3.1)
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
BARS	Barnes Akathisia Rating Scale
BP	Blood pressure
CDRS-R	Children's Depression Rating Scale-Revised
CGI-BP-C	Clinical Global Impressions for Bipolar Disorder-Change from Preceding Phase
CGI-BP-S	Clinical Global Impressions for Bipolar Disorder-Severity of Illness
CI	Confidence interval
eCRF	Electronic case report form
CRO	Contract research organization
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
DAE	Discontinuation due to adverse event
DM	Data Management
DNA	Deoxyribonucleic acid
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)

Abbreviation or special term	Explanation
eDC	Electronic data capture
EPS	Extrapyramidal symptoms
EU	European Union
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GEE	Generalized estimating equation
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries, the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version
LIMS	Laboratory Information Management System
MedDRA	Medical Dictionary for Regulatory Activities
OAE	Other Significant Adverse Event (ie, AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 12.1.2
OC	Observed case
MAOI	Monoamine oxidase inhibitor
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measurements
PI	Principal investigator
PP	Per Protocol
SAE	Serious adverse event (see definition in Section 7.3.2).
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SDV	Source data verification
Seroquel	Quetiapine fumarate
S-β-hCG	Serum beta human chorionic gonadotrophin pregnancy test
eRT	eResearch Technology

Abbreviation or special term	Explanation
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
US	United States
WBC	White blood cell
XR	Extended release
YMRS	Young Mania Rating Scale

1. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

1.1 Medical emergencies and contacts

The Principal Investigator (PI) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such, see Section 7.3.4**

In the case of a medical emergency, the investigator should contact the following personnel below.

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Name	Role in the study	Address & telephone number
Other contact information		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1.2 Overdose

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most subjects who overdosed reported no adverse events (AEs) 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 post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma. Subjects with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

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 subject recovers.

The definition of overdose for the study medication in this study is a dose in excess of the doses specified for the dose group. For recording purposes:

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the electronic data capture (eDC) system as an AE of "Overdose" unless there are associated symptoms or signs. The associated symptoms or signs will be the AE terms documented in the source documentation and eDC system.

- An Overdose with associated serious AEs (SAEs) must be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the source documentation and eDC system only.

- An Overdose with associated non-serious AEs must be recorded as the AE diagnosis/symptoms on the relevant AE forms in the source documentation and in eDC, and on the separate AstraZeneca "Clinical Study Overdose Report Form". Only overdoses of study medication will be reported.

- An Overdose without associated symptoms must be only reported on the separate AstraZeneca "Clinical Study Overdose Report Form".

Information on overdoses in study subjects is collected by AstraZeneca or representative and forwarded to AstraZeneca's clinical patient safety data entry sites. Should a subject experience an overdose during the course of the study (whether accidental or deliberate), the investigator or qualified designee must contact AstraZeneca or representative within **five business days** of the investigator or qualified designee first becoming aware of the overdose. Follow-up information on the outcome of the overdose will be forwarded to AstraZeneca.

Any event associated with, or observed in conjunction with, a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is considered an AE and should be reported as such (see Section 7.3.3). If an SAE occurs in conjunction with the overdose, then the reporting time frame for an SAE (**one business day**) must be met. AstraZeneca or representative will provide instructions on how to collect this information (see Section 7.3.4).

1.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca or representative on the pregnancy form.

1.3.1 Maternal exposure

Requirements for contraception in girls of child-bearing potential are specified in exclusion criteria #10 (see Section 5.2).

In the event of pregnancy, pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous

miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

If a subject, including the female partner(s) of a male study subject, should become pregnant during the course of the study, the investigator or qualified designee must inform the appropriate AstraZeneca representative or representative no later than the end of the next business day of the investigator or qualified designee first becoming aware of the pregnancy. AstraZeneca or representative will work with the investigator to ensure that all relevant information is provided to AstraZeneca's clinical subject safety data entry site within 30 calendar days.

If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (**one business day**) must be met. AstraZeneca or representative will provide instructions on how to collect pregnancy information.

AstraZeneca's Pregnancy Outcome Report, part 1, is used to report the pregnancy and the Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

2. INTRODUCTION

SEROQUEL (quetiapine) was first approved in 1997 in the United Kingdom for treatment of adult schizophrenia, first approved in Mexico in 2003 for adult bipolar mania, and first approved in the United States (US) in 2006 for bipolar depression in adults.

Quetiapine has been administered to children and adolescents (aged 10 to 18) in three different clinical studies. A 6-week trial in adolescents with schizophrenia enrolled 147 subjects who received quetiapine in daily doses between 400 to 800 mg. A second 3-week trial enrolled 188 subjects who received daily quetiapine doses between 400 to 600 mg for bipolar mania. A third open-label trial enrolled subjects from the first two trials for an additional 6 months of long-term safety data. In this third study, quetiapine was administered in doses of 400 to 800 mg per day to 380 subjects with 129 subjects having received placebo treatment in one of the first two trials. Thus, quetiapine has been administered to 464 children and adolescent subjects between the ages of 10-18 years. Quetiapine was found to be safe and well tolerated with the majority of subjects having received quetiapine for over 6 months.

2.1 Background

SEROQUEL™ (quetiapine fumarate or quetiapine) is a dibenzothiazepine derivative (bis[2-(2-[4-dibenzo[b,f][1,4]-thiapin-11-yl) piperazin-1-yl]ethoxy)ethanol]fumarate) that has been developed as a first-line oral treatment for adult schizophrenia and bipolar disorder.

The efficacy and safety of the immediate release (IR) and the extended release (XR) formulations of SEROQUEL have been established in over 23,000 subjects in Phase-II/III/IV controlled trials. The outcomes of such trials have shown that the drug has both short-term and long-term efficacy in the treatment of adult subjects with schizophrenia, bipolar disorder and major depressive disorder. The safety of the drug has been established in both Phase I/II/III/IV controlled and uncontrolled trials and from extensive post-marketing use. This has revealed that SEROQUEL has a favorable side-effect profile, in particular a low incidence of extrapyramidal symptoms (EPS) and no sustained effect on serum prolactin concentrations. The IR formulation is currently marketed for the treatment of acute and chronic psychoses, including schizophrenia, and for both the manic and depressive episodes associated with bipolar disorder.

An extended release (XR) formulation of SEROQUEL has been developed. [redacted].

AstraZeneca intends to perform genetic research in the SEROQUEL clinical development program to explore how genetic variations may affect the clinical parameters associated with quetiapine XR. Collection of deoxyribonucleic acid (DNA) samples from populations with well described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets. Blood samples from qualified and assenting subjects whose parent or legal guardian has provided informed consent will be used to prepare DNA samples.

Future research may suggest other genes or gene categories as candidates for influencing not only response to quetiapine XR but also susceptibility to bipolar I or bipolar II disorder for which quetiapine XR may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

2.2 Research hypothesis

The primary goal of this study is to test the hypothesis that quetiapine XR administered once daily will demonstrate superiority over placebo in decreasing depression symptoms as measured by change from baseline to final assessment (Day 57) in the Children's Depression Rating Scale-Revised (CDRS-R) total score.

The secondary hypotheses tested are:

1. Quetiapine XR will achieve significantly greater remission than placebo at final assessment (Day 57) as measured by the proportion of subjects with CDRS-R total score $\leq$28.

2. Quetiapine XR will achieve significantly greater response than placebo at final assessment (Day 57) as measured by the proportion of subjects with ≥50% reduction from baseline in the CDRS-R total score.

3. Quetiapine XR administered once daily will demonstrate similar magnitude and direction of response compared to placebo in decreasing depression symptoms in rapid cyclers and non-rapid cyclers as measured by CDRS-R.

4. Quetiapine XR administered once daily will demonstrate similar magnitude and direction of response compared to placebo in decreasing depression symptoms in both bipolar I and bipolar II disorder as measured by CDRS-R.

5. Quetiapine XR will be significantly better than placebo as measured by the Clinical Global Impressions for Bipolar Disorder-Severity of Illness (CGI-BP-S) scale and CGI-BP-Change from Preceding Phase (CGI-BP-C) scale by overall bipolar illness rating and proportion of subjects with a change rating of "Much" or "Very much" improved at final assessment (Day 57).

6. Quetiapine XR is safe and tolerable in the treatment of bipolar depression in subjects as measured by the absence of discontinuation of AEs, presence of SAEs, presence of significant laboratory abnormalities or any other significant untoward findings.

7. Quetiapine XR administered once daily will demonstrate similar magnitude and direction of response compared to placebo in decreasing depression symptoms in younger (10-12 years) and older (13-17 years) subjects as measured by CDRS-R.

8. Possible associations of quetiapine XR may be tested against future exploratory genetic research on potential associations with drug responses (efficacy and safety) and/or susceptibility to bipolar I or bipolar II disorder.

2.3 Rationale for conducting this study

The demonstrated efficacy and safety of quetiapine in adults with bipolar disorder, the similarity of the pharmacokinetics of quetiapine in adults and younger subjects, and the results of Studies 5077IL/0038 and 5077US/0018 suggest that quetiapine could be an effective and safe treatment for bipolar depression in adolescents. Quetiapine has also been studied in children and adolescents with bipolar mania where it appeared to be effective, safe and generally well tolerated. It is therefore possible that quetiapine may be of benefit in a different phase of the same disease (bipolar disorder) in children and adolescents 10 to 17 years of age.

This study is being conducted to fulfill the post-marketing study commitment as stated in the approval letter of [redacted] for the treatment of bipolar depression in adults and as required under the Pediatric Research Equity Act (PREA).

The rationale for the primary objective is to demonstrate the efficacy of quetiapine XR, administered once daily, in pediatric bipolar depression for subjects between 10 to 17 years of age, inclusive.

The rationale for the secondary objectives is as follows:

1. To demonstrate consistency of the quetiapine XR effect between rapid cyclers and non-rapid cyclers.

2. To demonstrate consistency of the quetiapine XR effect between bipolar I and bipolar II disorder.

3. To confirm that a higher proportion of children and adolescents with bipolar depression will benefit from quetiapine XR than placebo.

4. To confirm that quetiapine XR is significantly more effective than placebo in the clinician's assessment of overall improvement.

5. To describe the safety and tolerability of quetiapine XR in the treatment of bipolar depression in children and adolescents.

2.4 Benefit/risk and ethical assessment

Pediatric bipolar disorder significantly impacts the lives of both the subject and their family. Children and adolescents suffering from bipolar disorders have disturbed interpersonal relationships (including hypersexuality), are more likely to become substance abusers, perform poorly academically, experience legal difficulties, have multiple hospitalizations and have increased rates of suicide attempts and completion (Akiskal et al 1985, Lewinsohn et al 1995, Strober et al 1995).

Despite the significant number of drugs approved to treat adult bipolar disorder, only lithium is approved for the treatment of pediatric bipolar disorder. However, this approval is as an anti-manic agent and only for children who are aged 12 years and above. Currently, risperidone and aripiprazole are approved for pediatric mania by the US Food and Drug Administration (FDA).

The efficacy of quetiapine in adult bipolar depression was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or bipolar II adult subjects. Recognizing the morbidity and mortality associated with pediatric bipolar disorder, a pressing need exists for controlled trials to determine whether medications commonly used to treat the disorder in children are significantly superior to placebo.

Psychiatrists have consistently requested carefully controlled, rigorous clinical studies to provide them with data on safe and effective doses of mood stabilizers and atypical antipsychotics to assist them in the effective treatment of pediatric bipolar disorder.

Although the use of placebo in the pediatric age group has come under challenge by some, placebo-controlled studies are recognized by many bioethicists, pediatric pharmacologists, professional societies and health authorities as ethically justifiable when they are supported by rigorous science and do not expose research participants to excessive risks. And, in most instances, placebo-controlled clinical trials are required for approval of new agents in the field of psychiatry. The special case of placebo-controlled trials in pediatric psychiatry was addressed in a special communication supporting the need for properly designed placebo-controlled trials in pediatric psychopharmacology (March et al 2004a).

This study is the first double-blind, placebo-controlled study which will provide information to prescribing physicians regarding the safety and efficacy of quetiapine XR in the treatment of children and adolescents 10 to 17 years of age with bipolar depression.

3. STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study and its associated variable is described in Table 1.

Table 1 Primary objective

Primary Objective: To evaluate whether quetiapine XR formulation at a dose of 150 mg to 300 mg/day demonstrates superior efficacy compared to placebo in children and adolescents 10 to 17 years of age with bipolar depression after 8 weeks of treatment, as assessed by change in the CDRS-R total score from baseline to final assessment (Day 57).	
Dependent variable	**Description**
Change in the CDRS-R total score from baseline to final assessment (Day 57)	The CDRS-R is a 17-item rating scale used to assess the severity of depression in children and adolescents (Poznanski et al 1985). Items are scored on a 5-point scale (1-5) for 3 items or a 7-point scale (1-7) for 14 items, with higher scores indicating more severe depression. The 17-item scores are summed to give the total score (total score range 17-113).

3.2 Secondary objectives

The secondary objectives and associated variables are described in Table 2.

Table 2 Secondary objectives

Secondary Objective 1: To evaluate whether quetiapine XR is superior to placebo in achieving remission in bipolar depression in children and adolescents.	
Dependent variable	**Description**
Proportion of subjects with remission	Remission is defined as a CDRS-R total score ≤28 at final assessment (Day 57). Please refer to CDRS-R description in Table 1.
Secondary Objective 2: To evaluate whether quetiapine XR is superior to placebo in achieving depressive symptom response in bipolar depression in children and adolescents.	
Dependent variable	**Description**
Proportion of subjects with response	Response is defined as ≥50% reduction from baseline to final assessment (Day 57) in the CDRS-R total score. Please refer to CDRS-R description in Table 1.
Secondary Objective 3: To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in both rapid and non-rapid cyclers.	
Dependent variables	**Description**
Change in the CDRS-R total score from baseline to final assessment (Day 57) among rapid cycler subjects Change in the CDRS-R total score from baseline to final assessment (Day 57) among non-rapid cycler subjects	Please refer to CDRS-R description in Table 1.
Secondary Objective 4: To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in children and adolescents with bipolar I or bipolar II disorder.	
Dependent variables	**Description**
Change in the CDRS-R total score from baseline to final assessment (Day 57) among subjects with bipolar I disorder Change in the CDRS-R total score from baseline to final assessment (Day 57) among subjects with bipolar II disorder	Please refer to CDRS-R description in Table 1.

Table 2 Secondary objectives

Secondary Objective 5: To evaluate whether quetiapine XR is significantly more effective than placebo in the treatment of a broad range of bipolar depression symptoms in children and adolescents.	
Dependent variables	**Description**
Change from baseline to final assessment (Day 57) in the CGI-BP-S	CGI-BP-S rates the severity of the subject's illness at the time of assessment (Spearing et al 1997). Each CGI-BP-S item is scored on a scale from 1 to 7 (1=normal, not ill to 7=very severely ill). Higher CGI-BP-S scores indicate greater illness severity.
CGI-BP-C score at final assessment (Day 57) Proportion of subjects at final assessment (Day 57) with a CGI-BP-C of "Much" or "Very much" improved in overall bipolar illness assessment	CGI-BP-C rates how much the subject's illness has improved or worsened compared to the phase immediately preceding treatment (Spearing et al 1997). Each CGI-BP-C item is scored on a scale from 1 to 8 (1=very much improved to 7=very much worse. 8=not applicable). CGI-BP-C scores >4 indicate worsening, while scores <4 indicate improvement.
Secondary Objective 6: To evaluate the safety and tolerability of quetiapine XR in the treatment of bipolar depression in children and adolescents.	
Dependent variables	**Description**
Incidence of AEs, discontinuation due to AEs, SAEs, death	AEs will be collected throughout the study (ie, from randomization to final assessment [D57]).
Incidence of AEs of EPS and other specific safety areas, including QTc prolongation, somnolence, suicidality, neutropenia/agranulocytosis, and thyroid function	AEs of EPS and other specific safety areas will be identified by AstraZeneca or representative in a blinded fashion from an exhaustive list of all treatment-emergent AEs (TEAEs).
Incidence of AEs of mania or hypomania and/or YMRS total score ≥16 on 2 consecutive assessments or at final visit	AEs of mania or hypomania will be identified by AstraZeneca or representative in a blinded fashion from an exhaustive list of all TEAEs. The YMRS (Young et al 1978) is an 11-item instrument used to assess the severity of mania in subjects with a diagnosis of bipolar disorder. A score of 12 or less usually indicates remission, 13-19 indicates minimal symptoms, 20-25 indicates mild mania, 26-37 indicates moderate mania, and 38-60 is indicative of severe mania.

Table 2 Secondary objectives

Change from baseline to each visit, when measured, in clinical laboratory test results (ie, clinical chemistry and hematology), ECG results, vital signs, and weight	Laboratory assessments will be performed at screening, Day 29, and final assessment (Day 57). 12-lead ECG will be performed at screening and final assessment (Day 57). Vital signs and weight measurement will be performed at every scheduled visit.
Categorized change from baseline to Day 29 and Day 57 in SAS total score: improved vs. no change/worse	The SAS (Simpson and Angus 1970) is a 10-item instrument used to evaluate the presence and severity of parkinsonian symptomatology. The 10 items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness. Items are rated for severity on a 5-point scale (0-4), with definitions given for each anchor point. The SAS total score is obtained by adding the 10 items.
Categorized change from baseline to Day 29 and Day 57 in AIMS total score: improved vs. no change/worse	The AIMS (Guy 1976) is a 12-item instrument assessing abnormal involuntary movements associated with antipsychotic drugs, such as tardive dystonia and chronic akathisia, as well as "spontaneous" motor disturbance related to the illness itself. Items are rated for severity of movement in three main anatomic area (facial/oral, extremities, and trunk), based on a 5-point scale (0=none, 4=severe). The AIMS total score will be calculated as the sum of the first 7 individual-item scores.
Categorized change from baseline to Day 29 and Day 57 in BARS global score: improved vs. no change/worse	The BARS (Barnes 1989) is a 4-item scale to assess the presence and severity of drug-induced akathisia. Global assessment is rated on a scale of 0-5 (0=absent; 1=questionable; 2=mild akathisia; 3=moderate akathisia; 4=marked akathisia; 5=severe akathisia).

Table 2 Secondary objectives

Proportion of subjects with suicidal behavior and suicidal ideation occurrences after baseline up to final assessment (Day 57) as measured by the C-SSRS	The C-SSRS (Posner et al 2007) assesses the suicidal behavior and suicidal ideation in subjects. Occurrence of suicidal behavior is defined as having answered "yes" to at least one of the 4 suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation. Occurrence of suicidal ideation after baseline up is defined as having answered "yes" to at least one of the 5 suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any post-baseline evaluation.
Secondary Objective 7: To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in younger (10-12 years) and older (13-17 years) subjects.	
Dependent variables	**Description**
Change in the CDRS-R total score from baseline to final assessment (Day 57) among younger (10-12 years) subjects	Please refer to CDRS-R description in Table 1.
Change in the CDRS-R total score from baseline to final assessment (Day 57) among older (13-17 years) subjects	
Secondary Objective 8: To collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety and tolerability of quetiapine XR in subjects with bipolar I or bipolar II disorder.	
Dependent variable	**Description**
Pharmacogenetics	Optional genetic analyses may be performed to establish a panel of DNA samples from those subjects who provide separate consent, to enable future exploratory genetic research on potential associations with drug response (efficacy and safety) and/or susceptibility to bipolar I or bipolar II disorder.

4. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subjected to a peer review according to AstraZeneca's standard procedures.

4.1 Overall study design and flow chart

This is an 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine XR 150 mg to 300 mg/day in the treatment of male and female children and adolescents aged 10 to 17 years (inclusive) with bipolar I or bipolar II disorder with current (or most recent) episode depressed (296.50-296.54 and 296.89, respectively) (Appendix E).

This study will be conducted in approximately 75 centers globally. Approximately 194 subjects will be randomized to obtain 184 evaluable subjects. Evaluable is defined as those who have assessments at baseline and have taken at least one dose of study medication after randomization.

Subjects will be randomly assigned to blinded study treatment in a 1:1 ratio and treated as outpatients. Double-blind treatment will be preceded by a medication washout period lasting 7 to 28 days (depending on the medications involved and at the discretion of the investigator) before randomization. This study consists of an up to 35-day enrollment period, an 8-week treatment period with 1 of 2 treatment regimens (quetiapine XR 150 to 300 mg/day or placebo), and a 1-week safety follow-up assessment. If the subject has increased sitting systolic or diastolic blood pressure (BP) >95th percentile based on the mean measurement on the final study visit (or at study discontinuation), a follow-up visit for BP measurement will be arranged 2-4 weeks after the final study visit or after study discontinuation. Subjects will be stratified by age.

Subjects will undergo K-SADS-PL, CDRS-R, YMRS, C-SSRS, and safety evaluations at screening (Visit 1). A CDRS-R total score of ≥45 and YMRS ≤16 are required at both screening and at enrollment (Visit 2) prior to randomization, and a Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR; American Psychiatric Association 2000) primary diagnosis of bipolar I or bipolar II disorder with current episode depressed, as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL; Kaufman et al 1997) prior to washout. If the subject does not meet the diagnostic criteria and/or CDRS-R total score is <45 or YMRS >16, then the subject will be considered a screen failure and will not be randomized to treatment. Subjects with psychotic features will be allowed in the study.

The screening/washout/enrollment period, double-blind treatment period, final visit or study discontinuation, and 1-week safety follow-up post-treatment period are described below.

1. Screening/washout/enrollment period: Visit 1 (Up to 35 days [Day -35 to Day -1])

Eligible subjects (10 to 17 years of age, inclusive) will be evaluated using the K-SADS-PL at screening (Visit 1). Subjects who meet the DSM-IV-TR diagnosis of bipolar I or bipolar II disorder with current episode depressed confirmed by the K-SADS-PL will then undergo CDRS-R, YMRS, C-SSRS (to obtain current and life history of suicidal behavior and suicidal ideation) and safety evaluations at screening (Table 3):

If the CDRS-R total score is <45 or YMRS >16, the subject will be considered a screen failure and will not be enrolled or randomized to treatment.

If the subject qualifies for enrollment based on the inclusion/exclusion criteria, then the subject will commence a washout of all psychotropic medications lasting at least 7 days and up to 28 days, depending on the medications discontinued before randomization (Visit 2) (Table 5). The screening/enrollment/washout period may take up to 35 days, depending on the washout period of psychotropic medications and the time needed to obtain laboratory results to confirm subject eligibility and enrollment.

If the washout period is 14 days or longer, safety assessments (Table 3, footnote c) will be repeated at the end of the washout period. The physical examination will include a regular, ophthalmoscopic (hand-held) eye examination that can be performed by the PI or sub-investigator.

2. 8-week double-blind, randomized, placebo-controlled treatment period (Visits 2 through 9 [Days 1 to 56])

This study includes the option for randomized subjects to participate in optional exploratory genetic research, where permitted. A 9-mL sample of blood will be collected from qualified and assenting subjects whose parent or legal guardian has provided consent and who have provided individual assent for optional exploratory genetic research. The blood sample can be collected anytime after a subject has qualified for the study, but it is preferred that collection be done at the baseline/randomization visit (Visit 2, Day 1).

Subjects will undergo a pre-randomization CDRS-R and YMRS evaluation that is at least 7 days after the screening visit (Visit 1). A CDRS-R total score of ≥45 and YMRS ≤16 are required at both screening and at enrollment (Visit 2) prior to randomization. If the CDRS-R total score is <45 or YMRS >16, then the subject will be considered a screen failure and will not be randomized to treatment. Subjects who meet all eligibility criteria will be randomized on Day 1 (Visit 2) to 1 of 2 treatment groups: quetiapine XR 150 mg or placebo. Subjects will receive 8 weeks of study treatment from Day 1 to Day 56, and will be treated as outpatients during the course of the study.

Quetiapine XR or placebo will be administered orally, once daily in the evening. Quetiapine XR doses will be titrated up to reach the expected therapeutic dose of 150 mg over 3 days, starting on Day 1 with 50 mg, on Day 2 with 100 mg, and on Day 3 with 150 mg.

If at 2 or 3 weeks (Day 15±3 days or Day 22±3 days), there is a deterioration defined as CGI-BP-C ≥5, then the dose of quetiapine XR or placebo must be increased to 300 mg in a step-wise manner as follows:

- The dose is to be increased to 200 mg of quetiapine XR or placebo, then increased to 250 mg of quetiapine XR or placebo 1 day later, and again to 300 mg of quetiapine XR or placebo 1 day later until symptom control is achieved. The subject may continue at this dose of 300 mg if, in the investigator's opinion, the

subject is responding clinically and displays acceptable symptom relief (improved or unchanged symptoms [efficacy]) and AE tolerability. If in the PI's opinion, the subject's symptoms become stabilized and the subject can tolerate the prescribed dose, the subject can remain on this dose for the duration of the trial.

If the dose has not already been increased to 300 mg at 2 or 3 weeks (Day 15±3 days or Day 22±3 days), it will be increased at 4 weeks (Day 29±3 days) or later visits as follows. If at 4 weeks or more following randomization (Day 29±3 days), the subject displays deterioration or no improvement, defined as CGI-BP-S ≥4, then the subject's dose of study medication must be increased to 300 mg in a step-wise manner as follows:

- The dose is to be increased to 200 mg of quetiapine XR or placebo, then increased to 250 mg of quetiapine XR or placebo 1 day later, and again to 300 mg of quetiapine XR or placebo 1 day later until symptom control is achieved. The subject may continue at this dose of 300 mg if, in the investigator's opinion, the subject is responding clinically and displays acceptable symptom relief and AE tolerability. If in the PI's opinion, the subject's symptoms become stabilized and the subject can tolerate the prescribed dose, the subject can remain on this dose for the duration of the trial.

Efficacy and tolerability will be assessed by the clinical investigator based on changes in scores on the clinical rating scales, CGI-BP, ECG, and safety lab information.

At any visit, the investigator has the discretion to reduce the dose to 150 mg/day from a higher dose if tolerability is documented as poor. In case of documented poor tolerability, the dose can remain at 150 to 300 mg/day at the discretion of the investigator. If the PI determines that a dose reduction is needed, the dose can be reduced from 300 to 150 mg in 1 day. The subject must remain on a minimum dose of 150 mg/day in order to stay in the trial. If this minimum dose of 150 mg/day is not tolerated, the subject must be discontinued.

Subjects will undergo the procedures and assessments at designated visits per the Study Plan (Table 3).

Every effort will be made to have the subjects return during the 7-day interval between scheduled visits. The study visits will also allow for a ±3 day-window to accommodate scheduling conflicts.

3. Final Visit (Visit 10, Day 57) or Study Discontinuation

Final Visit: The final study visit will occur on Day 57 (Visit 10), one day after the last dose of study treatment. Subjects will undergo the procedures and assessments required at this visit per the Study Plan (Table 3).

Subjects who discontinue before the end of study treatment (Day 56) will be asked to return to the study center to complete all assessments required at the final visit (Day 57). For girls of

child-bearing potential, a serum β-hCG pregnancy test will be done at the final visit (Day 57) or at study discontinuation.

The final study visit (Day 57 or earlier if early discontinuation) will also allow for a ±3 day-window to accommodate scheduling conflicts.

Study discontinuation: Subjects must be discontinued from study medication and carefully evaluated to determine if hospitalization is indicated, if the condition under investigation worsens and they meet either of the following criteria:

- CDRS-R item 13 score of >3
- worsening of symptoms at Day 15 (Visit 4) or later, as indicated by a CGI-BP-C score of 6 (much worse) or more

Subjects will be discontinued from the study if hospitalized for either of the above criteria, and all final assessments required at Day 57 (Final Visit) will be conducted.

End of study: The end of the double-blind study will be defined as the date of the last subject completing last visit.

4. 1-week safety follow-up post-treatment period (Visit 11 [Day 57 to Day 63]) (telephone contact)

Subjects and their parents or legal guardians will be contacted by telephone by site clinical research staff in order to perform a safety assessment during the 1-week post-treatment period (either from Day 57 through Day 63 or after study discontinuation). Data on treatment discontinuation signs and symptoms (if subject stopped medications), AEs, and concomitant medications will be collected and recorded in the clinical research file.

The interval between Visits 2 through 11 is 7±3 days such that the shortest interval between visits will be no less than 4 days and no more than 10 days.

Every effort must be made to follow to follow-up with the subject, subject's parent or legal guardian (at least 3 telephone calls and a certified letter). If there is no response, the subject will be considered lost to follow-up.

5. 2-4 week follow-up visit if blood pressure >95th percentile at final visit (Day 57) or study discontinuation (Visit 12 [Day 70 to Day 84])

If the subject has increased sitting systolic or diastolic BP >95th percentile (see Appendix F; NHBPEP 2005) based on the mean measurement on Day 57 (or at study discontinuation), a follow-up visit will be arranged 2-4 weeks (Day 70 to Day 84 or 2-4 weeks after discontinuation) after the measurement. During the follow-up visit, sitting BP, orthostatic BP, and pulse rate (sitting, supine and standing) will be measured as specified in the protocol for previous visits (see Section 7.3.8).

Table 3 Study plan

	Screening Enrollment Washout period	Double-blind treatment							Final Visit OR Study DC[g]	1-week safety follow-up (Phone)	If BP >95th percentile at Final Visit OR Study DC
		Randomization									
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Day	**D-35 to D-1**	**D1[a]**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D57 to D63**	**D70 to D84 (or 2-4 weeks after DC)**
Visit Window (days)	**Up to 35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Informed consent	X											
Demography	X											
Psychiatric diagnosis	X											
Inclusion/exclusion criteria	X	X										
Medical & psychiatric history	X											
Physical examination[b]	X									X		
Height	X									X		
Weight & waist circumference	X	X	X	X	X	X	X	X	X	X		
Vital signs (pulse, BP and temperature)	X	X	X	X	X	X	X	X	X	X		
BP												X
12-lead ECG	(X)[c]									X		

Table 3 Study plan

	Screening Enrollment Washout period	Double-blind treatment							Final Visit OR Study DC[g]	1-week safety follow-up (Phone)	If BP >95th percentile at Final Visit OR Study DC
		Randomization									
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Day	**D-35 to D-1**	**D1[a]**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D57 to D63**	**D70 to D84 (or 2-4 weeks after DC)**
Visit Window (days)	**Up to 35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Laboratory assessments												
Urine drug screen & urinalysis	(X)[c]											
Serum β-hCG pregnancy test	(X)[h]									(X)[h]		
Clinical chemistry	(X)[c]					X				X		
Hematology	(X)[c]					X				X		
Optional genetic sampling		X										
AE reporting		X	X	X	X	X	X	X	X	X	X	
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Rating scales												
K-SADS-PL	X											
CDRS-R[d]	X	X	X	X	X	X	X	X	X	X		
YMRS	X	X	X	X	X	X	X	X	X	X		

Table 3 Study plan

	Screening Enrollment Washout period	Double-blind treatment								Final Visit OR Study DC[g]	1-week safety follow-up (Phone)	If BP >95th percentile at Final Visit OR Study DC
		Randomization										
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Day	**D-35 to D-1**	**D1[a]**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D57 to D63**	**D70 to D84 (or 2-4 weeks after DC)**
Visit Window (days)	**Up to 35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
CGI-BP-S[e]		X	X	X	X	X	X	X	X	X		
CGI-BP-C[f]			X	X	X	X	X	X	X	X		
C-SSRS	X	X	X	X	X	X	X	X	X	X		
SAS		X				X				X		
BARS		X				X				X		
AIMS		X				X				X		
Study medication												
Dispense study medication		X	X	X	X	X	X	X	X			
Drug accountability			X	X	X	X	X	X	X	X		

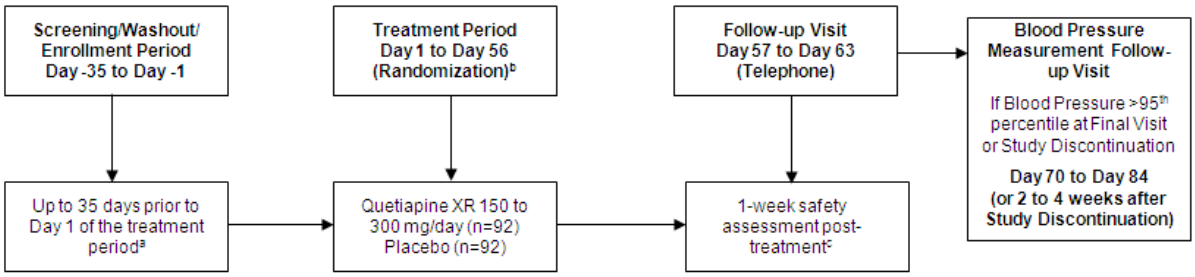
a Randomization must be at least 7 days from the enrollment visit.
b Physical examination includes a regular, hand-held ophthalmoscopic eye examination.
c Repeat tests will be performed if more than 14 days have elapsed between screening/enrollment (Visit 1) AND/OR if results at screening/enrollment (Visit 1) are borderline abnormal after discussion with and approval from the Medical Monitor. If repeat laboratory tests and/or a repeat ECG is required, the subject must come in for an unscheduled visit at least 72 hours (3 days) before randomization (Visit 2) to ensure test results are available and that the subject remains eligible for randomization.
d Subjects will be discontinued from the study if they have a CDRS-R item 13 score of >3.
e The CGI-BP-S is will be preformed at each visit from Visit 2 (Day 1) through Visit 10 (Final Visit) or at time of study discontinuation.
f The CGI-BP-C is added from Visit 3 through Visit 10 (Final Visit) or at time of study discontinuation. Subjects must be discontinued from the study if they have a worsening of symptoms at Day 15 (Visit 4) or later, as indicated by a CGI-BP-C score of 6 (much worse) or more.

g DC is study discontinuation.

h Serum β-hCG pregnancy test will be done for girls of child-bearing potential only at Visit 1 (Day 1) and Visit 10 (Day 57) or study discontinuation. This may be completed at any additional visit if clinically indicated. Visit 1 assessment is to be repeated if washout period is ≥14 days.

NOTE: The screening/enrollment visit (Visit 1) may be conducted over more than one visit before randomization to minimize family burden. The interval between Visits 2 through 11 is 7 days ±3 days such that the shortest interval between visits will be no less than 4 days and no more than 10 days.

Figure 1 Study flow chart



a The subject will commence a washout of all psychotropic medications lasting at least 7 days and up to 28 days depending on the medications discontinued before randomization.

b Approximately 194 subjects will be randomized to obtain 184 evaluable subjects. Subjects will be randomized to either quetiapine XR 150 to 300 mg/day or placebo based on the randomization schedule. Randomization will take place on Day 1 (Visit 2) of the treatment period.

c Subjects and their parents or legal guardian will be contacted by telephone for a safety assessment during the 1-week post-treatment period.

4.2 Rationale for study design, doses and control groups

An enrollment period of up to 35 days is required to allow the investigator to review the results of laboratory assessments which would confound the results of the study prior to washout of previous medications (Note: The duration of washout is based on the subject's previous medications and may require up to 28 days).

Subjects must meet defined severity criteria at two assessments, ie, initial screening visit and at least 7 days later in order to confirm the need for drug treatment and reduce the likelihood of placebo response. An 8-week treatment period is the minimum required to appropriately test the mood-stabilizing efficacy of quetiapine XR for depressive episode. The 1-week safety follow-up period is to assess the subjects' safety post-treatment.

In the comparative group, placebo to match the quetiapine XR formulation will be given. The doses used in this study are consistent with quetiapine IR effective dose in the children and adolescent bipolar mania registration trials.

Study subjects will be randomized to treatment for 56 days with quetiapine XR from 150 to 300 mg/day or placebo. Because this study involves the use of placebo, the following are important features inherent in the study program: establishment of a Data Safety Monitoring Board (DSMB) with regular meetings, close evaluation of all worsening of condition, provision of hospitalization as needed, inclusion of early termination or escape to active treatment, as well as close medical supervision and support persons for the safety of the subject.

Standard assessment tools for evaluating clinical efficacy and safety in this population are utilized. The efficacy measurements chosen for this study are those commonly used to evaluate efficacy endpoints in subjects with bipolar I or bipolar II disorder with symptoms of acute mania. Modeled after the Hamilton Rating Scale for Depression, the CDRS-R is an updated and standardized brief rating scale based on a semi-structured clinical interview that

has been used successfully in children and adolescents (Poznanski et al 1985). It is used to diagnose childhood depression and monitor treatment response, and captures slight but notable changes in symptoms.

The CGI-BP subscales (CGI-BP-S and CGI-BP-C) assess global severity of illness and change from preceding phase (Spearing et al 1997). The C-SSRS is a low-burden, clinician administered tool designed to track suicidal AEs throughout any treatment trial and is considered the "gold standard" for assessment (Posner et al 2007). The measure succinctly covers the full spectrum of suicidality addressing both behavior and ideation and is now required by the FDA in clinical trials. It is also the prospective version of the Columbia suicide classification system commissioned by the FDA, which provided the data for their safety analyses, and is used across numerous industry and National Institute of Mental Health (NIMH)-sponsored studies.

Severity of illness and psychopathology will be measured using the YMRS (Young et al 1978). The YMRS will be used to evaluate treatment-emergent mania and hypomania. The SAS (Simpson and Angus 1970), AIMS (Guy 1976), and BARS (Barnes 1989) will be used to assess treatment-emergent EPS.

The age range for eligible subjects was selected based on diagnostic age of onset data. It is expected that the ages of randomized subjects will reflect the natural age distribution of children and adolescents with bipolar depression. Accurate diagnosis of bipolar depression in children and adolescents is difficult because of factors such as variability of clinical presentation, comorbidity with other psychiatric disorders, and a child's inability to express symptoms. This study will employ the K-SADS-PL at screening to confirm the presence of DSM-IV-TR criteria for bipolar 1 or bipolar II disorder with current episode depressed (296.50-296.54 and 296.89, respectively) in eligible subjects. Single episode in the past of mania or hypomania is sufficient to qualify for the study. The K-SADS-PL is a validated and reliable semi-structured diagnostic interview that assesses current and past episodes of psychopathology, including bipolar depression, in the target population.

To ensure accurate diagnosis, the K-SADS-PL will be conducted or reviewed by a board-certified or board-eligible child psychiatrist. Exceptions may be allowed where the availability of child psychiatrists is limited. Adult psychiatrists with appropriate experience working with children and adolescents in this indication may be considered on a case-by-case basis. Subjects with Attention-Deficit Hyperactivity Disorder (ADHD) may, if judged necessary by the investigator, continue psychostimulant treatment during the study, if the FDA-prescribed dose has been stable for ≥30 days preceding randomization. Permitting conditional concomitant psychostimulant use is intended to avoid AEs associated with the withdrawal of these medications and disturbances of mood that could compromise subject safety in a vulnerable population.

To ensure consistency in scoring by raters within and between centers and countries, raters will be trained on the efficacy scales used for this study.

5. SUBJECT SELECTION CRITERIA

The subject population should be selected without bias.

Investigators must keep a record of subjects who entered pre-trial screening but were never enrolled, eg, subject screening log. Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

For inclusion in the study, subjects must fulfill the following criteria:

1. Provision of informed consent by one or both parents or by legal guardian prior to any study procedures at enrollment.

2. Provision of written assent by the subject prior to any study procedures at enrollment.

3. Male or female subjects aged 10-17 years (inclusive) at randomization (Visit 2).

4. Documented clinical diagnosis meeting the DSM-IV-TR criteria for bipolar I or bipolar II disorder, current episode depressed (296.50-296.54 and 296.89, respectively) (Appendix E) confirmed by psychiatric and K-SADS-PL diagnostic interviews at enrollment (Visit 1). Subjects with psychotic features will be allowed in the study.

5. CDRS-R total score of ≥45 at enrollment (Visit 1) and randomization (Visit 2).

6. Subjects must be able to understand and comply with the requirements of the study, as judged by the investigator at time of enrollment.

7. Outpatient status at the enrollment and randomization visits and believed likely to remain an outpatient for the duration of the study.

8. The duration of the current episode of depression should be ≥4 weeks at enrollment (Visit 2).

9. At enrollment, subjects must meet the DSM-IV-TR criteria for primary bipolar I or bipolar II depression confirmed by the K-SADS-PL. Subjects who meet the criteria for rapid cycling are permitted. Rapid cycling is understood to occur in approximately 10-20% of adult subjects with bipolar disorder and women comprise 70-90% of individuals with a rapid-cycling pattern. The prevalence of rapid cycling in the pediatric population is thought to be higher. Subjects may also have a secondary diagnosis of ADHD. Subjects with ADHD may, if judged necessary by the investigator, continue psychostimulant treatment if the FDA-prescribed dose has been stable for ≥30 days preceding randomization.

10. At enrollment, the subject must have a parent or legal guardian who will accompany the subject at each scheduled study visit, who can provide reliable information, and can be responsible for receiving and dispensing study medication.

11. Subjects must be able to swallow the study medication tablets.

5.2 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. At enrollment, diagnosis of another current DSM-IV-TR Axis I disorder with the exception of those noted in the inclusion criteria. Excluded diagnoses include Tourette's Disorder, Obsessive-Compulsive Disorder (OCD), acute (<3 months) Post-traumatic Stress Disorder (PTSD), Panic Disorder, and Pervasive Developmental Disorders (eg, Autistic Disorder and Asperger's Disorder).

2. Subjects are excluded whose YMRS total >16 at enrollment or randomization and/or subject meets criteria for bipolar I/II disorder, most recent episode mania/hypomania/mixed as confirmed by K-SADS-PL.

3. Subjects with a history of non-response to an adequate treatment (ie, of duration ≥6 weeks) with more than 2 antidepressants during their current episode at enrollment.

4. Current alcohol or other substance dependence or abuse as defined by DSM-IV-TR criteria at enrollment, except for caffeine and nicotine dependence.

5. Subjects are excluded if they use or need to use, within the 2 weeks (14 days) before randomization, drugs that strongly induce or inhibit the hepatic metabolizing cytochrome P450 (CYP) 3A4 enzymes. Subjects will also be excluded if they need to use these drugs during the study. Examples of inducers are carbamazepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine, and St. John's Wort. Examples of inhibitors are ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, indinavir, nelfinavir, ritonavir, and saquinavir) (Appendix D).

6. Use of the following medications:

   - Antipsychotic, mood stabilizer, antidepressant, anxiolytic, hypnotic or other psychoactive drugs within 7 days before randomization.

   - Fluoxetine within 28 days before randomization.

   - A depot antipsychotic injection within two dosing intervals (for the depot) before randomization.

- Lithium within 7 days before randomization and/or tapering off started at least 14 days before randomization.

- Irreversible monoamine oxidase inhibitors (MAOI) within 14 days before randomization.

7. Receipt of electroconvulsive therapy (ECT) within 30 days before randomization.

8. Subjects who in the investigator's opinion will require formalized psychotherapy during the study period, unless psychotherapy has been ongoing for a minimum of 3 months prior to randomization and is documented as such in the subject's medical record.

9. Subjects who, in the investigator's judgment, pose a current serious suicidal or homicidal risk, have a CDRS-R item 13 score of ≥3 at enrollment or randomization, or have made a suicide attempt within the past 6 months prior to enrollment.

10. Pregnancy or, if lactating, subject is nursing. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotrophin [β-hCG]) at enrollment prior to randomization and be willing to use a reliable method of birth control during the study. Acceptable methods of birth control include abstinence, double-barrier method, oral contraceptive, implant, dermal contraception, long-term injectable contraceptive, intrauterine device, or tubal ligation.

11. A diagnosis of diabetes mellitus.

12. Clinically significant deviation from the reference range in clinical laboratory test results at enrollment, as judged by the investigator and the Medical Monitor.

13. Subjects are excluded if they have conditions that could affect absorption or metabolism of study medication (eg, malabsorption syndrome, severe liver disease), as judged by the investigator and Medical Monitor at enrollment or randomization.

14. History of seizure disorder, except febrile convulsions at enrollment or randomization.

15. Evidence of a clinical disorder or clinical finding problematic to the study, as judged by the investigator at enrollment, such as renal (serum creatinine ≥1.5 mg/dL) or hepatic impairment (alanine transaminase [ALT] or aspartate transaminase [AST] 3x the upper limit of normal [ULN]), significant coronary artery disease, active viral hepatitis B or chronic active hepatitis C, or acquired immunodeficiency syndrome (AIDS).

16. An ANC of $<1.5 \times 10^9$/L at enrollment.

17. A thyroid-stimulating hormone (TSH) concentration more than 10% above the upper limit of the normal range of the laboratory used for sample analysis whether or not the subject is being treated for hypothyroidism at enrollment.

18. After the assessment by a centrally located, experienced cardiologist interpreting the ECG obtained at enrollment using centralized telephonically transmitted ECG methods, a subject will be excluded if this ECG result is considered to be clinically significant as determined by the investigator. In some rare clinical situations, the central reading cardiologist's interpretation will be exclusionary without the local investigator's interpretation.

19. An ECG QTcF measurement ≥450 ms at enrollment.

20. Subjects with a history of non-compliance as judged by the investigator at enrollment.

21. Subjects are excluded if they have a history of episodic, idiopathic orthostatic hypotension, with our without near-syncopal or syncopal episodes, or conditions that would predispose them to episodic hypotension, such as dehydration or hypovolemia at enrollment or randomization.

22. Known history of intolerance or hypersensitivity to quetiapine or to any other components in the tablets at enrollment or randomization.

23. Contraindications at enrollment or randomization as detailed in the country-specific prescribing information for quetiapine.

24. Participation (receiving investigational product) in another clinical study or compassionate use program within 30 days of enrollment or as required by local regulations.

25. Involvement of a first-degree relative in the planning and conduct of the study (applies to both AstraZeneca staff, their representatives and staff at the investigational site).

26. CDRS-R decreased >20% between enrollment and randomization.

27. Previous enrollment or randomization of treatment in the present study.

28. Subject is unable to swallow the study medication.

For the subject to be qualified for the optional genetic research, the subject must not:

1. Have had previous bone marrow transplant.

2. Received whole blood transfusion within 120 days prior to the date of genetic sample collection.

If either of these two exclusion criteria is present, the subject cannot participate in the optional genetic research.

5.3 Procedures for handling incorrectly included subjects

Subjects who do not meet the inclusion/exclusion criteria for the study should not, under any circumstances, be enrolled–there can be no exceptions to this rule.

Procedures included in the protocol for the discontinuation of incorrectly enrolled subjects must be followed. These procedures must take into consideration ethical and safety factors and how these subjects will be treated in the analyses.

When an incorrectly enrolled subject is identified, the AstraZeneca Study Team Physician or representative and the investigator will participate in a discussion to determine whether or not to continue the subject in the study. The AstraZeneca Study Team Physician or representative will ensure all such decisions are appropriately documented.

5.4 Withdrawal of subjects

5.4.1 Criteria for discontinuation from the study

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

- Voluntary discontinuation by the subject or subject's parent or legal guardian who is at any time free to discontinue the subject's participation in the study, without prejudice to further treatment.
- Severe non-compliance to protocol.
- Incorrectly enrolled subjects.
- Subject is lost to follow-up.
- The subject has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca or representative, or the subject, the subject's parents, or legal guardian.
- Safety reasons as judged by the investigator, particularly:
  - If the subject's complete blood count (CBC) with white blood cell (WBC) differential shows the ANC is $<1.0 \times 10^9$/L, the test must be repeated within 24 hours. If it remains $<1.0 \times 10^9$/L, the subject must be discontinued.
  - Subject becomes pregnant.
- The condition under investigation worsened:

- CDRS-R item 13 score of >3.

- The subject has a worsening of symptoms at Day 15 or later, as indicated by a CGI-BP-C score of ≥6.

- The subject is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 6.5.

- The subject is unable to tolerate the assigned dose of study medication and is unable to taper down to a tolerable and allowable dose.

- Withdrawal of informed consent or assent to the use of biological samples collected as an integral part of the study, see Section 8.5.

5.4.2 Procedures for discontinuation of a subject from the study

Subjects who discontinue from the study should always be asked about the reasons for discontinuation and the presence of any AEs. If possible, the subject will be seen and assessed by an investigator during the study discontinuation visit. AEs will be followed up (see Sections 7.3.3 and 7.3.4) and the investigational study drugs should be returned by the subject's parent or legal guardian.

If a subject discontinues from the study, all assessments required on Day 57 (Final Visit) will be conducted whenever possible. Any subject who discontinues and has clinically significant or abnormal results for any safety assessments will have a follow-up visit 1 week after discontinuation and at appropriate intervals thereafter, as determined by the investigator until the abnormality resolves or for up to 30 days. If no clinically significant or abnormal results are found at the time of discontinuation, a follow-up visit will be performed by telephone 7±3 days after the final discontinuation visit.

Subjects who are withdrawn from the study because of worsening of symptoms related to bipolar I or bipolar II disorder may, according to the investigator's clinical judgment, be hospitalized. The investigator must notify AstraZeneca or representative of this hospitalization. Hospitalization is an SAE and should be reported as described in Sections 7.3.2 and 7.3.4. If a subject is hospitalized, the subject will be discontinued from the study and all final assessments required at Day 57 (Final Visit) will be conducted.

5.4.3 Procedures for discontinuation from optional genetic research

Subjects who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their assent or consent for this genetic research. It must be established whether the subject or subject's parent or legal guardian:

- agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.

- withdraws consent or assent for the sample to be kept for genetic research in the future and wishes for the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The PI is responsible for providing written notification to AstraZeneca or representative of any subject who has withdrawn assent or whose parent or legal guardian has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca or representative will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

6. STUDY CONDUCT

6.1 Restrictions during the study

Use of concomitant medications is restricted as detailed in Section 6.5, Table 6.

6.2 Subject enrollment and randomization

The PI will:

1. Obtain signed informed consent from the subject's parent or guardian/legal representative and signed assent from the subject before any study specific procedures are performed.

2. Assign potential subject a unique enrollment number, beginning with "E#".

3. Determine subject eligibility. See Sections 5.1 and 5.2.

4. Assign an eligible subject unique randomization code (subject number), beginning with "#".

As subjects are screened for the study, they must be allocated an enrollment code (E-code). The E-code is a 7-digit number made up of the center number and the subject number within that particular center.

6.2.1 Procedures for randomization

Eligible subjects will be randomized in balanced blocks to receive quetiapine XR or matching placebo in a 1:1 ratio within age strata (10 to 12 years and 13 to 17 years). The actual treatment given to individual subjects will be determined by a randomization scheme that has been loaded into the IVRS database. The randomization scheme will be produced by a computer software program called GRand (AstraZeneca's Global Randomization system) that incorporates a standard procedure for generating random numbers. If a subject is discontinued from the study, his/her randomization or enrollment number will not be reused, and the

subject will not be allowed to re-enter the study. Randomized subjects who discontinue early from the study will not be replaced.

If a randomization number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The subject will continue with the allocated number and study material. AstraZeneca or representative should be notified as soon as the error is discovered. Subsequent subjects will continue using the first unallocated randomization number in the original numbering sequence.

6.3 Blinding and procedures for unblinding the study

6.3.1 Methods for ensuring blinding

Quetiapine and matching placebo tablets will be identical in size and color. Packaging and labeling of the investigational products will be performed in a way to ensure blinding throughout the study.

No member of the study team in AstraZeneca, at investigational centers or any CRO handling data will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's Investigational Products (IPS) and Patient Safety.

The randomization schedule for blinding of randomized treatment will be maintained by AstraZeneca and will not be disclosed until after database lock.

6.3.2 Methods for unblinding the study

Individual treatment codes from the IVRS, indicating the treatment randomization for each randomized subject, will be available to the investigator or pharmacist at the study center. Each center will be provided an IVRS user manual which describes this.

The treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomization. If the treatment code is broken, then the investigator must document and report to AstraZeneca or representative immediately.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

The DSMB will have access to blinded and unblinded data (see Section 13.5).

6.4 Treatments

6.4.1 Identity of investigational products

AstraZeneca will supply quetiapine XR and placebo tablets as shown in Table 4.

Table 4 Study medication

Investigational product	Dosage form and strength	Manufacturer
Quetiapine fumarate XR	50 mg tablets	AstraZeneca
Placebo to match quetiapine fumarate XR	50 mg tablets	AstraZeneca

Quetiapine fumarate or matching placebo tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. At each dispensing visit, subjects will be dispensed a bottle containing 1 week's worth of medication plus overage.

6.4.2 Doses and treatment regimens

Quetiapine XR or placebo will be administered orally, once daily in the evening. The tablets should be swallowed whole with fluid. Quetiapine XR doses will be titrated up to reach the expected therapeutic dose of 150 mg over 3 days in 50 mg increments, starting on Day 1 with 50 mg, on Day 2 with 100 mg, and on Day 3 with 150 mg.

If at 2 or 3 weeks (Day 15±3 days or Day 22±3 days), there is a deterioration defined as CGI-BP-C ≥5, then the dose of quetiapine XR or placebo must be increased to 300 mg in a step-wise manner as follows: the dose is to be increased to 200 mg (4 tablets) of quetiapine XR or placebo, then increased to 250 mg (5 tablets) of quetiapine XR or placebo 1 day later, and again to 300 mg (6 tablets) of quetiapine XR or placebo 1 day later until symptom control is achieved.

If the dose has not already been increased to 300 mg at 2 or 3 weeks (Day 15±3 days or Day 22±3 days), it will be increased at 4 weeks (Day 29±3 days) or later visits as follows. If at 4 weeks or more following randomization (Day 29±3 days), the subject displays deterioration or no improvement, defined as CGI-BP-S ≥4, then the subject's dose of study medication must be increased to 300 mg in a step-wise manner as follows: the dose is to be increased to 200 mg of quetiapine XR or placebo, then increased to 250 mg of quetiapine XR or placebo 1 day later, and again to 300 mg of quetiapine XR or placebo 1 day later until symptom control is achieved.

At any visit, the investigator has the discretion to reduce the dose to 150 mg/day from a higher dose if tolerability is documented as poor. In case of documented poor tolerability, the dose can remain at 150 to 300 mg/day at the discretion of the investigator. If the PI determines that a dose reduction is needed, the dose can be reduced from 300 to 150 mg in 1 day. The subject must remain on a minimum dose of 150 mg/day in order to stay in the trial. If this minimum dose of 150 mg/day is not tolerated, the subject must be discontinued.

6.4.3 Labeling

AstraZeneca will provide the investigational product to the study sites. Labeling of the investigational products will be performed in accordance with Good Manufacturing Practice.

The labels will be produced in the local language and in accordance with local regulations for each participating country. Bottle labels will state "Take as directed by your doctor". A dosing card will be provided.

6.4.4 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle, carton and the Investigator's Brochure (IB) specifies the appropriate storage and shipment.

6.5 Concomitant and post-study treatments

6.5.1 Pre-study medications

This study begins with a medication washout period of 7 to 28 days. During this time, all psychoactive and other medications must be discontinued as specified in Table 5.

All psychotropic medications are to be stopped prior to randomization and not permitted during the study.

Table 5 Discontinuation/washout of pre-study medications

Medication	Time of discontinuation
Fluoxetine	28 days before randomization
Clozapine	28 days before randomization
Atomoxetine hydrochloride (Straterra®)	14 days before randomization
Cholinesterase inhibitors	14 days before randomization
CYP3A4 inhibitors or inducers (potent)	14 days before randomization
Nefazodone, fluvoxamine, or irreversible MAOIs	14 days before randomization
Mood stabilizers	14 day before randomization
Anticonvulsants	Unless otherwise specified, 14 days before randomization
Psychostimulants	7 days before randomization (except as permitted per inclusion criterion #9)
Lithium	7 days before randomization and/or tapering off started at least 14 days before randomization
Antidepressants (except fluoxetine)	Unless otherwise specified, 7 days before randomization
Antipsychotics (except study medication)	Unless otherwise specified, 7 days before randomization
Anxiolytics and hypnotics	Unless otherwise specified, 7 days before randomization
Valproate	3-4 days before randomization

Table 5 Discontinuation/washout of pre-study medications

Medication	Time of discontinuation
Depot antipsychotics	2 dosing intervals before randomization

Subjects with ADHD may, if judged necessary by the investigator, continue on an FDA-approved dose of psychostimulant treatment if the prescribed dose has been stable for ≥30 days preceding randomization (see inclusion criterion #9, Section 5.1).

6.5.2 Concomitant medications

Medications prohibited, permitted with restrictions, or permitted during the screening or washout period and during the double-blind portion of the study are specified in Table 6. Potent CYP3A4 inhibitors and inducers must be discontinued (see Appendix D).

Subjects with ADHD may, if judged necessary by the investigator, continue on an FDA-approved dose of psychostimulant treatment if the prescribed dose has been stable for ≥30 days preceding randomization.

The administration of all medications (including investigational products) must be recorded in the appropriate sections of the source documentation and electronic case report form (eCRF). The subject's parent or legal guardian must be instructed to report all medications given to the subject, in addition to those prescribed by the investigator.

Table 6 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
Prohibited	Anticonvulsants	eg, carbamazepine, lamotrigine
	Antidepressants	eg, fluoxetine, nefazodone, mirtazapine, fluvoxamine, paroxetine, MAOIs
	Antipsychotics	eg, olanzapine, haloperidol (except study medication)
	Anxiolytics and hypnotics not specifically permitted (see medications allowed with restrictions, below)	eg, buspirone, alprazolam, diazepam, zolpidem, zaleplon
	Atomoxetine hydrochloride	Straterra®
	Cholinesterase inhibitors	
	CYP3A4 inducers (potent)	eg, phenytoin, carbamazepine, barbiturates, rifampin, rifabutin, glucocorticoids, thiorizadine and St. John's Wort (see Appendix D)
	CYP3A4 inhibitors (potent)	eg, ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir (see Appendix D)
	Mood stabilizers	eg, lithium, valproate
	Opiates	

Table 6 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
Permitted with restrictions	Psychostimulants	Subjects with ADHD may, if judged necessary by the investigator, continue on an FDA-approved dose of psychostimulant treatment if the prescribed dose has been stable for ≥30 days preceding randomization. No dose adjustment is permitted during the study period.
Permitted	Non-psychoactive medications, including over-the-counter counter medications, taken by the subjects before entry into the study	
	Medications required to treat illness or complaints that occur during the study	May be used at the discretion of the investigator
	Medications which are considered necessary for the subject's safety and well-being	May be given at the discretion of the investigator. Includes medication and devices for contraception.

6.6 Treatment compliance

The administration of the investigational products must be recorded in the appropriate section of the source documentation and eCRF. Subjects will be asked to return all unused study medication and empty containers.

Compliance will be assessed using returned-tablet counts. The percent compliance will be calculated as the number of tablets taken (dispensed – returned) divided by the prescribed number of tablets (number of days times number of tablets per day) expressed as a percent. For data analysis purposes only, a subject who is at least 75% and under 120% compliant with study medication during study participation will be classified as compliant.

6.6.1 Accountability

The medication provided for this study is for use only as directed in the protocol. It is the investigator's/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca or representative are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly as stated on the label.
- Study treatments are only dispensed to study subjects in accordance with the protocol.

The study personnel will account for all study medications dispensed and returned.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the investigator. This record is in addition to any drug accountability information recorded in the subject's source documentation and in the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file.

7. COLLECTION OF STUDY VARIABLES

7.1 Recording of data

The investigator will ensure that all data collected in the study are provided to AstraZeneca or representative. The investigator will ensure the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the eCRF and according to any instructions provided.

The PI will provide AstraZeneca or representative with all data produced during the study from the scheduled study assessments. The PI will ensure the accuracy, completeness, legibility, and timeliness of the data reported to AstraZeneca or representative in the eCRF and in all required reports.

Data will be entered in the eDC system at the study site. Trained study personnel will be responsible for entering data specified in the protocol into the eDC system and according to the eCRF instructions. When data have been entered reviewed, edited and Source Data Verification (SDV) performed by AstraZeneca or representative, the data will be frozen to prevent further editing. The PI will be notified to sign the eCRF electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study site.

7.2 Screening and demography procedures

The following data will be collected at screening/enrollment (Visit 1):

- Informed consent and subject assent.
- Demography (date of birth, sex, and race).
- Psychiatric diagnosis.
- DSM-IV-TR diagnosis, confirmed by K-SADS-PL assessment.
- CDRS-R, YMRS, and C-SSRS assessments.
- Inclusion/exclusion criteria.
- Vital signs (supine and standing BP and pulse rate) and temperature.
- Significant medical, surgical and psychiatric history.
- Prior and concomitant medication history.
- 12-lead ECG.
- Physical examination (height, weight and waist circumference), including a regular, ophthalmoscopic (hand-held), eye examination performed by the PI or sub-investigator.
- Laboratory assessments, including hematology, clinical chemistry, serum prolactin concentration, serum β-hCG pregnancy test, and thyroid function tests.
- Urine drug screen and urinalysis. The urine drug screen is part of a general assessment for the presence of substance abuse disorders but will not be used by itself as a criterion for exclusion.

The data listed above will be recorded on specifically designed eCRFs. If the enrollment/washout period (Visit 1) is 14 days or longer OR if results at enrollment (Visit 1) are borderline abnormal after discussion with and approval from the Medical Monitor, the laboratory assessments, serum β-hCG pregnancy test, vital sign measurements, and 12-lead ECG must be repeated before randomization (Visit 2).

If repeat laboratory tests and/or a repeat ECG is required, the subject must come in for an unscheduled visit at least 72 hours before randomization (Visit 2) to ensure test results are available and that the subject remains eligible for randomization.

The screening/enrollment visit may be conducted over more than one visit before randomization to minimize family burden.

7.2.1 Follow-up procedures

Subjects and their parents or legal guardians will be contacted by telephone by site clinical research staff in order to perform a safety assessment during the 1-week post-treatment period (either from Day 57 through Day 63 or after study discontinuation). Data on treatment discontinuation signs and symptoms (if subject stopped medications), AEs, and concomitant medications will be collected and recorded in the clinical research file.

7.3 Safety

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The PI is responsible for ensuring this.

7.3.1 Definition of AEs

An AE 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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). 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.

The term AE is used to include both serious and non-serious AEs.

7.3.2 Definitions of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

For further guidance on the definition of an SAE, see Appendix B to the CSP.

Psychiatric hospitalization is at times required and is expected for bipolar depression. If hospitalization is needed due to the exacerbation of, or for the stabilization of for bipolar depression, it will be reported as an SAE. The psychiatric assessments will reflect the worsening of the subject's condition and the need for hospitalization. These hospitalizations will be reported in the eCRF. Further guidance on the reporting of deterioration of the subject's condition with respect to bipolar depression is contained in the following Section 7.3.3.

7.3.3 Recording of AEs

All AEs that occur after consent and assent has been signed, before washout, during washout, or during the treatment period including the 1-week safety follow-up post-treatment period, whether or not related to the study drug, must be recorded on the eCRF. Unsolicited AE reports occurring up to 1 week after the last dose of investigational product should be recorded together with concomitant medications in the appropriate sections of the eCRF.

Variables

The following variables will be recorded in the eCRF for each AE; description of the AE, the date when the AE started and stopped (duration of AE), maximum intensity, whether the AE is serious or not, causality rating (yes or no), action taken with regard to investigational product (eg, AE caused subject to discontinue study, etc) and outcome.

Intensities will be reported for each AE in the following categories:

- 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 7.3.2. 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.

The investigator will assess the causal relationship (ie, the relationship to study treatment) between the investigational product and AEs, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

For SAEs, causal relationship will also be assessed. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as yes".

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Worsening symptoms of the primary study condition (ie, bipolar I or bipolar II disorder) should not be recorded as an AE. However, if hospitalization results from worsening psychiatric symptoms, the hospitalization should be recorded as an SAE in the eCRF.

Study drug abuse is an SAE, even when there are no symptoms or additional AEs, and should be reported according to the guidelines in Section 7.3.4. Misuse of study drug is an AE but is not considered an SAE unless accompanied by serious sequelae.

Should an overdose occur, it must be reported in accordance with the procedures described in Section 1.2, Overdose. All overdoses, with or without associated symptoms, should be reported as AEs.

Suicide and attempted suicide, irrespective of the method, but occurring in connection with the use of study drug, should be reported as AEs (serious or nonserious). This event should be identified as suicide or attempted suicide, and the method of the suicide or attempt should be provided. If an attempted suicide meets the criteria for an SAE, the event must be reported according to the guidelines in Section 7.3.4.

The latest version of the AE dictionary, Medical Dictionary for Regulatory Activities (MedDRA), will be used by the CRO staff for the classification and analysis of AEs entered in the study database. For regulatory reporting, SAEs will be processed in the Global Patient Safety Database Clintrace and coded using MedDRA.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 1.3, Pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

AEs based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "*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 will be recorded separately.

AEs based on examinations and tests

Deterioration as compared to baseline in the protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfill 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 will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AEs.

Wherever possible, the reporting investigator will use the clinical, rather than the laboratory term (eg, anemia vs. low hemoglobin value).

Follow-up of unresolved AEs

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary.

7.3.4 Reporting of SAEs

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 eCRF. SAEs will be recorded from the time of informed consent. All SAEs must be reported within **one business day** to AstraZeneca or representative.

The investigator and/or AstraZeneca or representative are responsible for informing the Ethics Committee (EC) and/or the Regulatory Authority of the SAE as per local requirements.

For studies in countries implementing the EU Clinical Trials Directive, informing the Ethics Committees and Regulatory Authorities will be performed by AstraZeneca or representative. If any SAE occurs in the course of the study, then the investigator or other site personnel must inform the appropriate AstraZeneca representative or representative immediately but no later

than the end of the next business day of when the investigator or site personnel becomes aware of it.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform the appropriate AstraZeneca representative or representative of any follow-up information on a previously reported SAE immediately but no later than the end of the **next business day** of when the investigator or site personnel becomes aware of it.

The designated AstraZeneca representative or representative will work with the investigator to ensure that all the necessary information is provided to the appropriate AstraZeneca clinical patient safety data entry site within **one business day** for fatal and life threatening events and within **five calendar** days for other SAEs. If the report arrives late in the day, it can be sent the following morning. If the report arrives during a weekend or public holiday, the information is forwarded as early as possible on the first business day following the weekend or holiday. The clock start date is then the next business day.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

7.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken at the times given in the Study Plan (Table 3).

The following clinical laboratory tests will be performed at screening (Visit 1), Days 29 (Visit 6) and 57 (Final Visit or study discontinuation) (Table 7). The date and time of each collection will be recorded on the appropriate CRF.

Table 7 Laboratory measurements

Hematology	Clinical Chemistry	Urinalysis
B-Hemoglobin	S-Creatinine	Specific gravity
B-Leukocyte count	S-Urea	pH
B-Leukocyte (WBC) differential count	S-Bilirubin, total	Glucose
B-Platelet count	S-Albumin	Protein
B-Neutrophil count (ANC in 10^9/L)	S-Alkaline phosphatase	Ketones
Red blood cells	S-ALT	Blood/hemoglobin
B-Hematocrit	S-AST	Leukocytes
	S-Potassium, S-Calcium, S-Sodium	Nitrates
	S-Chloride	Bilirubin
	S-Bicarbonates	Urobilinogen
	S-Glucose	Urine osmolality
	S-Insulin	Microscopic examination (if the urine dipstick is abnormal for leukocytes or blood)
	S-Lipids	**Urine drug screen**
	Total cholesterol	Cocaine
	Triglycerides	Cannabinoids
	High density lipoprotein (HDL) cholesterol	Phencyclidine
	Low density lipoprotein (LDL) cholesterol	Amphetamines class
		Benzodiazepines class
	S-Thyroid function tests	Barbiturates class
	Free triiodothyronine (T_3)	Opiates class
	Free thyroxine (T_4)	Propoxyphene
	TSH	Methaqualone
	S-Prolactin	Methadone
		Ethanol
	Pregnancy test	
	S-β-hCG	

Prefix: B for blood and S for serum.

If the enrollment/washout period (Visit 1) is 14 days or longer OR if results at enrollment (Visit 1) are borderline abnormal after discussion with and approval from the Medical Monitor, the central laboratory (QLAB) assessments and serum β-hCG pregnancy test must be repeated before randomization (Visit 2). If repeat laboratory tests are required, the subject must come in for an unscheduled visit at least 72 hours (3 days) before randomization to ensure test results are available and that the subject remains eligible for randomization.

If a subject tests positive for cannabis or ethanol during the initial drug screen, the subject can be included in the study. The subject can be retested, but if the second test is still positive, the subject should be excluded from the study.

Subjects should fast (including all fluids except water) for at least 8 hours the day before the laboratory assessments.

Samples should be taken by adequately trained study personnel and handled in accordance with the given instructions. Volumes of blood samples are described in Section 8.1. The central laboratory (Section 1.1) will perform clinical laboratory determinations. Up-to-date reference lists will be provided during the study and laboratory results will be compared to the laboratory standard normal ranges and flagged if they are outside the normal range. The investigator should make an assessment of the available results with regard to clinically significant abnormalities. The paper copy should be signed and archived in the eCRF and is the source data for laboratory variables at site.

7.3.6 Physical examination, height and weight

A complete physical examination should be completed by a physician, including an ophthalmologic examination (hand-held ophthalmoscope). The physical examination will be conducted according to standard medical practice at enrollment and at end of study as outlined in Table 3, and recorded by body system on the appropriate sections of the source documentation and eCRF.

Height will be measured at screening/enrollment and at the final visit (Day 57 or early study discontinuation). Weight and waist circumference will be measured at every scheduled visit. Weight will be measured in kilogram (kg) with the subject wearing light clothing and without shoes. If possible, weight should be recorded using the same scale at each visit.

7.3.7 ECG

7.3.7.1 Resting 12-lead ECG

Twelve-lead ECGs will be performed at screening and on Day 57 (or early discontinuation). Heart rate, P and QRS durations, PR, QT and QTc intervals will be recorded from standard lead of the computerized quantitative 12-lead ECG.

ECGs for all subjects at all centers will be conducted at the center using a machine provided by the central ECG laboratory (eRT) and will be transmitted back to eRT (Section 1.1).

Quality assurance of the ECG waveform and subject demographics will be conducted by a central laboratory operator at eRT. ECGs will be processed through a computer interpretation program and then reviewed, first by an ECG analyst and then by a board-certified cardiologist. Results will be faxed and a hard copy report mailed to the center.

QTc intervals will be calculated using the Fridericia formula (Puddu et al 1988). At the ECG assessment at the final visit on Day 57 (or study discontinuation), the previous dose of the study drug and the time of administration will be recorded on the eCRF. The time of the ECG will be recorded in the central ECG laboratory database and will be signed and dated by the PI.

Abnormal values shall not be recorded as AEs unless deemed clinically significant.

7.3.8 Vital signs

7.3.8.1 Pulse, blood pressure and temperature

Sitting BP, orthostatic BP, pulse rate (sitting, supine and standing) and oral temperature will be measured at screening/enrollment, at randomization (Day 1), and on Days 8, 15, 22, 29, 36, 43, 50 and on Day 57 (or at study discontinuation). In the event of increased sitting systolic or diastolic BP >95th percentile (see Appendix F; NHBPEP 2005) based on the mean measurement on Day 57 (or at study discontinuation), a follow-up visit will be arranged 2-4 weeks after the measurement at that final visit. This will fall on Day 70 to Day 84 if the final visit occurs at Day 57. During the follow-up visit, sitting BP, orthostatic BP, and pulse rate (sitting, supine and standing) will be measured as specified in the protocol for previous visits.

At each visit listed above, sitting BP and pulse will be first measured after the subject has been sitting quietly for 5 minutes. During measurement of BP, the subject will be seated with his or her back supported, feet on the floor, right arm supported and cubital fossa at heart level. The preferred method of BP measurement is auscultation (the investigator will document whether ausculatory method was used). The right arm will be used to measure BP for consistency unless not feasible (as in the circumstance of right arm injury such as orthopedic cast, etc.). The investigator will document which arm was used in the measurement. To ensure correct measurements of BP, a cuff that is appropriate to the size of the subject's upper right arm will be used (NHBPEP 2005). At each visit, sitting BP will be recorded 3 times. Each reading will be taken at least 1 minute apart after fully deflating the cuff between measurements. These 3 consecutive sitting BP measurements will determine the mean visit BP.

Orthostatic BP measurements will be taken after measuring BP in the sitting position. Pulse and orthostatic BP measurement will be obtained (one measurement) first with the subject in the supine position for 3 minutes and again (both pulse and BP) within 3 minutes of the subject attaining a standing position (one measurement). Standing and supine BP will be measured with the right arm at heart level.

Management of BP changes will be based on the investigator's judgement.

7.3.9 Other safety assessments

7.3.9.1 YMRS

The YMRS is a reliable, comparatively simple and short instrument and it is a commonly used assessment tool of proven validity, which has been used in clinical practice since 1978.

The YMRS is an 11-item instrument used to assess the severity of mania in with a diagnosis of bipolar disorder. The 11 items are: Elevated Mood, Increased Motor Activity-Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language-Thought Disorder, Content, Disruptive-Aggressive Behavior, Appearance and Insight. A score of 12 or less usually indicates remission, 13-19 indicates minimal symptoms, 20-25 indicates mild mania, 26-37 indicates moderate mania, and 38-60 is indicative of severe mania.

The 11-item YMRS will be administered at screening/enrollment, randomization (Day 1) and at each scheduled visit by a trained rater (Table 3).

7.3.9.2 Neurological assessments

EPS will be assessed as follows: Parkinsonian symptoms will be assessed using SAS, dyskinesia will be assessed using AIMS, and akathisia will be measured by BARS. Assessments will be recorded on the appropriate sections of the eCRF.

7.3.9.2.1 SAS

The SAS is a 10-item instrument used to evaluate the presence and severity of parkinsonian symptomatology. It is the most commonly used rating scale for Parkinsonism in clinical trials over the past 25 years. The ten items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness. Items are rated for severity on a 0-4 scale, with definitions given for each anchor point.

The SAS instrument will be administered by study staff (eg, nurse or physician) at randomization (Day 1) and at the specified visits at Days 29 (Visit 6) and 57 (Final Visit or study discontinuation) to assess EPS (Table 3).

7.3.9.2.2 AIMS

The AIMS is a 12-item instrument assessing abnormal involuntary movements associated with antipsychotic drugs, such as tardive dystonia and chronic akathisia, as well as “spontaneous” motor disturbance related to the illness itself. Scoring the AIMS consists of rating the severity of movement in three main anatomic area (facial/oral, extremities, and trunk), based on a 5-point scale (0=none, 4=severe).

The AIMS instrument will be administered by study staff (eg, nurse or physician) at randomization (Day 1) and at the specified visits at Days 29 (Visit 6) and 57 (Final Visit or study discontinuation) to assess EPS (Table 3).

7.3.9.2.3 BARS

The BARS is a 4-item scale to assess the presence and severity of drug-induced akathisia. It is the most widely used comprehensive rating scale for akathisia, including both objective items (eg, observed restlessness) and subjective items (eg, subject's awareness of restlessness and related distress), together with a global clinical assessment of akathisia.

Global assessment is made on a scale of 0 to 5 with comprehensive definitions provided for each anchor point on scale: 0=absent; 1=questionable; 2=mild akathisia; 3=moderate akathisia; 4=marked akathisia; 5=severe akathisia.

The BARS instrument will be administered by study staff (eg, nurse or physician) at randomization (Day 1) and at the specified visits at Days 29 (Visit 6) and 57 (Final Visit or study discontinuation) to assess EPS (Table 3).

7.3.9.2.4 C-SSRS

The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

Occurrence of suicidal behavior is defined as having answered "yes" to at least one of the 4 suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation.

Occurrence of suicidal ideation after baseline up is defined as having answered "yes" to at least one of the 5 suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any post-baseline evaluation.

The C-SSRS will be administered at the screening visit, randomization (Day 1, Visit 2) and at each scheduled post-randomization visit (Table 3) by a trained primary rater. The trained rater will record the clinical observation on the scale which will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS.

7.4 Efficacy

7.4.1 Primary efficacy variable

The primary study endpoint is the change from baseline in the CDRS-R total score at final assessment (Day 57).

7.4.1.1 CDRS-R

The CDRS-R is an efficient way to diagnose childhood depression and monitor treatment response, and captures slight but notable changes in symptoms. It assesses the severity of depression in children and adolescents.

The CDRS-R is a brief rating scale based on a semi-structured interview with the child (or an adult informant who knows the child well). Designed for 6- to 12-year olds, and successfully used with adolescents, it can be administered in just 15 to 20 minutes and easily scored in a few minutes more. The interviewer rates 17 symptom areas (including those that serve as DSM-IV criteria for a diagnosis of depression). The 17 items are: Impaired Schoolwork, Difficulty Having Fun, Social Withdrawal, Appetite Disturbance, Sleep Disturbance, Excessive Fatigue, Physical Complaints, Irritability, Excessive Guilt, Low Self-Esteem, Depressed Feelings, Morbid Ideation, Suicidal Ideation, Excessive Weeping, Depressed Facial Affect, Listless Speech and Hypoactivity.

The 17-item CDRS-R will be administered at screening/enrollment, randomization (Day 1) and at each scheduled post-randomization visit by a trained and certified rater (Table 3).

The individual-item scores will be recorded on a specifically designed eCRF. The same individual should administer the CDRS-R to the subject at each visit to reduce scoring variability. In the event that the primary rater is not available, a designated back-up rater may perform the CDRS-R. The back-up rater must meet the same qualifications as the primary rater and be authorized by the PI.

7.4.2 Secondary efficacy variables

7.4.2.1 CGI-BP-S and CGI-BP-C

The CGI-BP version is a 3-part, clinician-administered scale that assesses global illness severity and global assessments of improvement during treatment compared to the phase immediately preceding treatment.

For this study, only the first two items of the CGI-BP scale will be used:

- CGI-BP-S: Item I of the scale, Severity of Illness, requires the clinician to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Each CGI-BP-S item is scored on a scale from 1 to 7. A CGI-BP-S score of 1 indicates that a subject is "Normal, not ill" and a score of 7 indicates that a subject is "Very severely ill". Higher CGI-BP-S scores indicate greater illness severity. The CGI-BP-S will be administered at randomization (Visit 2) and at every scheduled post-randomization visit through Day 57 (Final Visit or study discontinuation) by a trained rater (Table 3).

- CGI-BP-C: Item II of the scale, Change from Preceding Phase (where phase refers to treatment phase), requires the clinician to rate how much the subject's illness has improved or worsened compared to the phase immediately preceding treatment.

Each CGI-BP-C item is scored on a scale from 1 to 8. A CGI-BP-C score of 1 indicates that a subject is "Very much improved", a score of 7 indicates that a subject is "Very much worse", and a score of 8 indicates "Not applicable". CGI-BP-C scores greater than 4 indicate worsening, while scores less than 4 indicate improvement. The CGI-BP-C will be administered at every scheduled post-randomization visit starting from Day 8 (Visit 3) through Day 57 (Final Visit or study discontinuation) by a trained rater (Table 3).

The CGI-BP-S and CGI-BP-C will be performed by the primary rater. The data will be recorded on a specifically designed eCRF. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the CGI-BP scales.

7.5 Pharmacokinetics-Not applicable

7.6 Pharmacodynamics-Not applicable

7.7 Pharmacogenetics

7.7.1 Collection of samples

The blood samples for the optional genetic research will be obtained from subjects after randomization. Samples will be collected, labeled, stored and shipped as detailed in the laboratory manual (see Section 8.2.1).

For blood volume, see Section 8.1.

7.8 Health economics-Not applicable

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Volume of blood

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

Table 8 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (including lipid panel)	**5**	**3**[a]	**15.0**
	Hematology	**2**	**3**[a]	**6.0**
	Thyroid function and prolactin concentration	**5**	**2**[a]	**10.0**
Pharmacogenetics		**9**	**1**	**9**
Total			**9**	**40**

a Additional blood samples will be required for repeat screening laboratory tests if washout period is ≥14 days.

For subjects who participate in optional genetic sampling, an additional 9-mL blood sample will be collected after randomization.

8.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed after analyses or retained for further use as described here.

The central laboratory will provide detailed instructions of all laboratory procedures, handling and shipment of laboratory samples before the study start. The samples should be properly taken, handled, labeled and shipped in accordance with the instructions provided by the central laboratory. Samples should be shipped to the central laboratory by courier unless otherwise agreed.

The analyte stability limits defined by the central laboratory will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory will not analyze samples that fall outside these stability limits. Analytical data found to have been derived from a sample that fell outside these stability limits would not be reported. The standards of procedures followed by the central laboratory may be amended in accordance with their Standard Operating Procedures. The central laboratory will inform AstraZeneca of the stability limits relevant to this study before the first subject gives assent and whose parent or legal guardian has provided informed consent to take part in the study.

8.2.1 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA

number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee or representative working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. The link between the subject enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

8.3 Labeling and shipment of biohazard samples

The PI ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria (see International Airline Transportation Association [IATA] 6.2 Regulations Guidance in Appendix C).

Any samples identified as Infectious Category A materials are not shipped and further samples taken from the subject unless agreed with AstraZeneca or representative and appropriate labeling, shipment and containment provisions are approved.

8.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The PI at each center keeps full tractability of collected biological samples from the subjects while in storage at the center until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full tractability of the samples while in storage and during use until used or disposed.

AstraZeneca or representative will keep oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in AstraZeneca's bio-bank system during the entire life cycle.

8.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent or assent to the use of biological samples donated, the samples will be disposed/destroyed, if not already analyzed and documented.

If collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

If collection of the biological samples is a voluntary part of the study, then the subject may continue in the study.

The PI will ensure:

- Subject's withdrawal of informed consent or assent is notified immediately to AstraZeneca or representative.
- Biological samples from that subject, if stored at the study site, are immediately identified, disposed/destructed and the action documented.
- The laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

AstraZeneca or representative will ensure the central laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

9.2 Subject data protection

The Informed Consent and Child Assent Forms will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

For study centers within the US or in studies where non-US subjects' protected health information (subject data) will come into the US through a covered entity (eg, Central lab/Reader), the Informed Consent and Child Assent Forms will incorporate, or be accompanied by, a separate document incorporating Health Insurance Portability and Accountability Act (HIPAA)-compliant wording by which subjects authorize the use and disclosure of their Protected Health Information by the investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent and Child Assent Forms 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 or representative will be identified by subject enrollment number, randomization number, and study code. The Master Informed Consent and Child Assent Forms will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) may require direct access to parts of the hospital or practice records relevant to the study, including the subject's medical history.

9.3 Ethics and regulatory review

An EC/IRB must approve the final study protocol, including the final versions of the Informed Consent and Child Assent Forms and any other written information to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB must be given in writing. The investigator must submit the written approval to AstraZeneca or representative before enrollment of any subject into the study. Study investigational product will not be distributed to the site until such approval is in place.

The EC/IRB must approve all advertising used to recruit subjects for the study.

AstraZeneca must approve any modifications to the Informed Consent and Child Assent Forms that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the EC/IRB annually.

Before enrollment of any subject into the study, the final study protocol, including the final versions of the Informed Consent and Child Assent Forms, a notification to the national regulatory authority is done and is approved by the national regulatory authority according to local regulations.

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca.

In the EU, AstraZeneca will provide the EC/IRB and PIs with safety updates/reports according to local requirements.

In the US, the PI is also responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca or representative will provide this information to the PI.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the EC/IRB according to local regulations and guidelines.

9.4 Informed consent

The PI at each center will:

- Ensure that the both the subject (assent) and the parent or legal guardian (consent) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure that the subjects are notified that they are free to discontinue from the study at any time.
- Ensure that the subjects are given the opportunity to ask questions and allowed time to consider the information provided.
- Obtain and document the subject's signed and dated assent and parents' or legal guardian's signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent and Child Assent Forms are stored in the Investigator's Study File.
- Ensure that copies of the signed Informed Consent and Child Assent Forms are given to the subject and parent or legal guardian.

Where genetic analyses are included, special account of these will be made in the consent and assent forms, as it is recognized that special provisions need to be made to retain confidentiality of medical information. These factors have been taken into account in the design of the consent and assent forms. Forms specific for giving assent or consent for taking samples for genotyping will be used. The subject's, parent's or legal guardian's signed and dated Child Assent and Informed Consent must be obtained before conducting any procedure specifically for the genetic sampling. The PI must store the original, signed Child Assent and Informed Consent Forms. A copy of the signed Child Assent/Informed Consent Forms must be given to the subject, parent or legal guardian.

If modifications are made according to local requirements, the new versions of the Informed Consent and Child Assent Forms have to be approved by AstraZeneca.

9.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the co-ordinating investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and in a new version of the study protocol (Amended Protocol).

The amendment must be approved by each EC/IRB and if applicable, also the national regulatory authority, before implementation. Local requirements must be followed for amended protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to the EC/IRB, see Section 9.3.

If a protocol amendment requires a change to a center's Informed Consent and Child Assent Forms, AstraZeneca and the center's EC must approve the revised Informed Consent and Child Assent Forms before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

9.6 Audits and inspections

Authorized representatives of AstraZeneca, the regulatory authority, or the EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an 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, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca or representative immediately if contacted by a regulatory agency about an inspection at the center.

10. STUDY MANAGEMENT

10.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for AstraZeneca or representative to discuss with and/or visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca and the investigator.

10.2 Training of study site personnel

Before the first subject is entered into the study, AstraZeneca or representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the eDC system utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

Raters must receive training and certification on the CDRS-R; certification is required only once per rater during the entire course of the study. If needed, additional training will be provided but re-certification is not required. For all other rating scales, training only is required. Details of the training will be provided in the Rater Training Manual.

10.3 Monitoring of the study

It is understood that AstraZeneca or its representative will contact and visit the investigator regularly for monitoring purposes. During this study, there will be both remote monitoring and on-site monitoring visits. During remote monitoring and on-site monitoring visits, the Study Monitor will review the eCRFs to evaluate them for completeness, legibility, and consistency.

The Study Monitor will be allowed, on request, to inspect the various records of the trial (eCRFs, source documents, signed Informed Consent Forms and Child Assent Forms, and any other pertinent data) provided that subject confidentiality is maintained in accord with local requirements. It will be the Study Monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The Study Monitor must have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The investigator (or her/his designee[s]) agrees to cooperate with the Study Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

During the remote monitoring and on-site monitoring visits, the Study Monitor will also:

- Provide information, support and training to the investigator and investigational staff (as needed).
- Confirm that investigational facilities are adequate and remain acceptable throughout the trial.
- Confirm that the investigational team is adhering to the protocol, data are being recorded accurately and timely in the eCRFs, and that investigational product accountability checks are being performed.
- Verify subject existence for all subjects who sign the Informed Consent and Child Assent Forms.

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the subject.

Source documents

The investigator shall permit the authorized sponsor, agents of the sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect and copy all records relating to an investigation, including subject records. Completed eCRFs must be made available by the investigator for review by the sponsor, agents of the sponsor, the Study Monitor and the regulatory agencies. To ensure the accuracy of data submitted, it is mandatory that representatives of the sponsor and of the regulatory agencies have direct access to source documents (eg, subject medical records, charts, laboratory reports, signed Informed Consent Forms and Child Assent Forms). The eCRFs will be compared with the source documents to ensure that there are no discrepancies between critical data. Subject confidentiality will be protected at all times.

10.3.1 Source data

The location of source data is described in the CSA.

10.4 Study agreements

The PI at each center must comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail.

Agreements between AstraZeneca and the PI must be in place before any study-related procedures can take place, or subjects be enrolled.

10.5 Study timetable and end of study

The end of the entire study is defined as the date of the last subject completing last visit. The study is expected to start in the [redacted] and to be completed by the [redacted]

Before a subject's enrollment in the study and any study-related procedures are undertaken, the following should be fulfilled:

- signed CSP and other agreements between AstraZeneca and the PI/study center
- written approval of the study by the IRB/IEC
- written approval of the study, if applicable, by the regulatory authority
- signed and dated FDA Form 1572 (US centers only)

- signed and dated Financial Disclosure forms for all study personnel listed on the most recent version of FDA Form 1572 (US centers only)

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with quetiapine XR.

11. DATA MANAGEMENT

Data entered in the eDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the PI has signed the eCRF electronically as per eCRF instructions, then the subject's data will be locked.

Electronic case report forms

The eCRF and the protocol are both confidential. The eCRF will be created by the CRO and programmed into the eDC system. All sites will need internet access to access the eCRFs and will only have access to data for subjects at their own sites. Data Management (DM) and other co-ordinator teams will have access to data at all sites.

AstraZeneca or its representative will supply the eCRFs. All eCRFs are to be completed by an authorized member of the investigational staff and reviewed and signed by the investigator. All entries, corrections, and alterations are to be made by the responsible investigator or an authorized member of the investigational staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the subject's eCRF correspond to the entries on the subject's medical records.

The eCRFs for any subject leaving the study should be completed at the time study medication is terminated for whatever reason.

eCRFs must accurately reflect data contained in subject's records (eg, source documents).

Dataflow

After data is entered into the eCRF by site, autoqueries that are generated by the eDC system should be addressed by site. At the monitoring visit, the Study Monitor must perform the SDV of the required fields on completed forms and if there are no open queries, freeze the form. DM will run manual consistency checks outside of the eDC system and will raise manual queries for sites to address; if the form is frozen, DM will unfreeze to allow sites to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data is entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries

closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made.

Database lock

Once all subject casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all applicable quality control checks were performed.

Coding

All AEs and Medical Histories recorded in the eCRF will be coded using MedDRA and all medications coded using AstraZeneca's Drug Dictionary (AZDD). The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

Investigator site file

At the beginning of the study, an investigator's study file will be established at the study center. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

SAE reconciliation

The CRO will perform SAE reconciliation between the CRO Clinical Study database and the AstraZeneca Clinical Patient Safety database.

Biological samples

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

ECG data

ECG data will be processed by a central laboratory and the results will be sent electronically to AstraZeneca or its representative.

Genetic data

In the case of genotypic data, only the date the subject's parent or legal guardian gave consent and the subject gave assent to participation in the genetic research, and the date the blood sample was taken from the subject will be recorded in the eCRF and database.

Genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system, separate from the database used for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the CSR for the main study.

12. EVALUATION AND CALCULATION OF VARIABLES

12.1 Calculation or derivation of safety variables

12.1.1 Adverse events

A TEAE is defined as any AE that started on or after the first dose of study medication up to 30 days after the last dose of study medication. AEs already present at the time of the first dose of study medication that worsens in intensity following exposure to study medication or AE with an unknown/not reported onset date will also be considered as treatment-emergent.

12.1.1.1 Adverse events of EPS

During the evaluation of the AE data, AstraZeneca or representative will review the list of AEs. Based on the expert's judgment, AEs of EPS will be identified and reported as such in the CSR.

12.1.1.2 Adverse events of mania or hypomania

During the evaluation of the AE data, AstraZeneca or representative will review the list of AEs. Based on the expert's judgment, AEs of mania or hypomania will be identified and reported as such in the CSR.

12.1.2 Other significant adverse events (OAE)

During the evaluation of the AE data, AstraZeneca or representative will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

12.1.3 Laboratory safety assessments

Changes from baseline to Days 29 and 57 for all subjects who have a baseline laboratory test and the corresponding post-baseline laboratory test (Day 29 or 57) will be calculated as the post-baseline test value (Day 29 or 57) minus the baseline test value.

Laboratory test results will also be compared to the laboratory reference ranges, and values that are outside the applicable reference range will be flagged as high (H) or low (L).

12.1.4 Physical examination

Changes from baseline to final visit for physical examination will be reported.

12.1.5 Weight and waist circumference

Changes from baseline to each visit in weight and waist circumference will be calculated as the visit assessment minus the baseline value, if applicable.

12.1.6 ECG

Changes from baseline to Day 57 for interval data and rate data will be derived by subtracting the screening value from the final assessment value. Values outside the reference range will be flagged as high (H) or low (L).

12.1.7 Vital signs

Changes from baseline at each visit will be derived as the value at the visit minus the baseline value for the same assessment and position, if applicable. In addition, the change within a visit between the standing and supine BP assessments (orthostatic change) will be calculated for both systolic and diastolic blood pressures. This difference will be calculated as the supine value minus the standing value. A subject will be classified as having postural hypotension if either the systolic BP difference indicates a decrease >20 mmHg or the diastolic BP difference indicates a decrease >15 mmHg.

12.1.8 Other safety assessments

12.1.8.1 Neurological assessments

12.1.8.1.1 SAS

The SAS total score will be calculated as the sum of the 10 individual-item scores. The change from baseline to each study visit, when measured, will be calculated as the visit score minus the baseline score.

Subjects with ≥1 point change at a particular visit will be deemed as worsened; those with ≤-1 point change will be deemed as improved; all others will be deemed as no change.

12.1.8.1.2 BARS

For each BARS individual-item, change from baseline to each study visit, when measured, will be calculated as the visit score minus the baseline score.

Subjects with ≥1 point change at a particular visit in BARS global score will be deemed as worsened; those with ≤-1 point change will be deemed as improved; all others will be deemed as no change.

12.1.8.1.3 AIMS

The AIMS total score will be calculated as the sum of the first 7 individual-item scores. The change from baseline in AIMS total score to each study visit, when measured, will be

calculated as the visit score minus the baseline score. The changes from baseline in AIMS individual-item scores 8, 9, and 10 will be summarized separately and similarly than the change from baseline in AIMS total score.

Subjects with ≥1 point change at a particular visit in AIMS total score will be deemed as worsened; those with ≤-1 point change will be deemed as improved; all others will be deemed as no change.

12.1.8.2 Treatment-emergent mania and hypomania

Treatment-emergent mania and hypomania is defined as the new onset of AE of mania or hypomania after exposition to study drug and/or YMRS total score >16 on 2 consecutive assessments or at final visit (Day 57).

12.1.8.2.1 YMRS

The YMRS total score will be calculated as the sum of the 11 individual-item scores.

12.1.8.3 C-SSRS

Occurrence of suicidal behavior after baseline up to final assessment (Day 57) will be defined as having answered "yes" to at least one of the four suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation.

Occurrence of suicidal ideation after baseline up to final assessment (Day 57) will be defined as having answered "yes" to at least one of the five suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any post-baseline evaluation.

12.2 Calculation or derivation of efficacy variables

12.2.1 Children's Depression Rating Scale-Revised

The CDRS-R total score will be calculated as the sum of the 17 individual-item scores. The changes from baseline to each study visit will be calculated as the visit total score minus the baseline total score.

Response will be defined as ≥50% reduction from baseline to final assessment (Day 57) in CDRS-R total score. Remission will be defined as a CDRS-R total score ≤28 at final assessment (Day 57).

12.2.2 Clinical Global Impressions Bipolar-Severity Scale

The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

12.2.3 Clinical Global Impressions Bipolar-Change from Preceding Phase Scale

Because the CGI-BP-C score assesses changes in the subject's condition, changes from the baseline score will not be calculated.

12.3 Calculation or derivation of pharmacokinetic variables-Not applicable

12.4 Calculation or derivation of pharmacodynamic variables-Not applicable

12.5 Calculation or derivation of pharmacogenetic variables-Not applicable

12.6 Calculation or derivation of health economics variables-Not applicable

13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

13.1 Description of analysis sets

Data analyses will be based on 3 subject populations, as defined below.

13.1.1 Analysis of Safety population

All randomized subjects who received at least 1 dose of study treatment (quetiapine XR or placebo) will be included in the safety population. Throughout the safety results sections, erroneously treated subjects (eg, those randomized to Treatment A but actually given Treatment B) will be accounted for in the actual treatment group. The safety population will be used to assess safety and tolerability variables.

13.1.2 Analysis of mITT population

All randomized subjects who received at least 1 dose of study treatment (quetiapine XR or placebo) and who have baseline assessments and at least one post-baseline efficacy assessment in CDRS-R will be included in the modified Intent-to-Treat (mITT) population. Throughout the efficacy results sections, erroneously treated subjects (eg, those randomized to Treatment A but actually receiving Treatment B) will be accounted for in the randomized treatment group. The mITT population will be used for the efficacy analyses.

13.1.3 Analysis of PP population

All ITT subjects without significant protocol violations or deviations (eg, subjects who were deemed to be non-compliant using returned-tablet counts as defined in Section 6.6) will be included in the per protocol (PP) population. The efficacy analyses will be repeated on the PP population to test for homogeneity of treatment effects. Subjects will be classified according to treatment actually received.

13.2 Methods of statistical analyses

General aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before unblinding of the data.

Baseline will be defined as the latest non-missing value collected prior to or on the same day of randomization (Day 1, Visit 2).

All statistical comparisons will be based on a 2-sided test using an alpha (α) level of significance of 0.050, unless otherwise specified. Secondary analyses will report nominal 5% levels of significance. No other correction to the reported p-values will be made for the analysis of secondary measures. Where appropriate, 95% confidence intervals (CIs) will be presented.

Descriptive statistics for continuous data will include n, mean, median, standard deviation, minimum and maximum values. Descriptive statistics for categorical data will include n, frequency, and percentage.

13.2.1 Primary analysis

The change in CDRS-R total scores from baseline to final assessment (Day 57) will be analyzed using mixed model for repeated measurements (MMRM) analysis. The repeated-measures mixed model will include baseline CDRS-R total score as covariate; age stratum, treatment group, visit, and visit-by-treatment group interaction as fixed effects; and centers and subjects within treatment group as random effects. The contrast of interest will be between the quetiapine 150 mg to 300 mg/day treatment group and the placebo treatment group at final assessment (Day 57).

13.2.2 Secondary analyses

Changes from baseline to final assessment (Day 57) in CDRS-R total score in rapid cycler subjects, non-rapid cycler subjects, subjects with bipolar I, subjects with bipolar II disorder, younger subjects, and older subjects will also be analyzed separately via MMRM analysis. Each of the six repeated-measures mixed models will include baseline CDRS-R total score as covariate; age stratum, treatment group, visit, and visit-by-treatment group interaction as fixed effects; and centers and subjects within treatment group as random effects.

Change from baseline to final assessment (Day 57) in CGI-BP-S total score will be analyzed using MMRM analysis. The repeated-measures mixed model will include baseline CGI-BP-S total score as a covariate; age stratum, treatment group, visit, and visit-by-treatment group interaction as fixed effects; and center and subjects within treatment group as random effects.

CGI-BP-C scores at Day 57 will be analyzed using a MMRM analysis, with baseline CGI-BP-S total score as a covariate along with age stratum, treatment, visit, and visit-by-treatment interaction as fixed effects. Center and subjects within treatment group will be considered as random effects.

Logistic regression will be used to assess the differences between quetiapine XR and placebo in CDRS-R response rates at Day 57 and in the incidence of subjects with remission at Day 57. Factors will include age stratum, treatment, center, and baseline CDRS-R total score.

Logistic regression will also be used to assess the differences between quetiapine XR and placebo in the proportion of subjects with a CGI-BP-C of "Much" or "Very much" improved in overall bipolar illness assessment at Day 57. Factors will include age stratum, treatment, center, and baseline CGI-BP-S total score.

13.2.3 Safety analyses

TEAEs will be coded using the MedDRA. Number of events and proportions will be tabulated by preferred term and system organ class. An event that occurred once or more times on the date of or subsequent to first dose of study medication will contribute one observation to the numerator of the proportion. The denominator of the proportion will comprise all subjects exposed to study treatment. TEAEs will also be summarized by intensity and separately, by causality. Should a subject experience the same preferred term/system organ class within multiple intensity or causality categories, the subject's worst occurrence (most severe/most related) will be retained in the tabulations. SAEs will be summarized in a similar manner than TEAEs.

Logistic regression will be used to assess the differences between quetiapine XR and placebo in the incidence of TEAEs of EPS. Factors will include age stratum, treatment and center.

Logistic regression will be used to assess the differences between quetiapine XR and placebo in the incidence of treatment-emergent mania or hypomania, in the proportion of subjects who improved in SAS total score, BARS global score, and AIMS total score assessment at Day 57, in the occurrence of suicidal behavior during the course of the study, and in the occurrence of suicidal ideation during the course of the study. Factors will include age stratum, treatment, center, and the appropriate baseline measurement (ie, baseline YMRS total score, baseline SAS total score, baseline BARS global score, baseline AIMS total score, baseline suicidal behavior status, and baseline suicidal ideation status, respectively).

Other safety variables will be analyzed using a descriptive statistics approach.

13.2.4 Descriptive statistics

13.2.4.1 Safety population

TEAEs, SAEs, TEAEs leading to death and TEAEs leading to study withdrawal, TEAEs of EPS, and TEAEs of mania or hypomania will be tabulated for each treatment group. Commonly occurring TEAEs, ie, those which occur in 5% or more of the subjects in either treatment group, will be summarized using descriptive statistics.

All laboratory test results, vital signs, ECG results, weight, and waist circumference will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline.

The proportion of subjects who improved in SAS total score, BARS global score, and AIMS total score will also be summarized for each treatment group using descriptive statistics at each visit. The overall incidence of TEAEs of EPS at Day 57 will be presented for each treatment group.

The overall incidence of TEAEs of mania or hypomania and/or YMRS total score >16 on 2 consecutive assessments or at final visit will be presented for each treatment group. The YMRS total score will also be tabulated for each treatment group using descriptive statistics at each visit, displaying the raw numbers.

The proportion of subjects with suicidal behavior and suicidal ideation will be presented for each treatment group at each visit. The proportion of subjects within each of the four suicidal behavior categories and within each of the five suicidal ideation sub-categories will also be presented for each treatment group at each visit. Descriptive statistics on the total number of attempts, total number of interrupted attempts, and total number of aborted attempts will be summarized for each treatment group at each visit.

13.2.4.2 ITT and PP populations

The CDRS-R and CGI-BP-S total scores will be summarized for each treatment group using descriptive statistics at each visit, displaying both the raw numbers and changes from baseline.

The CGI-BP-C total scores will also be summarized for each treatment group using descriptive statistics at each visit, displaying the raw numbers.

13.3 Determination of sample size

At 85% power for a 2-sided test at α=0.05 comparison between quetiapine XR and placebo, using a treatment difference of 4 units in change from baseline to final assessment (Day 57) in CDRS-R total score, with a pooled standard deviation of 9. This size of effect is a conservative but clinically meaningful effect and the variability is consistent with published literature for adolescents with depression in controlled clinical trials (March et al 2004b, Wagner et al 2003, Wagner et al 2004), and is reasonable based on quetiapine experience in adolescents and children with mania (AstraZeneca Study D1441C00149). With 1:1 randomization, this yields a planned sample size of 194 randomized to yield 184 evaluable subjects (92 per treatment arm). With an expected 30% screen failure rate, 277 subjects would need to be enrolled.

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 2.2.

13.4 Interim analyses

No interim analysis for efficacy is planned. Safety will be monitored throughout the trial as described in Section 13.5.

13.5 Data safety monitoring board

A DSMB will be established to assist in the safety surveillance of this study for the duration of the study. The primary responsibilities of the board will be to observe emerging safety findings and to assess critical safety data variables. This independent board will have access to unblinded data if needed and will report any findings or make recommendations to the study steering committee without revealing subject treatment assignment. Detailed operating procedures of the DSMB will be agreed between this board and AstraZeneca or representative and will be presented in a separate document prior to the start of the study.

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Clinical Study Protocol Appendix B	
Drug Substance	Quetiapine fumarate
Study Code	D144AC00001
Edition Number	1.0
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 patient 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 patient'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).

Hospitalization

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient 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, hospitalization, disability or incapacity but may jeopardize the patient 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 anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- 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 patient 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 etiology 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 recognized 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 Study Protocol Appendix C

Drug Substance	Quetiapine fumarate
Study Code	D144AC00001
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Date	[redacted]

Appendix C
IATA 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Cat A pathogens are eg. Ebola, Lassa fever virus

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Cat B pathogens are eg. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Cat B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D

Drug Substance	Quetiapine fumarate
Study Code	D144AC00001
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Date	[redacted]

Appendix D
Cytochrome P450 3A4 Inducers and Inhibitors Potent

CYTOCHROME P450 3A4 INDUCERS AND INHIBITORS POTENT

Inducers

Barbiturates

Carbamazepine

Glucocorticoids

Grape fruit juice

Phenytoin

Rifampin

Rifabutin

Thioridazine

Saint John's Wort

Inhibitors

Clarithromycin

Erythromycin

Fluconazole

Indinavir

Itraconazole

Ketoconazole (except for topical use)

Nelfinavir

Ritonavir

Saquinavir

Troleandomycin

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Clinical Study Protocol Appendix E

Drug Substance	Quetiapine fumarate
Study Code	D144AC00001
Edition Number	1.0
Date	[redacted]

Appendix E
DSM-IV-TR Diagnostic Criteria For Bipolar I and Bipolar II Disorders

1. DIAGNOSTIC CRITERIA FOR BIPOLAR I DISORDER, MOST RECENT EPISODE DEPRESSED

Diagnostic criteria for 296.50-296.54 Bipolar I Disorder, Most Recent Episode Depressed

(a) Currently (or most recently) in a Major Depressive Episode.

(b) There has previously been at least one Manic Episode or Mixed Episode.

(c) The mood episodes in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Specify (for current or most recent episode):

- Severity/Psychotic/Remission Specifiers
- Chronic
- With Catatonic Features
- With Melancholic Features
- With Atypical Features
- With Postpartum Onset

Specify:

- Longitudinal Course Specifiers (With and Without Inter-episode Recovery)
- With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes)
- With Rapid Cycling

2. DIAGNOSTIC CRITERIA FOR BIPOLAR II DISORDER

Diagnosis of this Bipolar Disorder requires neither a Manic nor a Mixed Episode, but does require at least one episode of hypomania in addition to an episode of Major Depression.

Diagnostic criteria for 296.89 Bipolar II Disorder

(a) Presence (or history) of one or more Major Depressive Episodes.

(b) Presence (or history) of at least one Hypomanic Episode.

(c) There has never been a Manic Episode or a Mixed Episode.

(d) The mood symptoms in Criteria (a) and (b) are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

(e) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify current or most recent episode:

- Hypomanic: if currently (or most recently) in a Hypomanic Episode
- Depressed: if currently (or most recently) in a Major Depressive Episode

Specify (for current or most recent Major Depressive Episode only if it is the most recent type of mood episode):

- Severity/Psychotic/Remission Specifiers
- Chronic
- With Catatonic Features
- With Melancholic Features
- With Atypical Features
- With Postpartum Onset

Specify:

- Longitudinal Course Specifiers (With and Without Inter-episode Recovery)
- With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes)
- With Rapid Cycling

Criteria for a major depressive episode DSM-IV-TR

Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) or (2).

1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (eg, appears tearful). Note: In children and adolescents, can be irritable mood.

2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3. significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

4. Insomnia or Hypersomnia nearly every day

5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6. fatigue or loss of energy nearly every day

7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

The symptoms do not meet criteria for a Mixed Episode.

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).

The symptoms are not better accounted for by Bereavement, ie, after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Criteria for a hypomanic episode DSM-IV-TR

1. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non depressed mood.

2. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

   - inflated self-esteem or grandiosity
   - decreased need for sleep (eg, feels rested after only 3 hours of sleep)
   - more talkative than usual or pressure to keep talking
   - flight of ideas or subjective experience that thoughts are racing
   - distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
   - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   - excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

3. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

4. The disturbance in mood and the change in functioning are observable by others.

5. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

6. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism).

Criteria for a mixed episode DSM-IV-TR

1. The criteria are met both for a Manic Episode and for a Major Depressive Episode (except for duration) nearly every day during at least a 1-week period.

2. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

3. The symptoms are not due to the direct physiological effects of a substance (eg, an illicit drug, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism).

Criteria for a manic episode DSM-IV-TR

1. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary).

2. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

   - inflated self-esteem or grandiosity, potentially including grandiose delusions
   - decreased need for sleep (eg, feels rested after only 3 hours of sleep) or persistent difficulty falling asleep
   - more talkative than usual or pressure to keep talking
   - flight of ideas or subjective experience that thoughts are racing
   - distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
   - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   - excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

3. The symptoms do not meet criteria for a Mixed Episode.

4. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

5. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

AstraZeneca

Clinical Study Protocol Appendix F	
Drug Substance	Quetiapine fumarate
Study Code	D144AC00001
Edition Number	1.0
Date	[redacted]

Appendix F
Blood pressure for boys and girls by age and height percentile

1. BLOOD PRESSURE FOR BOYS BY AGE AND HEIGHT PERCENTILE*

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP = Blood pressure.

* National High Blood Pressure Education Program [NHBPEP] Working Group on Hypertension Control in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program. NIH Publication No. 05-5267. Bethesda, MD; Revised May 2005.

2. BLOOD PRESSURE FOR GIRLS BY AGE AND HEIGHT PERCENTILE*

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP = Blood pressure.

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