AstraZeneca

**Clinical Study Protocol**

| | |
|---|---|
| Drug Substance | quetiapine fumarate |
| Study Code | D1441C00149 |
| Edition No. | 1.0 |
| Date | [redacted] |

# A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

# ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of a medical emergency, contact the Clinical Study Team leader. If the Clinical Study Team leader is not available, contact the Clinical Study Team Physician or the Clinical Study Team Safety Drug Physician at the AstraZeneca Research and Development site shown below.

| | | |
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| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] |
| [redacted] | | [redacted] |

For further clarifications regarding:

- Procedures in case of medical emergency, see Section 9.2.
- Procedures in case of overdose, see Section 9.3.
- Procedures in case of pregnancy, see Section 9.4.

# PROTOCOL SYNOPSIS

## A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

### Investigator

Not applicable

### Study center(s) and number of patients planned

Approximately 330 patients will be screened to obtain 264 evaluable patients, defined as those who have assessments at baseline and at least 1 post-baseline visit. Approximately 30 centers will participate, with an enrollment target of 12 patients per center. It is expected that enrollment will continue for approximately 24 months.

| **Study period** | | **Phase of development** |
|---|---|---|
| Estimated date of first patient enrolled | June 2004 | IIIB |
| Estimated date of last patient completed | July 2006 | |

### Objectives

The primary objective of this study is to compare the efficacy of 2 doses of quetiapine (400 mg/day and 600 mg/day) with that of placebo in the treatment of bipolar mania in children and adolescent patients with Bipolar I disorder, as assessed by the change from baseline to Day 21 in the Young Mania Rating Scale (YMRS) total score (primary outcome variable). The primary hypotheses are as follows:

1. Quetiapine 400 mg/day is superior to placebo in reducing YMRS total score at Day 21 compared with baseline

2. Quetiapine 600 mg/day is superior to placebo in reducing YMRS total score at Day 21 compared with baseline

Secondary objectives are as follows:

1. To compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on a broad range of mania symptoms, as assessed by

    the change from baseline to Day 21 in the Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness score

    the CGI-BP Global Improvement score at Day 21

    the percentage of patients with remission, defined as a YMRS total score ≤12 at Day 21

    the percentage of patients with response, defined as a ≥50% reduction from baseline in the YMRS total score, at Days 4, 7, and 21

    the change from baseline to Day 4 and to Day 7 in the CGI-BP Severity of Illness score and YMRS

2. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on level of functioning, as assessed by the change from baseline to Day 21 in the Children's Global Assessment Scale (CGAS) total score

3. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on depressive symptoms, as assessed by the change from baseline to Day 21 in the Children's Depression Rating Scale-Revised (CDRS-R) total score

4. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on agitation and aggression, as assessed by

    the change from baseline to Day 21 in the Overt Aggression Scale-Modified (OAS-M) total score

    the changes from baseline to Day 4 and to Day 7 in the OAS-M total score

    the changes from baseline to Day 21 in the scores for YMRS items 5 and 9 (irritability and disruptive-aggressive behavior, respectively)

5. to evaluate the safety and tolerability of quetiapine compared with placebo in the treatment of bipolar mania in children and adolescent patients with Bipolar I disorder, as assessed by

    the incidence and nature of overall adverse events (AEs)

    the incidence of emergent depression, defined as a CDRS-R total score ≥40, at Day 21 for patients whose baseline CDRS-R score was <40

the changes from baseline to Day 21 in clinical laboratory test results (eg, prolactin concentration), vital signs, weight, body mass index (BMI), and electrocardiogram (ECG) results

the change from baseline to Day 21 in the Simpson-Angus Scale (SAS) total score

the change from baseline to Day 21 in the Barnes Akathisia Rating Scale (BARS) global score

the change from baseline to Day 21 in the Abnormal Involuntary Movement Scale (AIMS) total score

the incidence of anticholinergic medication use for treatment of emergent extrapyramidal symptoms (EPS)

Exploratory objectives are as follows:

1. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on sleep, as assessed by

   the changes from baseline to each assessment in the YMRS sleep-item score

   the changes from baseline to each assessment in the CDRS-R sleep-item score

2. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on overall caregiver burden, as assessed by the changes from baseline to Day 21 in the results of the Caregiver Strain Questionnaire (CGSQ)

3. to establish a panel of DNA samples from those patients who provide separate consent, to enable future exploratory genetic research on potential associations with drug response (efficacy and safety/tolerability) and/or susceptibility to bipolar disease

**Study design**

This is a 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 600 mg/day) with placebo in patients aged 10 to 17 years with bipolar I mania. Patients will be randomly assigned to blinded study treatment in a 1:1:1 ratio within age strata (10 to 12 years and 13 to 17 years). Double-blind treatment will be preceded by a medication washout period of 1 to 28 days (depending on the medications involved and at the discretion of the investigator) during which time the patient may be hospitalized if deemed clinically necessary. The patient may be treated as an inpatient or outpatient throughout the course of the study, according to the clinical judgment of the investigator. Upon completing double-blind treatment, patients may enter an open-label study (D1441C00150) designed to assess the safety and tolerability of quetiapine for up to 6 months.

**Target patient population**

The study will recruit male and female inpatients and outpatients, aged 10 to 17 years, with a DSM-IV diagnosis of Bipolar I mania as confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version (K-SADS-PL). A YMRS total score of ≥20 at both screening and randomization is required.

**Investigational product, dosage and mode of administration**

Quetiapine tablets will be administered orally in blinded fashion. Treatment will begin with a 50-mg dose on the evening of Day 1. The dose will be escalated daily in increments of 100 mg thereafter, to reach a target fixed dose of 400 mg/day by Day 5 or 600 mg/day by Day 7, according to randomized treatment assignment. Study treatment should be administered twice daily. However, in the event of tolerability issues, if deemed necessary in the clinical judgment of the investigator, study treatment may be administered 3 times daily according to the instructions on the study medication card.

**Comparator, dosage and mode of administration**

Placebo to match 25-mg and 100-mg quetiapine tablets will be administered orally in blinded fashion, according to randomized treatment assignment. Study treatment should be administered twice daily. However, in the event of tolerability issues, if deemed necessary in the clinical judgment of the investigator, study treatment may be administered 3 times daily.

**Duration of treatment**

This study will begin with a washout period of 1 to 28 days for patients who are taking medications not permitted by the protocol. Qualified patients will be randomized on Day 1 to 1 of 3 treatment groups: quetiapine 400 mg/day, quetiapine 600 mg/day, or placebo. Randomization and subsequent dosage regimen will be stratified by age (10 to 12 years or 13 to 17 years). The total duration of double-blind treatment will be 21 days. Patients who complete the 3 weeks of double blind treatment will be given the option to enter an open-label study (D1441C00150) that will assess the safety and tolerability of quetiapine for up to 6 months.

**Early rescue from double-blind treatment**

Patients must be discontinued from double-blind treatment or hospitalized if they meet the following criteria:

- worsening of symptoms at Day 14 or later as indicated by a CGI-BP Global Improvement score of 6 (much worse) or more

Patients who are discontinued due to worsening of their symptoms according to the above criteria may be given the option to enter the 6-month, open-label, quetiapine safety and tolerability study (D1441C00150), if the investigator believes they will benefit from quetiapine treatment.

Patients who are discontinued from double-blind treatment due to an adverse event that was not related to quetiapine and that occurs after Day 14, may be given the option to enter the 6-month, open-label, quetiapine safety and tolerability study (D1441C00150), if the investigator believes they will benefit from quetiapine treatment.

**Outcome variables**

- **Efficacy**

  **Primary outcome variable**: change in YMRS total score from baseline to Day 21

  **Secondary outcome variables**:

  Changes from baseline to each corresponding visit in the following assessment scores: YMRS total (Days 4, and 7), YMRS individual items (Days 4, 7, and 21), CGI-BP Severity of Illness (Days 4, 7, and 21), CGAS (Day 21), CDRS-R (Day 21), and OAS-M (Days 4, 7, and 21)

  Percentage of patients with remission, defined as a YMRS total score ≤12 at Day 21

  Percentage of patients with response, defined as a ≥50% reduction from baseline in the YMRS total score, at Days 4, 7, and 21

  CGI-BP Global Improvement score at Day 21

- **Patient Reported Outcomes (PROs)**

  Change from baseline to Day 21 in overall caregiver burden, as assessed by the CGSQ

- **Health Economics (not applicable)**

This study does not include health economics assessments.

- **Pharmacokinetic (not applicable)**

This study does not include pharmacokinetic assessments.

- **Pharmacodynamic (not applicable)**

This study does not include pharmacodynamic assessments.

- **Safety**

  incidence and nature of AEs

the incidence of emergent depression, defined as a CDRS-R total score ≥40

changes from baseline to each visit, when measured, in clinical laboratory test results (eg, prolactin concentration) and ECG results

changes from baseline to each visit in vital signs, weight, and BMI

changes from baseline to each visit in SAS, BARS, and AIMS scores

the incidence of anticholinergic medication use to treat emergent EPS

- **Genetic**

  exploratory research may be performed to test for association between genetic polymorphisms and drug response (ie, the above efficacy and safety/tolerability endpoints) and/or susceptibility to bipolar disease

**Statistical methods**

Efficacy analyses will be based on the intent to treat (ITT) population, which will comprise patients who have baseline and at least 1 set of post-baseline assessments. Safety analyses will include all patients who took at least 1 dose of study treatment.

The primary outcome variable, change from baseline in YMRS total score at Day 21, will be analyzed using repeated-measures analysis. If a patient withdraws from the study before Day 21, the observations from the final assessment will be carried forward (last observation carried forward, [LOCF]). The 2 contrasts of interest will be the 400-mg/day and 600-mg/day quetiapine groups versus the placebo group, and the Simes-Hommel step-up procedure will be used for adjustment of the 2 primary comparisons.

The secondary outcome variables, changes from baseline in CGI-BP Severity of Illness, CDRS-R, OAS-M, and SAS, BARS, and AIMS scores, and prolactin blood levels will also be analyzed using repeated-measures analysis. The CGI-BP Global Improvement score will also be analyzed via repeated-measures analysis, using the baseline CGI Severity of Illness score as a covariate. Analysis of covariance (ANCOVA) will be used to assess changes from baseline in CGAS and CGSQ. Generalized estimating equations (GEE) will be used to assess the differences between quetiapine and placebo in the rates of YMRS response and YMRS remission. The impact of psychostimulant use will be assessed by including a covariate for psychostimulant use and a term for psychostimulant use by treatment interaction in the appropriate secondary models for exploratory purposes only. Logistic regression will be-used-to assess the incidence of anticholinergic use between quetiapine and placebo. All laboratory test results, ECG results, vital signs, weight measurements and BMI 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 will be reported. Descriptive statistics for continuous data will include n, mean, median, standard deviation, and minimum and maximum values. Descriptive statistics for categorical data will include n, frequency, and percentage.

For all changes from baseline variables, baseline will be defined as the latest value prior to or on the same day of randomization.

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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 4.7) |
| AIMS | Abnormal Involuntary Movement Scale |
| ALT | Alanine transaminase |
| ANC | Absolute neutrophil count |
| ANCOVA | Analysis of covariance |
| Assessment | An observation made on a variable involving a subjective judgement (assessment) |
| AST | Aspartate transaminase |
| AstraZeneca | AstraZeneca Pharmaceuticals LP; the sponsor |
| β-hCG | The β subunit of human chorionic gonadotropin (hCG) |
| BARS | Barnes Akathisia Rating Scale |
| BMI | Body mass index; (weight in kg)/(height in meters)$^2$ |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CDRS-R | Children's Depression Rating Scale-Revised |
| CGAS | Children's Global Assessment Scale |
| CGI | Clinical Global Impression |
| CGI-BP | Clinical Global Impression – Bipolar |
| CGSQ | Caregiver Strain Questionnaire |
| CRF | Case Report Form |
| CYP | Cytochrome P450 |
| DM | Diabetes Mellitus |
| DNA | Deoxyribonucleic acid |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, 4$^{th}$ edition |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| ECT | Electroconvulsive therapy |

| Abbreviation or special term | Explanation |
|---|---|
| End of study | Date on which database lock occurs |
| EPS | Extrapyramidal symptoms |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GEE | Generalized estimating equations |
| GRand | AstraZeneca Global Randomization System |
| HbA1c | Glycosylated Hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IQ | Intelligence quotient |
| IRB | Institutional Review Board |
| ITT | Intent to treat |
| International Coordinating investigator | If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the investigators and/or activities internationally. |
| K-SADS-PL | Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version |
| LOCF | Last observation carried forward |
| Measurement | An observation made on a variable using a measurement device |
| MedDRA | Medical Dictionary for Regulatory Affairs |
| MAOI | Monoamine Oxidase Inhibitor |
| NDA | New Drug Application |
| NOS | Not otherwise specified |
| PDD | Pervasive Developmental Disorders |
| PTSD | Post-traumatic Stress Disorder |
| OAE | Other significant Adverse Event (ie, an adverse event of special interest in this clinical development; see definition in Section 4.7). The classification of OAEs will be performed by AstraZeneca drug safety physicians after the study is complete. |
| OAS-M | Overt Aggression Scale - Modified |
| OL | Open label |
| Outcome variable | A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective |

| Abbreviation or special term | Explanation |
|---|---|
| PP | Per protocol |
| Parameter | A quantity (usually unknown) that characterizes the distribution of a variable in a population of patients |
| Principal investigator | A person responsible for the conduct of a clinical study at an investigational study center. Every investigational study center has a principal investigator. |
| SAE | Serious adverse event (see definition in Section 4.7) |
| SAS | Simpson-Angus Scale |
| SAS® | SAS software (statistical analysis software used for analysis) |
| SD | Standard deviation |
| T4 | Thyroxine |
| TSH | Thyroid-stimulating hormone |
| Variable | A characteristic or a property of a patient that may vary eg, from time to time or between patients |
| YMRS | Young Mania Rating Scale |
| WBC | White blood cell (count) |

# 1. INTRODUCTION

## 1.1 Background

Quetiapine fumarate is a dibenzothiazepine derivative that is designated chemically as 2-(2-[2-(4-(dibenzo [*b*,*f*] [1,4]thiazepin-11-yl-1 piperazinyl)ethoxy]-ethanol] fumarate (2:1). This atypical antipsychotic was developed by AstraZeneca and was approved by the Food and Drug Administration (FDA) on 26 September 1997 for the treatment of schizophrenia in the dose range of 150 mg/day to 800 mg/day, administered in 2 or 3 divided doses.

An open-label study conducted by AstraZeneca in 10 adolescent patients, aged 12 to 16 years, with psychotic disorders (Study 5077IL/0038) indicated that the pharmacokinetic profile of quetiapine was similar in adolescents and adults. The study results also indicated that quetiapine, at doses of up to 800 mg/day, was generally well tolerated and safe in this patient population. The most frequently reported adverse events (AEs) were postural tachycardia (9 patients) and insomnia (5 patients). There were no serious AEs (SAEs) and no withdrawals due to AEs. The results of this study were published by McConville et al in 2000.

A subsequent clinical study program conducted in adult patients with acute bipolar mania has shown quetiapine to have a beneficial effect on manic symptoms, with a safety profile similar to that observed in patients with schizophrenia. As a result, on 11 January 2004, the FDA approved the use of quetiapine for the short-term treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex.

Bipolar disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive (Lish et al 1994). While onset of bipolar disorder most commonly occurs in adolescence or early adulthood, 20% to 40% of adults with bipolar disorder report onset during childhood (Lish et al 1994). The estimated prevalence among children and adolescents aged 9 to 17 years is 1.2% (Kessler et al 1994). Children and adolescents with bipolar mania, like affected adults, have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family (Findling et al 2003, Papolos and Papolos 1999). Adolescents with bipolar disorder have an increased risk of substance-abuse disorders (Wilens et al 1999). Because bipolar disorder is often manifest early in life and has been associated with poor outcomes, there is a need for early recognition of the disorder and effective treatments for young patients (Strober et al 1995, Geller et al 2002).

For adults with bipolar mania, FDA-approved treatment options include the mood stabilizers lithium and divalproate and the atypical antipsychotics quetiapine and olanzapine. Conventional antipsychotics, such as haloperidol, are used to treat acute mania, but their utility is limited because of the risk of extrapyramidal side effects (Hunt and Silverstone 1991, Kane 1988, Baldessarini et al 1988, Mukherjee et al 1986). There are currently no agents

specifically approved by the FDA for treatment of bipolar mania in patients across the entire age range of 10 to 17. Published studies suggest that lithium and divalproate may be effective treatments for some children and adolescents with mania, but many patients in these studies did not respond to mood-stabilizer treatment (Geller et al 2000, Kowatch et al 2000, West et al 1995). In addition, these agents require blood monitoring to maintain therapeutic levels and avoid toxicity. Lithium treatment may be associated with such adverse effects as impaired thyroid function, tremor, and acne. Divalproate treatment may be associated with hepatotoxicity or pancreatitis (PDR® 2002-2003).

The reported efficacy and relative safety of atypical antipsychotics in adults with acute bipolar mania suggest that these medications may offer an important treatment option for children and adolescents. A recently reported double-blind, randomized, placebo-controlled study of quetiapine as adjunctive therapy with divalproex in adolescent patients with acute bipolar mania reported by DelBello et al (2002) showed that treatment with quetiapine and divalproex was more effective than treatment with divalproex alone, as indicated by reductions from baseline Young Mania Rating Scale (YMRS; Young et al 1978) scores. Published case series indicate that risperidone and olanzapine may effectively treat manic symptoms as monotherapy or as adjunctive therapy with a mood stabilizer (Chang and Ketter 2000, Frazier et al 1999, Soutullo et al 1999).

This study will compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo in patients aged 10 to 17 who have bipolar mania.

## 1.2 Rationale for this study

The demonstrated efficacy and safety of quetiapine in adults with bipolar mania and the similarity of the pharmacokinetics of quetiapine in adults and younger patients suggest that quetiapine could be an effective and safe treatment for bipolar mania in children and adolescents.

AstraZeneca has received from the FDA a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act, for pediatric information on quetiapine. The Written Request, dated 11 February 2003, specifically asked that AstraZeneca conduct a randomized, double-blind, parallel-group, placebo-controlled efficacy study in patients aged 10 to 17 years who have bipolar mania as part of Bipolar I disorder. This study has been designed to provide the FDA with the information specified in the Written Request.

Extensive evidence indicates that, for many drugs, variation within genes controlling absorption, metabolism, distribution, and elimination can strongly influence pharmacokinetics. Similarly, genetic factors are implicated in susceptibility to adverse effects of many drugs. Finally, family studies have consistently implicated genetic factors in the etiology of bipolar disease. Thus, deoxyribonucleic acid (DNA) samples will be collected from patients who provide separate, optional consent to genetic research so that genetic studies of response to study drug and susceptibility to psychotic disorders can be carried out in an exploratory manner at a later time.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

The primary objective of this study is to compare the efficacy of 2 doses of quetiapine (400 mg/day and 600 mg/day) with that of placebo in the treatment of bipolar mania in children and adolescent patients with Bipolar I disorder, as assessed by the change from baseline to Day 21 in the YMRS total score (primary outcome variable). The primary hypotheses are as follows:

1. Quetiapine 400 mg/day is superior to placebo in reducing YMRS total score at Day 21 compared with baseline

2. Quetiapine 600 mg/day is superior to placebo in reducing YMRS total score at Day 21 compared with baseline

## 2.2 Secondary objectives

The secondary objectives of the study are as follows:

1. To compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on a broad range of mania symptoms, as assessed by

   the change from baseline to Day 21 in the Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness score (Spearing et al 1997)

   the CGI-BP Global Improvement score at Day 21

   the percentage of patients with remission, defined as a YMRS total score of ≤12 at Day 21

   the percentage of patients with response, defined as a ≥50% reduction from baseline in the YMRS total score, at Days 4, 7 and 21

   the change from baseline to Day 4 and to Day 7 in the CGI-BP Severity of Illness score and YMRS

2. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on level of functioning, as assessed by the change from baseline to Day 21 in the Children's Global Assessment Scale (CGAS) total score (Shaffer et al 1983)

3. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on depressive symptoms, as assessed by the change from baseline to Day 21 in the Children's Depression Rating Scale-Revised (CDRS-R) total score (Poznanski et al 1985)

4. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on agitation and aggression, as assessed by

    the change from baseline to Day 21 in the Overt Aggression Scale-Modified (OAS-M) total score (Coccaro et al 1991)

    the changes from baseline to Day 4 and to Day 7 in the OAS-M total score

    the changes from baseline to Day 21 in the scores for YMRS items 5 and 9 (irritability and disruptive-aggressive behavior, respectively)

5. to evaluate the safety and tolerability of quetiapine compared with placebo in the treatment of bipolar mania in children and adolescent patients with Bipolar I disorder, as assessed by

    the incidence and nature of overall AEs

    the incidence of emergent depression, defined as a CDRS-R total score ≥40, at Day 21 for patients whose baseline CDRS-R score was <40

    the changes from baseline to Day 21 in clinical laboratory test results (eg, prolactin concentration), vital signs, weight, body mass index (BMI), and electrocardiogram (ECG) results

    the change from baseline to Day 21 in the Simpson-Angus Scale (SAS) total score (Simpson and Angus 1970)

    the change from baseline to Day 21 in the Barnes Akathisia Rating Scale (BARS) global score (Barnes 1989)

    the change from baseline to Day 21 in the Abnormal Involuntary Movement Scale (AIMS) total score (Guy 1976)

    the incidence of anticholinergic medication use for treatment of emergent extrapyramidal symptoms (EPS)

## 2.3 Exploratory objectives

The following are exploratory objectives of this study:

1. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on sleep, as assessed by

    the changes from baseline to each assessment in the YMRS sleep-item score

    the changes from baseline to each assessment in the CDRS-R sleep-item score

2. to compare the effects of quetiapine 400 mg/day and quetiapine 600 mg/day with the effect of placebo on overall caregiver burden, as assessed by the changes from baseline to Day 21 in the results of the Caregiver Strain Questionnaire (CGSQ; Brannan et al 1997).

3. to establish a panel of DNA samples from those patients who provide separate consent, to enable future exploratory genetic research on potential associations with drug response (efficacy and safety/tolerability) and/or susceptibility to bipolar disease

# 3. STUDY PLAN AND PROCEDURES

## 3.1 Overall study design and flow chart

This is a 3-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo in patients aged 10 to 17 years with bipolar I mania who are either hospitalized or are outpatients. The study will be preceded by a medication washout period of 1 to 28 days based on the current medications at screening. Approximately 330 patients will be screened to obtain 264 evaluable patients, defined as those who have assessments at baseline and at least 1 post-baseline visit. Approximately 30 centers will participate, with an enrollment target of approximately 12 patients per center. Patients must have a YMRS total score ≥20 at screening and baseline and a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; American Psychiatric Association 2000) diagnosis of Bipolar I as confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL; Kaufman et al 1997).

The screening and washout period, double-blind treatment period, and optional entrance into open-label study are described below:

- Screening and Washout period (1 to 28 days)

  Eligible patients (10 to 17 years of age) will have YMRS, K-SADS-PL, and safety evaluations performed at screening. Patients who qualify for enrollment will discontinue all prohibited medications (Section 3.4.4.1, Table 4) and undergo a washout period of 1 to 28 days, depending on the medications discontinued. If the washout period is 14 days or longer, baseline safety assessments must be repeated at the end of the washout period. If deemed clinically necessary, the patient may be treated as an inpatient or outpatient during this period.

- Double-blind randomized treatment period (Days 1 to 28)

  Qualified patients will be randomized at Day 1 to 1 of 3 treatment groups: quetiapine 400 mg/day, quetiapine 600 mg/day, or placebo. The patient may be treated as an inpatient or outpatient, according to the clinical judgment of the investigator. Baseline assessments will be performed before the first dose of study

medication is given on Day 1. Study treatment will be given twice daily and will begin with an initial dose of 50 mg of quetiapine or matching placebo on the evening of Day 1. The dose will then be escalated as shown in Table 3 to reach the target fixed dose. If deemed necessary in the clinical judgment of the investigator, in the event of tolerability issues, study treatment may be administered 3 times daily. No single dose shall be greater than 400 mg. The total duration of double-blind treatment will be 21 days. YMRS assessments (used to evaluate the primary efficacy variable) will be performed on Days 1, 4, 7, 14, and 21. The complete schedule of assessments is shown in Table 1. The end of the double-blind study will be defined as the date on which database lock occurs.

- Optional entrance into a 6-month, open-label (OL) study (D1441C00150) of the safety and tolerability of quetiapine.

  Patients who complete the double-blind study and who in the investigator's clinical judgment may benefit from quetiapine treatment will be given the option to enter the OL study.

  Patients must be discontinued from double-blind treatment or hospitalized if they meet the following criteria:

  worsening of symptoms at Day 14 or later as indicated by a CGI-BP Global Improvement score of 6 (much worse) or more

Patients who are discontinued due to worsening of their symptoms according to the above criteria may be given the option to enter the 6-month, open-label, quetiapine safety and tolerability study (D1441C00150), if the investigator believes they will benefit from quetiapine treatment.

Patients who are discontinued from double-blind treatment due to an adverse event that was not related to quetiapine and that occurs after Day 14, may be given the option to enter the 6-month, open-label, quetiapine safety and tolerability study (D1441C00150), if the investigator believes they will benefit from quetiapine treatment.

## Table 1 Study plan: washout period and double-blind treatment

| **Study plan** | **Screening** | **Washout period** | **Randomization[b]** | **Double-blind treatment** | | | |
|---|---|---|---|---|---|---|---|
| **Visit[a]** | **1** | **Up to 28 days** | **2** | **3** | **4** | **5** | **6[c]/Final** |
| **Day** | **Screening** | | **1** | **4** | **7** | **14** | **21** |
| Informed consent, assent, and demography, history | √ | | | | | | |
| Inclusion/exclusion criteria | √ | | √ | | | | |
| Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) | √ | | | | | | |
| Physical examination[d] | √ | | | | | | √ |
| Tanner Staging | √ | | | | | | √ |
| Vital signs[f], height, weight, temperature | √[e] | | √ | √ | √ | √ | √ |
| 12-lead electrocardiogram | √[e] | | | | | | √ |
| Laboratory tests to include all of the following:<br>Clinical chemistry[g] including including lipid panel<br>HbA1c<br>Thyroid function and prolactin concentration<br>Hematology[h]<br>β hCG[i] | √[e] | | | | | | √ |
| Genetic Sampling[j] | √ | | | | | | |
| Urine drug screen and urinalysis | √ | | | | | | √ |
| Young Mania Rating Scale (YMRS) | √ | | √ | √ | √ | √ | √ |
| Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness and Global Improvement items[k] | | | √ | √ | √ | √ | √ |
| Children's Depression Rating Scale – Revised (CDRS-R) | | | √ | √ | √ | √ | √ |
| Overt Aggression Scale – Modified (OAS-M) | | | √ | √ | √ | √ | √ |
| Children's Global Assessment Scale (CGAS) | | | √ | | | | √ |
| Caregiver Strain Questionnaire (CGSQ)[l] | | | √ | | | | √ |

## Table 1 Study plan: washout period and double-blind treatment

| Study plan | Screening | Washout period | Randomization[b] | Double-blind treatment | | | |
|---|---|---|---|---|---|---|---|
| **Visit[a]** | **1** | **Up to 28 days** | **2** | **3** | **4** | **5** | **6[c]/Final** |
| **Day** | **Screening** | | **1** | **4** | **7** | **14** | **21** |
| Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) | | | √ | | √ | √ | √ |
| Adverse event recording | √ | | √ | √ | √ | √ | √ |
| Prior and concomitant medication recording | √ | | √ | √ | √ | √ | √ |
| Study drug dispensing | | | √[m] | √ | √ | √ | |
| Drug accountability and treatment compliance | | | | √ | √ | √ | √ |

[a] Visit window: ± 3 days of scheduled visit date.
[b] Study drug will be titrated up starting at Day 1 (see Table 5).
[c] End of double-blind treatment.
[d] Physical exam includes routine ophthalmologic assessment at Screening and on Day 21 or final visit.
[e] Assessment to be repeated only if washout period is ≥14 days.
[f] Blood pressure and pulse rate will be obtained in supine and standing positions.
[g] Blood samples collected for clinical chemistry should be obtained under fasting conditions. Fasting is defined as not having ingested food or liquids other than water for ≥8 hours. Fasting blood sample should be drawn between 8:00 AM and 10:00 AM.
[h] If the patient presents with a fever, pharyngitis, or other signs and symptoms of infection at any time, a CBC with differential should be completed.
[i] For female patients only and may be completed at any visit based on discussion with the patient.
[j] Genetic sampling is optional for both sites and patients at anytime during the study.
[k] The CGI-BP Global Improvement item which assesses change from baseline will not be recorded at randomization.
[l] To be completed by parent and legal guardian during visit.
[m] The first dose of study medication will be taken on the evening of Day 1, which must occur no more than 10 days after baseline safety assessments are obtained.

## 3.2 Rationale for study design, doses and control groups

This study was designed in accordance with the criteria outlined in a Written Request from the Food and Drug Administration dated 11 February 2003. As part of the request to provide pediatric information about quetiapine, the FDA asked that AstraZeneca conduct a randomized, double-blind, parallel-group, placebo-controlled efficacy study in patients aged 10 to 17 years who have bipolar mania as part of Bipolar I disorder with a minimum treatment duration of 3 weeks and evaluation of at least 2 fixed doses of quetiapine in either a monotherapy or adjunct-therapy setting.

This study will evaluate quetiapine as monotherapy rather than as adjunct therapy to simplify the study and thereby maximize the potential to detect any quetiapine effect. In addition, this design avoids use of adjunctive antimanic agents (ie, lithium and divalproex) that are not specifically approved for use in the entire age range included in this study and have the potential to increase side-effect liability.

Study patients will be randomized to treatment for 21 days with quetiapine 400 mg/day, quetiapine 600 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 worsenings 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 patient.

The primary outcome variable is the change from baseline in YMRS total score after 3 weeks of treatment. The selected study duration, quetiapine doses, and primary outcome variable are based on the results of the 2 monotherapy studies in adults included in sNDA 20-639/S-016 (Studies 5077IL/0104 and 5077IL/0105), which was approved by the FDA on 11 January 2004. In both of these studies, quetiapine showed a statistically significant decrease in YMRS score compared with placebo at 3 weeks. The effective dose of quetiapine in the adult monotherapy studies was in the range of 400 mg/day to 800 mg/day, and the mean last-week median dose was approximately 600 mg. Because the results of Study 5077IL/0038 indicated that the pharmacokinetics of quetiapine are similar in adults and younger patients, the doses chosen for this study are consistent with the doses shown to be effective in adults with bipolar mania.

The YMRS, used to assess the primary outcome, is a validated and reliable scale widely used in clinical studies to rate mania in adults (Young et al 1978). In addition, the YMRS has been deemed an acceptable instrument for rating mania in children and adolescents by a group of experts convened by the American Academy of Child and Adolescent Psychiatry to achieve consensus on methodology for clinical studies of children and adolescent patients with bipolar disorder (the Consensus Conference; Carlson et al 2003).

The age range for eligible patients was specified by the FDA in its Written Request. It is expected that the ages of randomized patients will reflect the natural age distribution of children and adolescents with bipolar disorder.

Accurate diagnosis of bipolar mania 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 (Findling et al 2003, Papolos and Papolos 1999). This study will employ the K-SADS-PL at screening to confirm the presence of DSM-IV criteria for mania in eligible patients. The K-SADS-PL is a validated and reliable semi-structured diagnostic interview that assesses current and past episodes of psychopathology, including mania, in the target population and was noted as a diagnostic tool by the Consensus Conference (Kaufman et al 1997, Carlson et al 2003).

To ensure accurate diagnosis, the K-SADS-PL, will be conducted only by an adequately trained clinician (eg, child psychiatrist or child psychologist).

Patients with a comorbid diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD) will also be eligible for this study and, if enrolled, may continue treatment with a stable dose of a psychostimulant as specified in Section 3.4.4.1. Children and adolescents with bipolar disorder frequently also have ADHD, and the prevalence of ADHD has been reported to be more than 90% among the younger patients in this population (Wozniack et al 1995, Faraone et al 1997, Geller et al 2000). While the Consensus Conference recommendation is to discontinue and wash out any psychostimulants before study treatment begins, such a restriction would likely limit the enrollment and retention of younger patients in this study.

## 3.3 Selection of study population

### 3.3.1 Study selection record

The investigator must keep a record of patients who were considered for enrollment but were never enrolled (eg, who were prescreened without formal consent).

Each patient who is enrolled will be assigned a unique, sequential number. Enrollment numbers will begin with the letter "E," followed by a 7-digit number comprising a 4-digit center number and a 3-digit patient number in the series beginning with 201. This enrollment number will identify the patient throughout his or her study participation, regardless of eligibility for randomization. If the patient is not randomized, the reason for screen failure will be reported on the termination case report form (CRF).

### 3.3.2 Inclusion criteria

For inclusion in the study, patients must fulfill all of the following criteria:

1. Provision of written informed consent by one or both parents or by legal guardian prior to any study procedure

2. Provision of written assent by the patient prior to any study procedure

3. Male or female, aged 10 to 17 year at randomization, hospitalized or outpatient

4. If female and of childbearing potential, must be using a reliable method of contraception. Reliable methods may include abstinence, hormonal contraceptives (eg, oral contraceptive or long-term injectable or implantable hormonal contraceptive), double-barrier methods (eg, condom and diaphragm, condom and foam, condom and sponge), intrauterine devices, and tubal ligation.

5. All female patients will need to have the absence of pregnancy confirmed by a negative serum beta hCG before randomization

6. DSM-IV criteria for Bipolar I mania (Appendix C) confirmed by the K-SADS-PL. Patients with rapid cycling or who are experiencing a first manic episode may be included. Patients may also have a secondary diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD). Patients with ADHD may, if judged necessary by the investigator, continue psychostimulant treatment if the prescribed dose has been stable for ≥30 days preceding randomization.

7. Willingness to agree not to harm self

8. YMRS score of ≥20 both at screening and at randomization (Day 1)

9. Have a parent or legal guardian who will accompany the patient at each scheduled study visit, can provide reliable information, and can be responsible for receiving and dispensing study medication

10. Willingness to adhere to the schedule of assessments

### 3.3.3 Exclusion criteria

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

1. Diagnosis of a current DSM-IV 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) PTSD, Panic Disorder, and Pervasive Developmental Disorders (eg, Autistic Disorder and Asperger's Disorder).

2. Premorbid intelligence quotient (IQ) <70 or diagnosis of mental retardation

3. Psychosis judged to be the direct physiological consequence of a medical condition or treatment. These conditions include degenerative neurological conditions (eg, Parkinson's disease, Huntington's disease), cerebrovascular disease (eg, stroke), metabolic conditions (eg, vitamin B12 deficiency), autoimmune. conditions (eg, systemic lupus erythematosis), viral or other infections (eg, hepatitis, mononucleosis, human immunodeficiency), and cancers.

4. Psychosis judged to be the direct physiological effect (eg, intoxication, withdrawal) of an abused medication or substance

5. Current manic episode judged to be the direct physiological effect of psychostimulant or antidepressant medication

6. History of any serious suicide attempt that required medical intervention or current suicidal risk that cannot be safely managed as determined by the clinical judgment of the investigator

7. Serious homicidal risk or homicidal behaviors within the past 3 months that resulted in adjudication

8. Known intolerance for or lack of response to quetiapine, as judged by the investigator

9. For female patients, pregnancy or lactation

10. Substance abuse or dependence (Appendix D) including alcohol (except for caffeine or nicotine dependence), as defined in DSM-IV, within 1 month prior to screening

11. Inability to discontinue psychoactive medications (see Section 3.4.4.1, Table 4) prior to randomization

12. Use of haloperidol decanoate, fluphenazine decanoate or risperidone microspheres within 1 dosing interval prior to randomization

13. Electroconvulsive therapy (ECT) within 30 days prior to screening

14. Use of potent cytochrome P450 (CYP) 3A4 inhibitors (eg, ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir) in the 14 days preceding randomization

15. Use of potent CYP 3A4 inducers (eg, phenytoin, carbamazepine, barbiturates, rifampin, glucocorticoids, Saint John's Wort) in the 14 days preceding randomization

16. Thyroid-stimulating (TSH) hormone concentration more than 10% above the upper limit of the normal range

17. Laboratory test results outside the reference range and considered by the investigator to be clinically significant

18. Baseline $QT_c$ interval (Fridericia formula; Puddu 1988) ≥450 milliseconds at baseline

19. Renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other disease or clinical finding that is unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication

20. Unstable Diabetes Mellitus (DM) with a baseline Glycosylated Hemoglobin (HbA1c) ≥8.5

21. Patients admitted to a hospital for treatment of diabetes or diabetes related illness in past 12 weeks

22. Not under the care of a physician responsible for the patient's DM care

23. DM clinically unstable in the opinion of the physician responsible for the patient's participation in the study

24. The patient has not been on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period should not be less than 8 weeks.

25. A patient taken insulin whose daily dose on one occasion in the past 4 weeks has been more than 10% above or below their mean dose in the preceding 4 weeks

26. If the patient's CBC with WBC differential shows an ANC < $1.0 \times 10^9$/L, repeat the test within 24 hours. If the remains < $1.0 \times 10^9$/L, the patient will be excluded.

27. Medical condition that would affect absorption, distribution, metabolism, or excretion of study medication

28. History of seizure disorder, except febrile convulsions

29. Use of experimental drug within 30 days of randomization (Day 1)

30. Previous participation in this study

31. Significant medical illness which could prevent patient from completing double-blind treatment

32. Patients with asthma treated with oral steroids within 3 months prior to randomization

33. Concurrent cognitive-behavioral therapy initiated within 6 weeks prior to randomization

### 3.3.4 Restrictions

Use of concomitant medications is restricted as detailed in Section 3.4.4.2, Table 5.

Any current course of cognitive-behavioral therapy initiated more than 6 weeks before randomization may be continued. Initiation of cognitive-behavioral therapy is prohibited within 6 weeks prior to randomization and thereafter. This does not exclude behavioral treatments aimed specifically at the management of ADHD symptoms.

### 3.3.5 Discontinuation of patients from treatment or assessment

#### 3.3.5.1 Criteria for discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are as follows:

1. Voluntary discontinuation by the patient who are at any time free to discontinue their participation in the study, without prejudice to further treatment

2. Voluntary discontinuation by the patient's parent or legal guardian who are at any time free to discontinue their child's participation in the study, without prejudice to further treatment

3. Safety reasons as judged by the investigator and/or AstraZeneca

4. Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca

5. Incorrect enrollment or randomization of the patient only after consultation with AstraZeneca (eg, if a risk or discomfort for the patient)

6. Unwillingness to be hospitalized as recommended by the investigator

7. The patient has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca, or the patient, the patient's parents, or legal representative

8. If the patient's CBC with WBC differential shows an ANC $< 1.0 \times 10^9$/L, repeat the test within 24 hours. If it remains $< 1.0 \times 10^9$/L, the patient must be discontinued.

9. The patient has worsening of symptoms at Day 14 or later, as indicated by a CGI-BP Global Improvement score of 6 (much worse) or more (patient must be withdrawn)

10. The patient is unable to comply with the restrictions on the use of concomitant

11. Medications as detailed in Section 3.4.4.2

12. The patient is unable to tolerate the assigned dose of study medication

13. The patient becomes pregnant

#### 3.3.5.2 Incorrect assignment of enrollment or randomization numbers

If a patient enrollment or randomization number is allocated incorrectly, no attempt should be made to change the treatment, and AstraZeneca personnel should be notified immediately. Subsequent patient numbers should be allocated according to the original allocation sequence.

#### 3.3.5.3 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and about the presence of any AEs. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up and investigational products should be returned by the patient's parents or legal guardian.

If a patient withdraws from the study, all assessments required on Day 21 will be conducted whenever possible. Any patient who withdraws and has clinically significant or abnormal results for any safety assessments will have a follow-up visit 1 week after withdrawal and at appropriate intervals thereafter, as determined by the investigator until the abnormality resolves or for up to 30 days.

Patients who are withdrawn from the study because of worsening of symptoms related to bipolar disorder may, according to the investigator's clinical judgment, be hospitalized or have their current hospitalization extended for stabilization. The investigator must notify AstraZeneca of the hospitalization or extension of hospitalization.

## 3.4 Treatments

### 3.4.1 Investigational products

#### 3.4.1.1 Identity of investigational product and placebo

AstraZeneca will supply quetiapine and placebo tablets as shown in Table 2.

**Table 2 Identity of investigational product and comparator**

| Treatment | Formulation number | Presentation |
|---|---|---|
| Quetiapine fumarate 25-mg tablets | F12804 | Peach, round tablet |
| Placebo to match 25-mg quetiapine fumarate tablets | F12636 | Peach, round tablet |
| Quetiapine fumarate 100-mg tablets | F12689 | Yellow, round tablet |
| Placebo to match 100-mg quetiapine fumarate tablets | F12637 | Yellow, round tablet |

Study medication will be packaged by AstraZeneca in double-blind wallets. Each wallet will contain a 1-week supply of tablets, plus enough tablets for 3 extra days of treatment to accommodate visit schedules. Study medication will be packaged to allow for administration 2 or 3 times daily. The wallet cards will be packaged in patient-specific cartons. Each carton

will contain 3 wallet cards, 1 for each study week (Days 1 to 7, Days 8 to 14, and Days 15 to 21).

#### 3.4.1.2 Doses and treatment regimens

At the study visits on Days 1, 7, and 14, the patient's parent or legal guardian will be given the wallet card containing study drug for the following week. The age-specific treatment regimens for each dose group (400 mg and 600 mg) are detailed below.

Patients will begin study treatment on the evening of Day 1 with a single dose of quetiapine 50 mg or matching placebo. Beginning on Day 2, blinded study drug will be given twice daily, with dose escalation thereafter according to the schedule shown in Table 3. Patients randomized to the 400-mg group will reach the target dose of quetiapine or matching placebo by Day 5. Patients randomized to the 600-mg group will reach the target dose of quetiapine or matching placebo by Day 7. Study treatment will end with a single dose on the morning of Day 21.

Administration of study drug may be changed to 3 times a day based upon the clinical judgment of the investigator. No more than 4 tablets may be administered at a single dose.

**Table 3 Quetiapine treatment regimens (mg/day) for administration twice daily**

| | | Study day | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose group** | **Time** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11-21** |
| 400 mg | AM | NA | 50 | 100 | 100 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| | PM | 50 | 50 | 100 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| 600 mg | AM | NA | 50 | 100 | 100 | 200 | 200 | 300 | 300 | 300 | 300 | 300 |
| | PM | 50 | 50 | 100 | 200 | 200 | 300 | 300 | 300 | 300 | 300 | 300 |

AM Morning. NA Not applicable. PM Evening.

#### 3.4.1.3 Labeling

Each patient-specific carton will have a single-panel blinded label that contains at least the following information: study number, randomization number, number of wallet cards in the carton, and storage conditions.

Each wallet card will be printed with instructions (eg, for clinical trial only, keep out of reach of children) and will have a permanently affixed label with a tear-off blinded portion. Both sides of the label will contain at least the following information: study number, randomization number, number of tablets, and storage conditions. When the wallet card is given to the parent or legal guardian during a study visit, the right-hand portion of the tear-off label will be removed from the wallet and affixed to the appropriate CRF as part of the patient's permanent record.

The wallet cards contain areas that are preprinted with “AM” and “PM” to indicate when doses are to be taken. If the investigator decides that study medication should be taken 3 times a day, the tablets in the shaded portion of the “AM” dose area will be used for the midday dose. The physician should instruct the patient on the number of tablets to be taken at each specific time. The card will provide space for the investigator’s written dispensing instructions.

#### 3.4.1.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions.

For centers in the US, study drug supply should be stored at 20-25°C (68-77°F) and protected from moisture. For centers outside the US, the label will state the local storage conditions.

#### 3.4.1.5 Accountability

The investigational materials are to be prescribed only by the investigator or the sub-investigators designated by the investigator. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol without prior AstraZeneca approval.

The investigator must maintain accurate records accounting for the receipt of the investigational materials and for the disposition of the material. This record keeping consists of a dispensing record that includes the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and documentation of any unused drug returned to the investigator. This record is in addition to any drug accountability information recorded on the CRFs. Patients must return all unused drug to the investigator. At the termination of the study or at the request of the sponsor, the Clinical Research Associate must return any unused supplies to USI, at the address listed below, for destruction. This return will be documented on the Investigational Product Return Invoice supplied by AstraZeneca.

For centers outside the US, returned and unused product is accounted for and returned to AstraZeneca for destruction, or destroyed locally upon agreement with, and approval from AstraZeneca. All returned product should be documented on a specific form supplied by AstraZeneca and as required by local regulations.

### 3.4.2 Method of assigning patients to treatment groups

This study will be established with a non-center-specific labelling randomization. Randomization will be stratified by age group (10 to 12 years or 13 to 17 years). Patients will be randomly assigned, in balanced blocks, to 1 of 3 treatments: placebo, quetiapine 400 mg, or quetiapine 600 mg. Within each age stratum, the ratio of patients in the 3 treatment groups will be 1:1:1. The actual treatment given to the patient will be determined by a randomization

schedule prepared by the AstraZeneca Quantitative Decision Sciences group using GRand to produce the randomization scheme.

Patients will be assigned randomization numbers in strict sequential order within age strata, as they are enrolled and deemed eligible. The randomization number will be in addition to the enrollment number assigned at screening. If a patient discontinues from the study, the randomization number will not be reused, and the patient will not be allowed to re-enter the study. If a randomization or enrollment number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the allocated number and study material. AstraZeneca should be notified as soon as the error is discovered. Subsequent patients will continue using the first unallocated randomization number in the original numbering sequence.

### 3.4.3 Blinding and procedures for unblinding the study

#### 3.4.3.1 Methods for ensuring blinding

All double-blind treatments will be packaged in an identical manner, as described in Section 3.4.1. Quetiapine and matching placebo tablets will be identical in size and color, and the number of tablets dispensed will be identical for all treatment groups.

No member of the study team in AstraZeneca, at investigational centers or the Clinical Research Organization (CRO) handling data will have access to the randomization scheme during the conduct of the study.

#### 3.4.3.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment assignment for each randomized patient, will be available to the investigator(s) or pharmacists at the study center via scrape-off labels.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code in order to report SAEs 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 patient have been made and documented.

The DSMB will have access to blinded and unblinded data (see Section 6.7).

### 3.4.4 Pre-study, concomitant and post-study treatments

#### 3.4.4.1 Pre-study medications

This study begins with a medication washout period of 1 to 28 days. During this time, psychoactive and other medications must be discontinued as specified in Table 4.

Other medications that are prohibited, permitted with restrictions, or permitted during the washout period are specified in Table 4. Potent CYP 3A4 inhibitors and inducers (Appendix E) must be discontinued.

**Table 4 Discontinuation of prestudy medications**

| Medication | Time of discontinuation |
|---|---|
| Anticonvulsants | Unless otherwise specified, 14 days before randomization |
| Antidepressant medication | Unless otherwise specified, 7 days before randomization |
| Antipsychotic medications | Unless otherwise specified, 1 day before randomization<br>Depot antipsychotic medications must be discontinued 1 dosing interval before randomization |
| Anxiolytics and hypnotics | Unless otherwise specified, 7 days before randomization. Ongoing treatment with lorazepam is permitted up to 4 mg a day, not to exceed 4 days in any study week. |
| Atomoxetine | 14 days before randomization |
| Cholinesterase inhibitors | 14 days before randomization |
| Clozapine | 28 days before randomization |
| Cytochrome P450 (CYP) 3A4 inhibitors or inducers (potent) | 14 days before randomization |
| Fluoxetine | 28 days before randomization |
| Lithium | 1 day before randomization |
| Nefazodone, fluvoxamine, or monoamine oxidase inhibitors (MAOI) | 14 days before randomization |
| Psychostimulants | Unless otherwise specified, 7 days before randomization. Ongoing treatment with select psychostimulants is allowed if needed in the clinical judgment of the investigator and if the dose has been stable ≥30 days before screening. No dose adjustment is permitted. |
| Valproate | 1 day before randomization |

### 3.4.4.2 Concomitant medications

Medications prohibited, permitted with restrictions, or permitted during screening or washout period and during the double-blind portion of the study are specified in Table 5.

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF. The patient's parent or legal guardian must be instructed to report all medications given to the patient, in addition to those prescribed by the investigator.

## Table 5 Concomitant medications that are prohibited, allowed with restrictions, or permitted

| Use category | Type of medication | Details |
|---|---|---|
| **Prohibited** | anticonvulsants | eg, carbamazepine, lamotrigine |
| | antidepressants | eg, venlafaxine, paroxetine |
| | antipsychotics (except study medication) | |
| | anxiolytics and hypnotics not specifically permitted (see medications allowed with restrictions, below) | eg, buspirone, alprazolam, diazepam, zolpidem, zaleplon |
| | atomoxetine | |
| | cholinesterase inhibitors | |
| | cytochrome P450 inducers (potent) | eg, phenytoin, carbamazepine, barbiturates, rifampin, glucocorticoids, Saint John's Wort (see Appendix E) |
| | cytochrome P450 inhibitors (potent) | eg, ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir (see Appendix E) |
| | lithium | |
| | opiates | |
| | psychostimulants not specifically permitted (see medications allowed with restrictions, below) | |
| **Permitted with restrictions** | benztropine for treatment of emergent extrapyramidal symptoms | not to be used prophylactically |
| | diphenhydramine for sleeplessness up to 50 mg/day at bedtime | not to be used prophylactically |
| | hydroxyzine for treatment of agitation or anxiety | up to 100 mg/day, not to exceed 4 days in any study week<br>can be administered orally or intramuscularly<br>not to be used on the same day with lorazepam<br>not to be given the morning before scheduled study assessments<br>not to be used as treatment for sleeplessness |
| | lorazepam for treatment of agitation or anxiety | up to 4 mg/day, not to exceed 4 days in any study week<br>can be administered orally or intramuscularly |

**Table 5 Concomitant medications that are prohibited, allowed with restrictions, or permitted**

| Use category | Type of medication | Details |
|---|---|---|
| | | not to be used on the same day with hydroxyzine<br>not to be given the morning before scheduled study assessments<br>not to be used as treatment for sleeplessness |
| | propranolol for treatment of emergent akathisia | not to be used prophylactically |
| | select psychostimulants: methylphenidate, dextroamphetamine, mixed amphetamine salts, dexmethylphenidate | ongoing treatment is allowed if needed in the clinical judgment of the investigator and if the dose has been stable ≥30 days before screening. No dose adjustment is permitted. |
| **Permitted** | nonpsychoactive medications, including over-the-counter medications, taken by the patients 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 |
| | other medications which are considered necessary for the patient's safety and well-being | may be given at the discretion of the investigator(s). Includes medication and devices for contraception. |

### 3.4.5 Treatment compliance

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 patient who is at least 75% compliant with study medication during study participation will be classified as compliant.

# 4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

## 4.1 Primary variable

The primary variable is the change from baseline to Day 21 in the YMRS total score. This variable was used as the basis for the sample size calculation (see Section 6.5).

## 4.2 Screening and demographic measurements

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

- date of birth, sex, and race
- significant medical surgical history and prior medication history
- DSM-IV diagnosis, confirmed by K-SADS-PL assessment
- laboratory assessments, including hematology, clinical chemistry tests, thyroid function tests, serum β-hCG pregnancy test, and prolactin concentration
- 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
- physical examination and Tanner staging
- vital signs (supine and standing blood pressure and pulse rate), temperature, height, and weight
- 12-lead ECG
- YMRS assessment

The data listed above will be recorded on specifically designed CRFs. If the washout period is 14 days or longer, the laboratory assessments, serum β-hCG pregnancy test, vital sign measurements, and 12-lead ECG must be repeated before randomization.

## 4.3 Patient-Reported Outcomes (PROs)

The methods for collecting Patient Reported Outcome (PRO) data are presented below.

### 4.3.1 Caregiver Strain Questionnaire

#### 4.3.1.1 Methods of assessment

The 21-item CGSQ (eg, assessment of caregiver burden) will be completed at randomization (Day 1) and at Day 21. The individual-item scores will be recorded on a specifically designed CRF. The same parent or legal guardian should complete the questionnaire at each assessment to reduce scoring variability.

#### 4.3.1.2 Derivation or calculation of variable

The CGSQ score will be calculated as a global score from the 21 individual-item scores. The change from baseline to Day 21 (or final assessment) will be calculated as the visit score minus the baseline score.

### 4.3.2 Administration of PRO questionnaires

The CGSQ will be completed by a parent or legal guardian during the scheduled visit. The data will be recorded on a specifically designed CRF. To reduce variability the same individual should be asked to complete each of the questionnaires.

## 4.4 Health Economic measurements and variables (Not applicable)

This study does not include health economic measurements.

## 4.5 Pharmacokinetic measurement and variables (Not applicable)

This study does not include pharmacokinetic measurements.

## 4.6 Efficacy and pharmacodynamic measurement and variables

The methods for collecting efficacy data are described below. This study does not include pharmacodynamic measurements.

### 4.6.1 Young Mania Rating Scale

#### 4.6.1.1 Methods of assessment

The 11-item YMRS will be administered at each scheduled visit by a trained and certified rater. The individual-item scores will be recorded on a specifically designed CRF. The same individual should administer the YMRS to the patient 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 YMRS. The back-up rater must meet the same qualifications as the primary rater and be authorized by the Principal Investigator.

#### 4.6.1.2 Derivation or calculation of variable

The YMRS total score will be calculated as the sum of the 11 individual-item scores. The baseline score will be the score recorded on Day 1 (randomization). The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

Response will be defined as a ≥50% reduction from baseline in the YMRS total score. Remission will be defined as a YMRS total score of ≤12.

### 4.6.2 Clinical Global Impression - Bipolar

#### 4.6.2.1 Methods of assessment

CGI-BP Severity of Illness and Global Improvement assessments will be performed by the Principal Investigator (primary rater). The data will be recorded on a specifically designed CRF. 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.

#### 4.6.2.2 Derivation or calculation of variable

The baseline CGI-BP Severity of Illness score will be the score recorded on Day 1 (randomization). The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

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

### 4.6.3 Children's Global Assessment Scale

#### 4.6.3.1 Methods of assessment

The 100-point single-item CGAS will be administered by the Principal Investigator (primary rater) on Day 1 (randomization) and on Day 21. The data will be recorded on a specifically designed CRF. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event that the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the CGAS.

#### 4.6.3.2 Derivation or calculation of variable

The baseline CGAS score will be the score recorded on Day 1 (randomization). The change from Day 1 to Day 21 (or early withdrawal) will be calculated as the visit score minus the baseline score.

### 4.6.4 Children's Depression Rating Scale - Revised

#### 4.6.4.1 Methods of assessment

The 17-item CDRS-R will be administered at each scheduled visit by a trained and certified rater. The individual-item scores will be recorded on a specifically designed CRF. The same individual should administer the CDRS-R to the patient 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.

#### 4.6.4.2 Derivation or calculation of variable

The CDRS-R score will be calculated as the sum of the 17 individual-item scores. The baseline score will be the score recorded on Day 1 (randomization). The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

### 4.6.5 Emergent depression

#### 4.6.5.1 Methods of assessment

Emergent depression will be assessed using the CDRS-R, as described in Section 4.6.4.

#### 4.6.5.2 Calculation or derivation of variable

Emergent depression will be a binary outcome variable, defined as a CDRS-R total score ≥40 for patients whose baseline CDRS-R score was <40.

### 4.6.6 Overt Aggression Scale - Modified

#### 4.6.6.1 Methods of assessment

The 25-item OAS-M will be administered by a trained and certified rater at each scheduled visit. The data will be recorded on a specifically designed CRF. The same individual should administer the OAS-M to the patient 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 OAS-M. The back-up rater must meet the same qualifications as the primary rater.

#### 4.6.6.2 Derivation or calculation of variable

The OAS-M score will be calculated as the sum of the 25 individual-item scores. The baseline score will be the score recorded on Day 1 (randomization). The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

## 4.7 Safety measurements and variables

Safety will be evaluated in terms of AEs (including SAEs), discontinuations due to AEs, clinical laboratory analyses, vital signs, weight, body mass index (BMI), ECG changes, physical examination, and anticholinergic use for the treatment of EPS.

Physical examination and any relevant test may be repeated if deemed clinically necessary at any time during the study.

**The methods for collecting safety data are described below.**

### 4.7.1 Adverse events

#### 4.7.1.1 Definitions

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

**(a) Adverse event**

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, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

**(b) Serious adverse event**

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills 1 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 patient or may require medical intervention to prevent one of the outcomes listed above.

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

Psychiatric hospitalization is at times required, and is expected for bipolar disorder. If hospitalization is needed due to the exacerbation of symptoms of mania, this will be reported as an SAE. However, hospitalization for other psychiatric symptoms, including depression, should be considered an SAE. The psychiatric assessments will reflect the worsening of the

patient's condition and the need for hospitalization. These hospitalizations will be reported in the CRF. Further guidance on reporting deterioration of the patient with respect to bipolar disorder is contained in Section 4.7.1.2, paragraph 5.

**(c) Other significant adverse event (OAE)**

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. 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. For each OAE, a narrative may be written and included in the Clinical Study Report.

### 4.7.1.2 Recording of adverse events

All AEs that occur before or during treatment, whether or not related to the study drug, must be recorded on the CRF provided by the sponsor. Unsolicited AE reports occurring up to 30 days after last dose of investigational product should be recorded together with concomitant medications in appropriate sections of the CRF. A description of the event, its intensity, duration, action taken (eg, treatment and follow-up tests), and outcome should be given, along with the investigator's causality assessment of the relationship of the event to the study drug. If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the AE in instances of well recognized syndromes (eg, fever, runny nose, cough can be recorded as "flu"). However, if a diagnosis of the patient's condition has not been made, or if the individual symptoms are not well recognized, then the individual symptoms should be recorded separately.

In general, abnormal laboratory test results or vital signs should not be reported as AEs unless they fulfill the criteria for an SAE or lead to discontinuation. If an abnormal laboratory test result or vital sign is associated with clinical signs and symptoms, the sign or symptoms should be reported as an AE, and the associated test result or vital sign should be recorded on the appropriate CRF.

A causality assessment must be recorded for all AEs. The CRF asks the question, "In your medical judgment, is there a reasonable possibility that the event may have been caused by the study therapy?" If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE, then this should be answered "yes". Otherwise, if no valid reason exists for suggesting a possible relationship, then this should be answered "no." If more than one AE is identified, a causality assessment must be made for each AE.

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 4.7.1.1(b). An AE of severe intensity need not necessarily be considered serious. For example, nausea which 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.

Worsening symptoms of the primary study condition (ie, bipolar disorder) should not be recorded as an adverse event (AE). However, if hospitalization results from worsening psychiatric symptoms, the hospitalization should be recorded as a SAE.

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 4.7.1.3. 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 9.3, Procedures in case of 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 4.7.1.3.

The latest version of the adverse event 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 Drug Safety Database Clintrace and coded using MedDRA.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4, Procedures in case of 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.

### 4.7.1.3 Reporting of serious adverse events

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

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the AstraZeneca Drug Safety Department (ie, Clintrace Data Entry Center) receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

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

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above.

All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the CRF. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

### 4.7.2 Laboratory safety measurements and variables

Blood and urine samples will be collected at screening and Day 21 (or final visit) for laboratory tests to be performed by the central laboratory listed below.

Samples should be taken by adequately trained study personnel and handled in accordance with given instructions. Volumes of blood samples are described in Section 4.10.
will perform all 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 CRF and is source data for laboratory variables at site.

[redacted]

#### 4.7.2.1 Methods of assessment

The following clinical laboratory tests will be performed at screening and on Day 21 (or withdrawal):

- Hematology: Complete blood count (CBC), including ANC white blood cell count, platelet count (total and differential), absolute neutrophil count (see Section 3.3.5.1, Criteria for discontinuation), red blood cell count; hemoglobin (Hb) concentration; hematocrit
- Serum chemistry: total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, plasma glucose, insulin, bicarbonate, high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol and total cholesterol
- Thyroid function tests: TSH, triiodothyronine resin uptake (T3RU), free thyroxine (free T4) and total thyroxine (total T4)
- Prolactin concentration
- HbA1c

- Serum β-hCG pregnancy test
- Urine drug screen (part of general assessment of substance abuse disorders) and urinalysis

#### 4.7.2.2 Calculation or derivation of outcome variables

Changes from baseline to Day 21 (or final assessment) for all patients who have a screening laboratory test and a final laboratory test will be calculated as the final test value minus the screening 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).

### 4.7.3 Vital signs and weight

Blood pressure and pulse rate (supine and standing) as well as oral temperature, and weight will be measured at screening, at randomization (Day 1), and on Days 4, 7, 14, and on Day 21 (or withdrawal).

#### 4.7.3.1 Methods of assessment

An appropriately sized cuff (ie, pediatric cuff, as needed) will be used to obtain systolic and diastolic blood pressure. The assessment will be done first with the patient in the supine position for 3 minutes and again within 3 minutes of the patient attaining a standing position.

Standing and supine blood pressure and pulse rate should be measured with the right arm at heart level. Weight will be measured in kilogram (kg) with the patient wearing light clothing and without shoes. If possible, weight should be recorded using the same scale at each visit.

#### 4.7.3.2 Calculations or derivations of outcome variables

Change from baseline at each visit will be derived as the value at the visit minus the screening value for the same assessment and position, if applicable. In addition, the change within a visit between the standing and supine blood pressure 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 patient will be classified as having postural hypotension if either the systolic blood pressure difference indicates a decrease >20 mmHg or the diastolic blood pressure difference indicates a decrease >15 mmHg. BMI will be calculated as (weight in kg)/(height in meters)$^2$.

### 4.7.4 ECG safety measurements and variables

#### 4.7.4.1 Methods of assessment

Twelve-lead ECGs will be performed at screening and on Day 21 (or withdrawal). ECGs for all patients at all centers will be conducted at the center using a machine provided by and will be transmitted to the central ECG laboratory. Quality assurance of the ECG waveform and patient demographics will be conducted by a central laboratory operator at Technology at the address listed below. 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 within 24 hours. $QT_c$ intervals will be calculated using the Fridericia formula (Puddu et al 1988). At the ECG assessment on Day 21, the previous dose of the study drug and the time of administration will be recorded on the CRF. The time of the ECG will be recorded in the central ECG laboratory database and will be signed and dated by the principal investigator.

#### 4.7.4.2 Calculations or derivations of outcome variables

Changes from baseline to Day 21 (or final assessment) 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).

### 4.7.5 Physical examination

#### 4.7.5.1 Methods of assessment

A complete physical examination should be completed by a physician, including direct ophthalmoscopy will be conducted, according to standard medical practice at enrollment and at subsequent visits as outlined in Table 1, and recorded by body system on the appropriate sections of the CRF.

#### 4.7.5.2 Calculation or derivation of outcome variables

Changes from baseline physical examination will be reported.

### 4.7.6 Neurological assessments and variables

EPS will be assessed as follows: Parkinsonian symptoms will be assessed using the SAS, dyskinesia will be assessed by the AIMS, and akathisia will be measured by the BARS.

Assessments will be recorded on the appropriate sections of the CRF.

#### 4.7.6.1 Simpson-Angus Scale

**Methods of assessment**

The SAS instrument will be administered by study staff (eg, nurse or physician) at the baseline visit and at specified visits (Table 1) to assess EPS.

**Calculation or derivation of outcome variables**

The SAS score will be calculated as the sum of the 10 individual-item scores. The baseline score will be the score recorded on Day 1 (randomization). The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

#### 4.7.6.2 Abnormal Involuntary Movement Scale

**Methods of assessment**

The AIMS instrument will be administered by study staff (eg, nurse or physician) at the baseline visit and at specified visit (Table 1) to assess EPS.

**Calculation or derivation of outcome variables**

The AIMS score will be calculated as the sum of the 10 individual-item scores. The baseline score will be the score recorded on Day 1 (randomization). The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

#### 4.7.6.3 Barnes Akathisia Rating Scale

**Methods of assessment**

The BARS instrument will be administered by study staff (eg, nurse or physician) at the baseline visit and at specified visits (Table 1) to assess EPS.

**Calculation or derivation of outcome variables**

The BARS score will be calculated as a global score from the 4 individual-item scores. The baseline score will be the score recorded on Day 1 (randomization). The change from baseline to each study visit will be calculated as the visit score minus the baseline score.

## 4.8 Collection of samples for genetic analysis

Consent for genetic research will be obtained prior to sample collecting on a form separate from the main consent. Genetic research is optional both for study centers and for individual patients. Specifically, patients who refuse consent for genetic research may still participate in the main clinical study. A 9 ml sample of blood will be collected from consenting patients. This will ordinarily be done at the baseline visit, but can be done at a subsequent visit if necessary. Technical requirements (tube type, shipping, etc.) for collecting and transporting blood samples for genetic analysis are presented to the centers in a separate document.

## 4.9 Genetic sampling, storage, and data management

Blood samples from consenting patients will be used to prepare DNA samples. The genetic samples obtained in this study will be used to study, in an exploratory manner, the effects of genetic polymorphisms on response (ie, safety, tolerability, and disposition) to study drug and/or susceptibility to bipolar disease. These samples will not be used for other purposes. Exploratory genetic research may involve comparisons with data from other clinical trials and/or control populations. All DNA samples and any remaining blood will be destroyed 15 years after study completion (defined here as database lock).

Blood samples for genetic research will be labelled only with patient numbers and not with personal identifiers (eg, patient names). Prior to DNA extraction, the original patient number will be replaced with a new code number. Clinical data will be similarly recoded prior to hypothesis testing. The purpose of recoding is to provide an additional layer of separation

between patient identity and genetic research results. A link between the original and new codes will be maintained in a restricted-access file at AstraZeneca. This link is maintained for the following reasons: (1) to permit audit by regulatory authorities (but only as required by local law), (2) to allow recoding of clinical data (which will occur after recoding of the genetic samples), and (3) to permit location and destruction of genetic samples in case of withdrawal of consent for genetic research, and (4) in case of medical emergency, to allow an AstraZeneca Safety Physician to investigate the cause. This link will be destroyed in 15 years, at the same time that the DNA samples are destroyed. Genetic research will be carried out only on recoded DNA samples, and will only utilize similarly recoded clinical data.

The results of any genetic research, any genetic sequences, cell lines, patents, diagnostic tests, drugs and biological products developed directly or indirectly from those samples, are the sole property of the study sponsor (and its successors, licensees, and assigns). Genetic data may be reviewed with research collaborators and published. Genetic data may be provided to the patient (or parent/guardian) if this is required by local law; however, this would be done only upon request. Moreover, any such information would be conveyed to the patient (or parent/guardian) only through a treating physician designated by him or her. Otherwise, no genetic data will be provided to the patient, the patient's family, the investigator, or any other physician who is treating the patient or who may treat the patient in the future. Neither the patient's insurance company nor the patient's employer will have any access to these research results. There is no direct benefit to the patient in having genetic research performed.

Patients who consent to genetic research may withdraw this consent at any time, whether or not consent is also withdrawn for the main study. If a patient withdraws consent for genetic research before completion of the main study, the study center should be contacted; otherwise, the study sponsor should be contacted directly. When a patient withdraws consent for genetic research, his or her DNA sample will be located and destroyed; however, any genetic data that has already been generated will not be destroyed.

## 4.10 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient for clinical laboratory tests in this study is shown in Table 6. For patients who participate in optional genetic sampling, an additional 9-ml blood sample will be collected at screening.

**Table 6 Volume of blood to be drawn from each patient**

| Assessment | Sample volume (mL) | Number of samples | Total volume (mL) |
|---|---|---|---|
| Clinical chemistry (including lipid panel) | 4.5 | 2[a] | 9.0 |
| Hematology | 4.0 | 2[a] | 8.0 |
| Thyroid function and prolactin | 4.0 | 2[a] | 8.0 |
| **Total** | | **6** | **25.0** |

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

laboratories 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 Laboratories. Samples should be shipped to Laboratories by courier unless otherwise agreed.

### 4.10.1 Analysis of biological samples

The analyte stability limits defined by Laboratories will be applied to all analyses performed on behalf of AstraZeneca. Laboratories 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 Laboratories may be amended in accordance with their Standard Operating Procedures. Laboratories will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

# 5. DATA MANAGEMENT

CRFs will be provided for recording of data. The forms will be in triplicate with carbonless paper. Data will be recorded legibly onto the CRFs with black ink, preferably with a ballpoint pen. If any data are not available, omissions will be indicated on the CRFs. Corrections should be made legibly and be initialed and dated. Correction fluid or covering labels must not be used. The top original and the first copy of the completed form will be collected and returned to AstraZeneca/AstraZeneca's agent and the second copy will be retained by the investigator.

The data will be double-entered into the Clinical Database at AstraZeneca/AstraZeneca's agent. Any missing, impossible or inconsistent entries in the CRF are to be queried to the site for clarification and the Clinical Database will be amended accordingly. The Clinical Database will undergo a full quality control review consisting of 100% check for critical variables (primary efficacy and safety). A quality control of all variables for 10% of the patients randomized will be completed. The quality control is a comparison between what is in the database compared to the CRF.

Data received electronically (eg, from or ) by AstraZeneca from a validated source will be loaded directly into the study database for analysis.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 6.1 Statistical evaluation – general aspects

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

Missing data for final assessments resulting from patient withdrawals will be imputed using the last observation carried forward (LOCF).

Randomization will be stratified by age group: 10 to 12 years, 13 to 17 years. The stratification will be incorporated into the statistical analyses, and descriptive statistics will also be provided for each stratum.

All statistical comparisons will be based on a 2-sided test using an alpha 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 will be presented.

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

For all changes from baseline variables, baseline will be defined as the latest value prior to or on the same day of randomization.

## 6.2 Description of outcome variables in relation to objectives and hypotheses

### 6.2.1 Primary hypotheses

The primary hypotheses are as follows:

- Quetiapine 400 mg/day is superior to placebo in reducing the YMRS total score at Day 21 compared with baseline.
- Quetiapine 600 mg/day is superior to placebo in reducing the YMRS total score at Day 21 compared with baseline.

### 6.2.2 Secondary hypotheses

Secondary hypotheses are as stated below.

**Hypotheses for individual quetiapine doses (400 mg/day and 600 mg/day) for efficacy**

- Quetiapine is superior to placebo in reducing the CGI-BP Severity of Illness score at Day 21 compared with baseline.

- Quetiapine is superior to placebo in reducing the CGI-BP Global Improvement score at Day 21.
- Quetiapine is superior to placebo in the percentage of patients who achieve remission as defined by a YMRS total score ≤12 at Day 21.
- Quetiapine is superior to placebo in the percentage of patients with a response as defined by a ≥50% reduction from baseline in the YMRS total score at Days 4, 7, and 21.
- Quetiapine is superior to placebo in reducing the CGI-BP Severity of Illness score at Days 4 and 7 compared with baseline.
- Quetiapine is superior to placebo in reducing the level of functioning as assessed by the CGAS total score at Day 21 compared with baseline.
- Quetiapine is superior to placebo in reducing the depressive symptoms as assessed by the CDRS-R total score at Day 21 compared with baseline.
- Quetiapine is superior to placebo in reducing the OAS-M total score at Days 4, 7, and 21 compared with baseline.
- Quetiapine is superior to placebo in reducing the scores for YMRS items 5 and 9 at Day 21 compared with baseline.
- Quetiapine is superior to placebo in reducing the YMRS total score at Days 4 and 7 compared with baseline.

**Hypotheses regarding safety and tolerability**

- Quetiapine is superior to placebo in reducing the SAS total score at Day 21 compared with baseline.
- Quetiapine is superior to placebo in reducing the AIMS total score at Day 21 compared with baseline.
- Quetiapine is superior to placebo in reducing the BARS global score at Day 21 compared with baseline.
- Quetiapine is associated with a lower incidence of anticholinergic medication for the treatment of emergent EPS as compared with placebo.
- Quetiapine does not cause greater elevation of serum prolactin concentration than placebo.

- Quetiapine is associated with a lower incidence of emergent depression, defined as a CDRS-R total score of ≥40 at Day 21 for patients whose baseline CDRS-R total score was <40, compared with placebo.

**Descriptive analyses of safety variables (no formal hypotheses)**

- Changes from baseline in vital signs, clinical laboratory results, ECG results, BMI and weight to final assessment

### 6.2.3 Exploratory hypotheses

**Hypothesis regarding overall caregiver burden**

- Quetiapine treatment compared with placebo treatment is associated with greater improvement from baseline to final assessment in overall caregiver burden as measured by the CGSQ.

**Descriptive analyses of exploratory variables (no formal hypotheses)**

- Changes from baseline in sleep item scores on the YMRS and CDRS-R rating scales at each assessment.

## 6.3 Description of analysis sets

Data analyses will be based on 3 patient populations, as defined below:

- The safety population will include all randomized patients who were given study treatment, classified according to the treatment actually received. The safety population will be used to assess safety and tolerability variables.

- The intent-to-treat (ITT) population will include all randomized patients who were given study treatment and who have baseline and at least 1 post-baseline efficacy assessment. The ITT population will be used for the efficacy analyses. Patients will be classified according to the treatment to which they were randomized.

- The per-protocol population (PP) will exclude the following: patients with significant protocol violations or deviations; any data collected after a patient was withdrawn from the assigned treatment group; all data from patients who were deemed to be non-compliant using returned-tablet counts as defined in Section 3.4.5. The primary analysis will be repeated on the PP population to test for homogeneity of treatment effects.

## 6.4 Method of statistical analysis

**Primary analysis:**

The changes from baseline YMRS total scores at Day 21 will be analyzed using repeated-measures analysis. Covariates will include age stratum, treatment, visit, visit-by-treatment

interaction, center, and baseline YMRS total score. If patients discontinue the study prior to Day 21, the last-visit observations will be carried forward (LOCF). The two contrasts of interest will be between the quetiapine 400-mg and 600-mg groups vs. the placebo group at Day 21.

The Simes-Hommel step-up procedure will be used to adjust for the 2 primary comparisons with placebo (Simes-Hommel 1988). The p-values obtained from the pair-wise comparisons will be ordered as follows: $P(1) \leq P(2)$. The following rule will be used to assess statistical significance:

1. If $P(2) \leq 0.050$, then reject both null hypotheses associated with P(2) and P(1); else proceed to the next step;

2. If $P(1) \leq 0.025$, then reject the null hypothesis associated with P(1).

**Secondary analyses:**

Changes from baseline in CGI-BP Severity of Illness score; YMRS item scores; CDRS-R, OAS-M, SAS, and AIMS total scores; and BARS global score to a specific assessment will also be analyzed via repeated-measures analysis. Covariates will include age stratum, treatment, visit, visit-by-treatment interaction, center, and baseline score for the appropriate scale.

Change from baseline in CGAS scores to Day 21 will be analysed via ANCOVA. Covariates will include age stratum, treatment, center, and baseline score.

CGI-BP Global Improvement scores at the Day 21 will be analyzed via repeated- measures analysis, with baseline CGI-BP Severity of Illness score as a covariate along with treatment, visit, visit-by-treatment interaction, age stratum, and center.

Generalized estimating equations (GEE; Liang and Zeger 1986) will be used to assess the differences between quetiapine and placebo in YMRS response rates. Response is defined as a ≥50% reduction from baseline in the YMRS total score at Day 21. Covariates will include age stratum, treatment, visit, visit-by-treatment interaction, center, and baseline YMRS total score.

GEE will also be used to assess the differences between quetiapine and placebo in the incidence of patients with remission, defined as a YMRS total score ≤12 at Day 21. Covariates will age stratum, treatment, visit, visit-by-treatment interaction, center, and baseline YMRS total score.

**Exploratory analyses:**

Changes from baseline in CGSQ global score at Day 21 will be analyzed via ANCOVA. Covariates will include age stratum, treatment, center, and baseline CGSQ global score.

To assess the impact of psychostimulant use, a covariate for psychostimulant use together with a psychostimulant use-by-treatment interaction will be included in the appropriate secondary models for exploratory purposes only. The impact of other potential confounding factors (eg, entry status [inpatient or outpatient] gender, secondary diagnoses, substance abuse) may also be assessed within these models.

**Safety analyses:**

Adverse events will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). Numbers of events and crude incidence rates will be tabulated by preferred term and system organ class. An event that occurred 1 or more times on the date of, or subsequent to, randomization will contribute 1 observation to the numerator of the crude incidence rate. The denominator of the rate will comprise all patients exposed to study treatment. If the intensity or seriousness of the AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences.

Logistic regression will be used to assess the incidence of anticholinergic medication use between quetiapine and placebo at Day 21. Covariates for this analysis will include age stratum, treatment, and center. Prior antipsychotic use may also be used as a covariate in the model.

GEE will be used to assess the incidence of emergent depression (defined as a CDRS-R total score of ≥40 at Day 21 for patients whose baseline CDRS-R total score was <40) between quetiapine and placebo at Day 21. Covariates for this analysis will include age stratum, treatment, visit, visit-by-treatment interaction, center, and baseline CDRS-R total score.

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

Repeated-measures analysis will be used to assess the change from baseline in prolactin concentration over time compared with placebo. Covariates for this analysis will be age stratum, treatment, visit, visit-by-treatment interaction, baseline prolactin concentration, and center.

**Descriptive statistics:**

**Safety population:**

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

Separate tabulations for orthostatic hypertension, dizziness, tachycardia, and syncope will also be produced.

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

from baseline. The proportions of patients who have a ≥7% weight gain compared with baseline will be tabulated.

The SAS, BARS, and AIMS scores will also be summarized for each treatment group using descriptive statistics at each visit, displaying both the raw numbers and changes from baseline.

**ITT population:**

Psychostimulant use, sleep medication use, and drug compliance will be tabulated for each treatment group. Time to withdrawal will be graphically summarized via Kaplan-Meier estimation.

Other descriptive statistics and graphical displays will be defined in the SAP.

## 6.5 Determination of sample size

Eighty-eight evaluable patients per treatment group (ie, a total of 264 patients) will provide at least 85% power to detect a difference of 6 points between either the 400-mg or 600-mg quetiapine treatment group and the placebo group with respect to mean change from baseline in YMRS total score. A Bonferroni correction using an alpha of 0.025 was used as a conservative approach for obtaining the sample size estimate. This sample size calculation assumes a standard deviation of 12 and a 2-tailed test at an overall experiment type I error rate of 0.050.

An additional 66 (20%) patients have been added to provide an estimate of 330 patients needed for screening. These additional patients have been added to account for those patients who may be screened but who may not become evaluable. The estimate of 20% is based on information from 2 acute mania quetiapine studies (5077IL/0104, 5077IL/0105) in the adult population in which 15% and 18% of patients, respectively, withdrew between screening and randomization. It is also expected that there will be few withdrawals from randomization to the 1$^{st}$ post-baseline visit.

The sample size estimation, based on the primary endpoint of mean change from baseline in YMRS total score to the end of the study, also utilized information from Studies 5077IL/0104 and 5077IL/0105 as well as a study reported by Tohen et al (1999). Differences in YMRS total score between quetiapine and placebo (5077IL/0104, 5077IL/0105) ranged from approximately 4 to 8 points, hence a 6-point difference in YMRS total score was used in the sample-size estimation.

## 6.6 Interim analyses

No interim analysis for efficacy is planned. Safety will be monitored throughout the study as described in Section 6.7.

## 6.7 Data and safety monitoring board

A DSMB will be established to assist in the safety surveillance of this 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 patient treatment assignment. Detailed operating procedures of the DSMB will be agreed between this board and AstraZeneca and will be presented in a separate document prior to the start of the study.

## 6.8 Steering committee

A steering committee will be formed and may consist of AstraZeneca study team members as well as others who have been involved in protocol development and implementation. The committee will meet on a regular basis to review the progress of the study and review DSMB recommendations.

# 7. STUDY MANAGEMENT

## 7.1 Monitoring

Before first patient into the study, a representative of AstraZeneca will visit the investigational study center to:

- determine the adequacy of the facilities
- discuss with the investigator(s) (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 between AstraZeneca and the investigator.
- In particular, as sampling for DNA extraction is required for genetic testing the consequences and procedures associated with this will be made clear to the investigator, including the importance of explaining to the subject background information about genetic studies and the intended use of the genetic material.

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the investigational center, including visits to:

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to

the study). This will require direct access to all original records for each patient (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center need information and advice.

The monitor(s) will verify data from the CRFs against source data before collecting the CRFs to ensure accuracy and completeness of documentation, and assure that the principal investigator/sub-investigator has submitted the CRFs to AstraZeneca. For any change or amendment in the collected CRFs, the monitor will assure that the principal investigator/sub-investigator has reported to the sponsor the change (or amendment), date, and the reason in a written form.

## 7.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her center.

## 7.3 Training of staff

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

To ensure consistency throughout the study, all investigators and designated study personnel will receive mandatory training in conducting the study assessments. Training and information on all study-related processes will be provided at the Investigator meetings, local initiation, and monitoring meetings. Annual retraining will be required.

[redacted]

## 7.4 Changes to the protocol

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

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be notified to or approved by each IRB or IEC, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular center's Informed Consent Forms, then AstraZeneca and the center's IRB or IEC must be notified. Approval of the revised Informed Consent Forms by AstraZeneca and by the IRB or IEC is required before the revised form is used.

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

## 7.5 Study agreements

The principal investigator at each center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

Administrative details regarding hospitalization or extension of hospitalization for restabilization of patients who are withdrawn due to worsening of symptoms, as described in Section 3.3.5.3, will be provided in the Clinical Study Agreement.

## 7.6 Study timetable and termination

It is estimated that the first patient will be enrolled by June 2004 and that the last patient will complete the study by July 2006. The recruitment period is estimated to begin in May 2004 and end in June 2006.

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

- signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/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
- signed and dated Financial Disclosure forms for all study personnel listed on the most recent version of FDA Form 1572

**Discontinuation or suspension of the whole study program**

If AstraZeneca decides to withdraw or suspend the study, the principal investigator, sub-investigator, the head of the institution, and regulatory authorities should be informed of the fact in a written form clarifying the reason.

The principal investigator or sub-investigator will immediately notify the decision to the patients, give appropriate medical treatment, take necessary measures, and record treatment or measures provided on the source documents.

**Completion of the study**

Upon terminating the study, the principal investigator or sub-investigator will report in writing the completion of the study as well as the summary of the results to the head of the institution in accordance with the institution's rules. The head of the institution who is informed of the termination by the investigator will notify in writing the fact with the summarized results to the IRB and AstraZeneca.

# 8. ETHICS

## 8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enroll any patient into the study.

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

The Principal Investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the principal investigator.

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

## 8.2 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 ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

In addition, AstraZeneca ensures that special precautions are taken for studies including genetic analysis, with regard to all the processes for ensuring confidentiality of data.

## 8.3 Written informed consent

The principal investigator(s) at each center will ensure that both the patient (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. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated assent and the parent's or legal guardian's signed and dated informed consent must be obtained before conducting any procedure specifically for the study, including the following:

- Withholding or discontinuation of treatment
- Collection of blood samples
- Completion of rating scales and questionnaires
- Lifestyle changes (eg, refraining from strenuous exercise, food, nicotine or caffeine)
- Physical examination

The principal investigator(s) must store the original, signed Informed Consent and Assent Forms. Copies of the signed Informed Consent and Assent Forms must be given to the patient and parent or legal guardian.

Where genetic analyses are included, special account of these will be made in the consent form, 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 form. Forms specific for giving assent or consent for taking samples for genotyping will be used. The patient's, parent's or legal guardian's signed and dated Assent and Informed Consent(s) must be obtained before conducting any procedure specifically for the genetic sampling. The principal investigator(s) must store the original, signed Assent and Informed Consent Form(s). A copy of the signed Assent/Informed Consent Form(s) must be given to the patient, parent or legal guardian.

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

## 8.4 Patient data protection

For study centers within the US or in studies where non-US patients' protected health information (patient data) will come into the US through a covered entity (eg, Central lab/Reader), the Informed Consent Forms will incorporate, or be accompanied by, a separate document incorporating HIPAA-compliant wording by which patients 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 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 will be identified by patient enrollment number, randomization number, and study code.

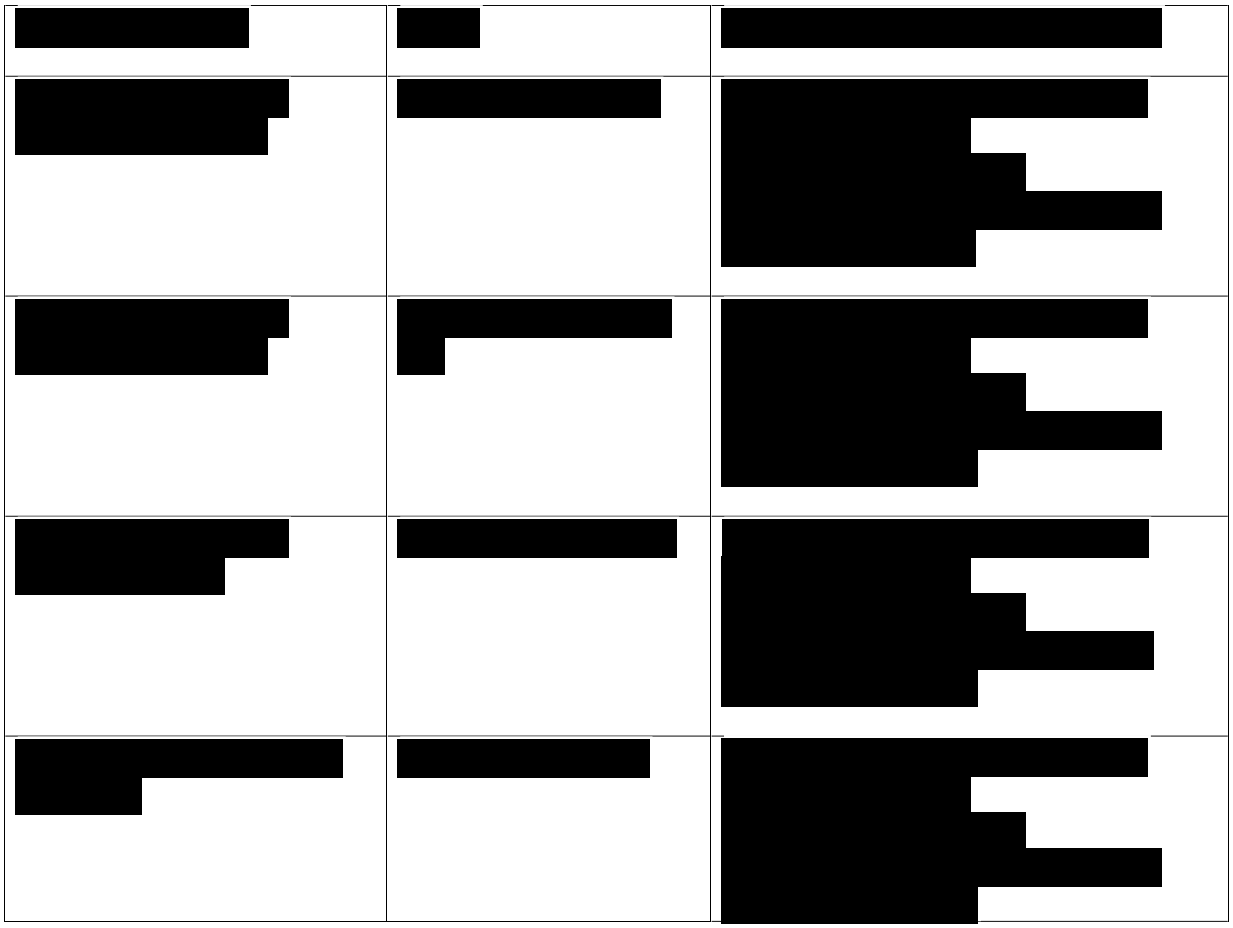
The Master Informed Consent Forms will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IRB or IEC may require direct access to parts of the hospital or practice records relevant to the study, including patient's medical history.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. This involves de-identification/anonymization of the samples and data. For de-identification this will mean that there is segregation of the databases containing coded genotyping and clinical information with protection of confidentiality achieved by limited access to the coding keys of each database. (Details of the procedure specific to this study are in Section 4.9).

# 9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE, OR PREGNANCY

## 9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact the Clinical Study Team leader. If the Clinical Study Team leader is not available, contact the Clinical Study Team Physician or the Clinical Study Team Safety Drug Physician at the AstraZeneca Research and Development site shown below.



## 9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

## 9.3 Procedures in case of overdose

Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRF as an AE of 'Overdose' unless there are associated symptoms or signs.

- An overdose with associated SAEs must be recorded on the relevant SAE and AE modules in the CRF as 'Overdose', as well as the associated SAE symptoms themselves

- An overdose with associated non-serious AEs must be recorded on the relevant AE modules in the CRF as 'Overdose', as well as the associated AE symptoms themselves. In addition, the overdose must be reported on the separate AZ "Clinical Study Overdose Report Form" as soon as possible.

- An overdose without associated symptoms should not be recorded as an AE in the CRF. The overdose must be reported on the separate AZ "Clinical Study Overdose Report Form" as soon as possible.

## 9.4 Procedures in case 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. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities, birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

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**Clinical Study Protocol: Appendix A**

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|---|---|
| Drug Substance | quetiapine fumarate |
| Study Code | D1441C00149 |
| Edition No. | 1.0 |
| Appendix Date | [redacted] |

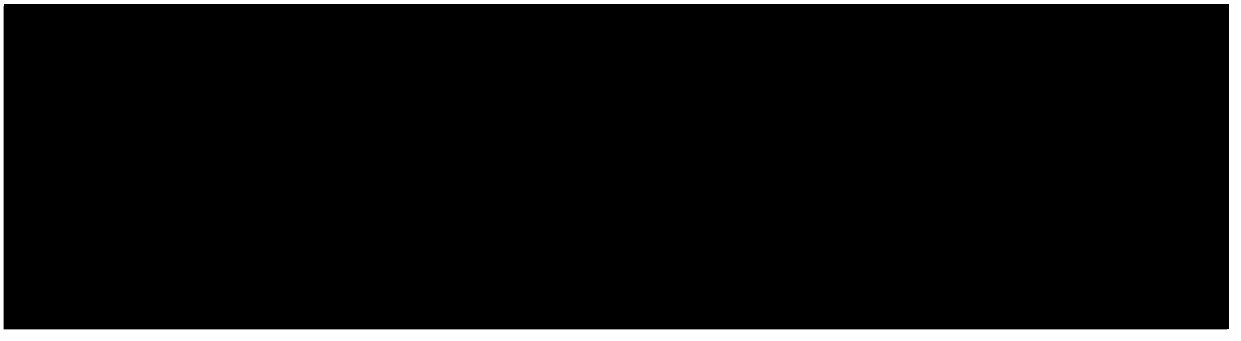
# Appendix A
# Signatures

# ASTRAZENECA SIGNATURE(S)

Study Title

**A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania**

I agree to the terms of this study protocol



# ASTRAZENECA SIGNATURE(S)

Study Title

**A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania**

I agree to the terms of this study protocol

[redacted]

# ASTRAZENECA SIGNATURE(S)

Study Title

**A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania**

I agree to the terms of this study protocol

[redacted]

# SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

Study Title

**A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Maniaa**

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

[redacted]

[redacted]

[redacted]

# SIGNATURE OF PRINCIPAL INVESTIGATOR

Study Title

**A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania**

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

[redacted]

[redacted]

[redacted]

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

# SIGNATURES OF COMMITTEE MEMBERS

Study Title

**A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania**

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

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| **Study Protocol: Appendix B** | |
|---|---|
| Drug Substance | quetiapine fumarate |
| Study Code | D1441C00149 |
| Edition No. | 1.0 |
| Appendix Date | [redacted] |

# Appendix B
# Additional Safety Information

# 1. 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 oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the 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.

Examples of such events are:

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

# 2. 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 recognised feature of overdose of the drug?

- Is there a known mechanism

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

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| **Clinical Study Protocol: Appendix C** | |
|---|---|
| Drug Substance | quetiapine fumarate |
| Study Code | D1441C00149 |
| Edition No. | 1.0 |
| Appendix Date | [redacted] |

# Appendix C
# DSM-IV Diagnostic Criteria for Bipolar I Disorder

- **Diagnostic Criteria for296.4x Bipolar I Disorder, Most Recent Episode Manic**

  (a) Currently (or most recently) in a Manic Episode (see below).

  (b) There has previously been at least one Major Depressive Episode (see below), Manic Episode (see below), or Mixed Episode (see below).

  (c) The mood episode 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.

- **Diagnostic Criteria for 296.6x Bipolar I Disorder, Most Recent Episode Mixed**

  (a) Current (or most recently) in a Mixed Episode (see below).

  (b) There has previously been at least one Major Depressive Episode (see below), Manic Episode (see below), or Mixed Episode (see below).

  (c) The mood episode 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.

- **Criteria for Manic Episode**

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

  (b) 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:

    (1) inflated self-esteem or grandiosity

    (2) decreased need for sleep (eg, feels rested after only three hours of sleep)

    (3) more talkative the usual or pressure to keep talking

    (4) flights of ideas or subjective experience that thoughts are racing

    (5) distractibility (eg, attention too easily drawn to unimportant or irrelevant external stimuli)

    (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

(c) The symptoms do not meet criteria for a Mixed Episode (see below).

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

(e) 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).

**Note:** Manic-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

- **Criteria for Mixed Episode**

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

(b) 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.

(c) 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).

**Note:** Manic-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

- **Criteria for Major Depressive Episode**

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

**Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (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 or 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

(b) The symptoms do not meet criteria for a Mixed Episode (see above).

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

(d) 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).

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

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| **Clinical Study Protocol: Appendix D** | |
|---|---|
| Drug Substance | quetiapine fumarate |
| Study Code | D1441C00149 |
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| Appendix Date | [redacted] |

# Appendix D
# DSM-IV Diagnostic Criteria for Psychoactive Substance Dependence and Abuse

- **Criteria for Substance Dependence**

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:

(a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect

(b) markedly diminished effect with continued use of the same amount of the substance

(2) withdrawal, as manifested by either of the following:

(a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal from the specific substances)

(b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substances (eg, visiting multiple doctors or driving long distances), use the substance (eg, chain-smoking), or recover from its effects

(6) important social, or occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (eg, current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

- **Criteria for Substance Abuse**

(A) A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

(2) recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use)

(3) recurrent substance-related legal problems (eg, arrests for substance-related disorderly conduct)

(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (eg, arguments with spouse about consequences of intoxication, physical fights)

(B) The symptoms have never met the criteria for Substance Dependence for this class of substance.

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| **Clinical Study Protocol: Appendix E** | |
|---|---|
| Drug Substance | quetiapine fumarate |
| Study Code | D1441C00149 |
| Edition No. | 1.0 |
| Appendix Date | [redacted] |

# Appendix E
# Cytochrome P450 3A4 Inducers and Inhibitors Potent

# Cytochrome P450 3A4 Inducers and Inhibitors Potent

## Inducers

barbiturates

carbamazepine

glucocorticoids

grape fruit juice

phenytoin

rifampin

Saint John's Wort

## Inhibitors

clarithromycin

erythromycin

fluconazole

indinavir

itraconazole

ketoconazole

nelfinavir

ritoavir

saquinavir

troleandomycin

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| **Clinical Study Protocol: Appendix F** | |
|---|---|
| Drug Substance | quetiapine fumarate |
| Study Code | D1441C00149 |
| Edition No. | 1.0 |
| Appendix Date | [redacted] |

# Appendix F
# Insurance and Indemnity

# INSURANCE AND INDEMNITY

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

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

AstraZeneca can forward a letter of indemnity if needed by the investigator(s)/institution.

For studies conducted in the US, this Appendix Insurance and indemnity is not applicable. Please refer to the clinical study agreement for information concerning AstraZeneca's obligation to insure and indemnify the Institution and investigator.