M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 10, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: April 8, 2009 Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC)

TO: Members, PDAC

This one-day PDAC meeting will focus on safety and efficacy issues for supplemental new drug applications (sNDAs) 22-047/S-010/S-011/S-012, quetiapine maleate (Seroquel XR), Astra Zeneca Pharmaceuticals LP, proposed for the acute and maintenance treatment of major depressive disorder (MDD), and 22-047/S-014/S-015, Seroquel XR (quetiapine maleate), Astra Zeneca Pharmaceuticals LP, proposed for the acute and maintenance treatment of generalized anxiety disorder (GAD). Seroquel XR is an extended release formulation of quetiapine, an atypical antipsychotic drug, and is approved (1) as monotherapy for the acute and maintenance treatment of schizophrenia, (2) as monotherapy for the acute treatment of bipolar depression and mania, and (3) as adjunctive therapy for the acute treatment of bipolar mania.

The sponsor has conducted both acute and maintenance trials to support these expanded claims for Seroquel XR into patients with MDD and GAD. As part of the background package, we have provided FDA's various review documents for these applications (primary medical officer reviews, team leader memos, and division director memos). The sponsor's background package will also provide data to support the safety and efficacy of these expanded claims. The sponsor has, in the Division's view, submitted sufficient data to support the conclusion that Seroquel XR is effective as acute monotherapy and acute adjunctive therapy and as maintenance monotherapy, in the treatment of MDD, and as acute monotherapy and as maintenance monotherapy in the treatment of GAD. The safety profile, to the extent that it can be characterized in these conditions, appears to be similar to that observed with this drug in other conditions.

There remains, however, a concern about longer-term risks with this drug, in particular risks related to metabolic changes with this drug and the possibility of tardive dyskinesia. There is also concern about a possible risk of sudden cardiac death with atypical antipsychotic drugs, including quetiapine (as detailed in a recent paper in NEJM by Wayne Ray; included in background package). These issues become even more important as the distribution of this drug to a much broader patient population is considered. FDA is completing its review of data pertinent to the metabolic risks of quetiapine in adult patients, and this review will also be provided to the Committee prior to the April 8th meeting.

Formal presentations at the meeting will include a summary of the safety and efficacy data for these expanded claims by the sponsor. The sponsor will also address the broader questions of the potential longer-term risks of expanding the use of Seroquel XR into a broader population. FDA's presentations will focus more specifically on the metabolic risks of quetiapine, and the concerns about a possible increased risk of sudden cardiac death with the atypical antipsychotic drugs generally. Dr. Wayne Ray from Vanderbilt University School of Medicine will present the results of his recent study, and FDA staff will also provide comments on this issue.

The Division of Psychiatry Products has not yet reached a final conclusion on these applications, and seeks the advice of the PDAC before reaching a conclusion.

After you have heard all the findings and arguments, we will ask you, first of all, to discuss and comment on several questions pertinent to the risks and benefits of Seroquel XR. Then we will ask you to vote on two questions.

The questions for discussion and comment are as follows:

1. What are the public health consequences of expanding the use of Seroquel XR into a much larger psychiatric population with MDD and GAD?

2. In particular, how should less well-defined concerns about longer-term metabolic risks, a potential risk for tardive dyskinesia, and a concern for an increased risk of sudden cardiac death be considered in this risk benefit discussion?

The questions for a vote by the committee are as follows:

1. Has Seroquel XR been shown to be effective for the treatment of MDD and GAD?

2. Has Seroquel XR been shown to be acceptably safe for the treatment of MDD and GAD?

cc:
HFD-130/TLaughren/MMathis/NKhin/RLevin/EHearst/KKohli-Chhabra/JCliatt/RGrewal

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/s/

Thomas Laughren
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MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 21, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Complete Response action for Seroquel (quetiapine) XR tablets for acute monotherapy, acute adjunctive therapy, and maintenance monotherapy of depressive episodes associated with major depressive disorder

TO: File NDA 22-047/S-010/011/012
[Note: This overview should be filed with the 2-27-08 original submission of these supplements.]

1.0 BACKGROUND

Seroquel (quetiapine immediate release) is an atypical antipsychotic that is approved (1) as monotherapy for the acute treatment of schizophrenia, (2) as monotherapy and as adjunctive therapy to lithium or valproate for the acute treatment of manic episodes associated with bipolar disorder, (3) as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder, and (4) as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar disorder. The extended release formulation of quetiapine (i.e., Seroquel XR) is approved (1) as monotherapy for the acute and maintenance treatment of schizophrenia, (2) as monotherapy for the acute treatment of bipolar depression and mania, and (3) as adjunctive therapy for the acute treatment of bipolar mania.

This supplement provides data in support of claims for Seroquel XR for acute monotherapy, acute adjunctive therapy, and maintenance monotherapy of depressive episodes associated with major depressive disorder.

The sponsor's proposed dose range of Seroquel XR for major depressive disorder is 50 to 300 mg/day.

The primary review of the efficacy and safety data was done by Earl Hearst, M.D., from the clinical group. Phillip Dinh, Ph.D., from the biometrics group, also reviewed the efficacy data.

We decided not to take this application to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

Seroquel XR is an approved product, and there were no CMC issues that required review as part of this supplement, except for an environmental assessment for which a request for categorical exclusion was made and accepted.

3.0 PHARMACOLOGY

Seroquel XR is an approved product. There were no pharm/tox issues that required review as part of these supplements.

4.0 BIOPHARMACEUTICS

Seroquel XR is an approved product, and there were no biopharmaceutics issues that required review as part of this supplement, other than pk data collected during the adjunctive clinical trials to assess for drug-drug interactions. Based on these data, OCP recommended a paragraph for labeling suggesting that, although no clear effect of Seroquel XR on co-administered antidepressant levels was demonstrated, there was wide inter-patient variability, and close monitoring is advised.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The sponsor submitted 7 studies in support of its new claims in MDD, including 4 short-term monotherapy studies in support of an acute monotherapy claim (studies 1, 2, 3, and 4), 2 short-term adjunctive therapy studies in support of an acute adjunctive therapy claim (studies 6 and 7), and a randomized withdrawal study (study 5) in support of a maintenance monotherapy claim. For all short-term studies, change from baseline to endpoint on the total MADRS score was the primary endpoint. All of the short-term studies were randomized, double-blind, parallel group, placebo-controlled trials in adult outpatients meeting DSM-IV criteria for MDD. Studies 1, 2, 6, and 7 were fixed dose studies, while studies 3 and 4 were flexible dose. Studies 2 and 4 included an active control arm.

Acute Monotherapy Studies

-Study 1 was a 6-week fixed dose US study including fixed Seroquel XR doses of 50, 150, and 300 mg/day. All 3 doses in Study 1 were superior to placebo, with only a slight numerical advantage for the 150 mg/day dose vs the 50 mg/day dose (Pbo: -11.1; 50 mg: -13.6; 150 mg: -14.5), and no numerical advantage for the 300 mg/day dose over the 150 mg/day dose (150 mg: -14.5; 300 mg: -14.2).
-Study 2 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day. Both doses were superior to placebo, with only a slight numerical advantage for the 300 mg/day dose over the 150 mg/day dose (Pbo: -11.2; 150 mg: -14.8; 300 mg: -15.3). Duloxetine was also superior to placebo.
-Study 3 was an 8-week flexible dose US study (Seroquel XR doses ranging from 150 to 300 mg/day). Seroquel XR was superior to placebo (Pbo: -13.1; Seroquel XR: -16.5; mean daily dose was 162 mg/day).
-Study 4 was an 8-week flexible dose non-US study (Seroquel XR doses ranging from 150 to 300 mg/day). Neither Seroquel XR nor the active control (escitalopram) was superior to placebo, i.e., this was a failed study.

Acute Adjunctive Therapy Studies

-Study 6 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day, added on to a stable dose of one of several other antidepressant products. Only the 300 mg/day dose was superior to placebo (Pbo: -11.7; 150 mg: -13.6; 300 mg: -14.7).
-Study 7 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day, added on to a stable dose of one of several other antidepressant products. Both doses were superior to placebo, with no numerical advantage for the 300 mg/day dose over the 150 mg/day dose (Pbo: -12.2; 150 mg: -15.3; 300 mg: -14.9).

Maintenance Study (Study 5)

This was a randomized withdrawal study involving an open stabilization period of at least 12 weeks of acute treatment with Seroquel XR (dose range of 50 to 300 mg/day; mean dose was 177 mg/day) in patients with MDD. Responders during the open label phase were randomized to either continue on Seroquel XR or receive placebo, and they were observed for relapse for up to 52 weeks. Time to depressive relapse was statistically significantly increased in patients randomized to continued treatment with Seroquel XR (Hazard Ratio = 0.36; $p < 0.001$). The relapse rates were 15% for Seroquel XR vs 34% for placebo.

5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

For the acute monotherapy studies, all 3 doses studied were superior to placebo, however, there was only a slight numerical advantage for the higher doses compared to the lower doses, and this was not consistently demonstrated. Nevertheless, given the suggestion at least of a possible advantage of higher doses and the fact that there was only 1 demonstration of efficacy at the 50 mg/day dose, it seems reasonable to recommend dosing within a range of 50-300 mg/day, but with cautionary language suggesting that there is no clear demonstration of an advantage of higher doses, and there are clearly dose-dependent adverse events.

For adjunctive therapy studies, the 300 mg/day dose was superior to placebo in 2 studies, and the 150 mg/day superior in only 1 of the 2 studies. Therefore, the proposed dose range of 150-300 mg/day seems reasonable.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis age, gender, and race. There was no indication of any difference in effectiveness based on these analyses.

Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline on the MADRS were similar to effect sizes seen in other positive trials.

Duration of Treatment

The randomized withdrawal study did demonstrate maintenance efficacy for Seroquel XR as monotherapy in MDD.

PREA Requirements

The sponsor will get a waiver for ages less than 7, and a deferral for ages 7-17 for the treatment of MDD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support claims for acute monotherapy, acute adjunctive therapy, and maintenance monotherapy for Seroquel XR in MDD.

5.2 Safety Data

The safety review for these supplements was based on data from the 6 acute studies and the maintenance study. Overall, the safety findings for these supplements were consistent with the known adverse event profile for quetiapine and no important new adverse events that could be considered causally related to quetiapine were discovered as a result of the safety review. We are currently reviewing a comprehensive submission from the sponsor regarding metabolic effects of quetiapine. Both Drs. Levin and Hearst feel that the safety profile of Seroquel XR in MDD can be adequately characterized in labeling. I agree that the safety profile we are seeing in the MDD population is not different from the profile we have already observed in other populations. However, it is of some concern that approving these claims will likely greatly expand the use of this product. Thus, we need to think carefully about the risks and benefits of such expanded use, particularly with regard to longer-term risks which are not yet fully established. Tardive dyskinesia is an accepted risk in schizophrenic and bipolar patients, and in fact, thought to be somewhat reduced in association with atypical antipsychotic drugs, such as quetiapine. However, the sponsor has not addressed this concern. Furthermore, there is accumulating evidence that quetiapine may have substantial metabolic risks (weight gain, hyperlipidemia, and hyperglycemia) with all the attendant longer-term cardiovascular and other risks. Thus, if these new claims are to be approved, it will be important to ensure that labeling, and perhaps other educational material, fully informs prescribers and patients about these known and potential risks.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling and asked them to make a number of additional modifications.

6.0 WORLD LITERATURE

The sponsor apparently provided literature references but without any comment on methodology or any assessment of what they provided. Dr. Hearst simply stated: "There were no new significant findings in the literature." In the CR literature we have mentioned the published literature as one possible source of information of the longer-term risks associated with the use of this drug, e.g., tardive dyskinesia.

7.0 FOREIGN REGULATORY ACTIONS

The reviewer does not comment on whether or not Seroquel XR is approved in any other countries for the treatment of MDD.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We have not, as yet, taken this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at three sites that enrolled patients from pivotal studies. The data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

Our proposal for labeling will be included in the CR letter.

11.0 CONCLUSIONS AND RECOMMENDATIONS

The sponsor has submitted sufficient data to support the conclusion that Seroquel XR is effective as acute monotherapy and adjunctive therapy and as maintenance monotherapy in the treatment of MDD. The safety profile, to the extent that it can be characterized, appears to be similar to that observed with this drug in other conditions. However, there remains a concern about longer-term risks with this drug, in particular risks related to metabolic changes with this drug and the possibility of tardive dyskinesia. These issues become even more important as the distribution of this drug to a much broader patient population is considered. Thus, we will ask the sponsor to strengthen labeling, particularly with regard to the metabolic concerns, and gather whatever additional evidence might be available to address the concern about tardive dyskinesia. Thus, I will issue a Complete Response letter for these supplements.

cc:
Orig NDA 22-047S-010/011/012
HFD-130
HFD-130/TLaughren/MMathis/RLevin/EHearst/RGrewal

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/s/

Thomas Laughren
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 22-047
Submission Number	S-010,011,012
Submission Code	N
Letter Date	Feb 27, 2008
Stamp Date	Feb 27, 2008
PDUFA Goal Date	Dec 27, 2008
Reviewer Name	Earl D. Hearst
Review Completion Date	10/31/2008
Established Name	quetiapine XR
(Proposed) Trade Name	Seroquel XR
Therapeutic Class	Atypical Antipsychotic
Applicant	AstraZenica
Priority Designation	S
Formulation	Extended Release Tablets
Dosing Regimen	50 to 300 mg daily
Indication	Short-term monotherapy, adjunct use and monotherapeutic maintenance in MDD
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend all three supplements S-010, 011 and 012 be approved.

1.2 Recommendation on Postmarketing Actions

There are no recommendations for actions other than the usual procedures.

1.2.1 Risk Management Activity

There are no recommendations for actions other than the usual procedures.

1.2.2 Required Phase 4 Commitments

AstraZeneca is currently working to fulfill the Written Request through the conduct of a pediatric clinical development program. On February 11, 2003, the Division issued a Pediatric Written Request for SEROQUEL Tablets (NDA 20-639) for the treatment of schizophrenia and bipolar mania. The Division agreed (October 11, 2005) that one pharmacokinetic study comparing the XR and immediate-release (IR) formulations of quetiapine will satisfy AstraZeneca's pediatric study obligations for SEROQUEL XR, provided that the IR formulation is demonstrated to be efficacious in pediatric patients in the Pediatric Written Request program.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The quetiapine XR MDD studies supporting the current registration package consists of the Following three supplements S-010,011 and 012:

Short-term Monotherapy: Studies 1, 2, 3 and 4

Short-term adjunct treatment: Studies 6 and 7

Maintenance treatment: Study 5

1.3.2 Efficacy

Quetiapine XR at doses of 50 mg/day, 150 mg/day, and 300 mg/day was superior to placebo as monotherapy in reducing the level of depressive symptoms through Week 6 or 8 in patients with MDD, as assessed by evaluation of Montgomery-Åsberg Depression Rating Scale (MADRS) total score in studies 1, 2 and 3. Study 4 was not significant..

Quetiapine XR at doses of 150 mg/day and 300 mg/day as adjunct to an antidepressant was superior to antidepressant therapy as adjunct to placebo in reducing the level of depressive symptoms at Week 6 in patients with MDD who had an inadequate response to previous antidepressant treatment, as assessed by evaluation of MADRS total score. See studies 6 and 7.

Maintenance treatment with quetiapine XR at flexible doses of 50 mg/day, 150 mg/day, or 300 mg/day statistically significantly increased the time to a depressed event in patients with MDD.

1.3.3 Safety

The safety data in this submission are generally consistent with current labeling for Seroquel SR. No new safety issues have been identified.

1.3.4 Dosing Regimen and Administration

The studies in this submission used SEROQUEL XR at doses of 50 mg, 150 mg, and 300 mg once daily. The sponsor recommends dosing as follows in their draft label.

Initial dosing should begin at 50 mg on Days 1 and 2, and be increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if necessary, adjustments can be made upwards or downwards within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

1.3.5 Drug-Drug Interactions

There was no evidence from the SAE reports that quetiapine XR interacted with other medications during the acute monotherapy, acute adjunct therapy, and maintenance studies. Adjunct therapy with quetiapine XR at doses of 150mg/day or 300mg/day did not appear to have a consistent overall effect on the plasma concentrations of any of the adjunct antidepressants and their metabolites.

1.3.6 Special Populations

Safety in special groups defined by sex, age and race was explored by tabulating adverse event incidence by those factors. The incidence of common AEs in patients was generally consistent across gender, age from 18 to 65 and race in both monotherapy and adjunct treatment trials, and did not give rise to any new safety issues regarding the use of quetiapine XR in special groups and situations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Approval is being sought for the use of quetiapine extended release (XR) for 3 supplements, S-010, 011 and 012, short-term monotherapy, adjunct use and monotherapeutic maintenance in MDD.

2.2 Currently Available Treatment for Indications

There are a number of approved products for these indications.

2.3 Availability of Proposed Active Ingredient in the United States

This is an available approved drug.

2.4 Important Issues With Pharmacologically Related Products

None to report.

2.5 Presubmission Regulatory Activity

Key agreements between FDA and AstraZeneca were as follows:

Approval for both the monotherapy and adjunct indications could be based on a single positive monotherapy and a single positive adjunct study.

Approval for both the short-term monotherapy and maintenance indications could be based upon a single positive short-term monotherapy and a single positive maintenance therapy study.

Data on elderly patients were not required for approval of the MDD sNDA.

The results of a Columbia University-type analysis of suicidality should be provided.

2.6 Other Relevant Background Information

n/a

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

n/a

3.2 Animal Pharmacology/Toxicology

The new nonclinical information reported in this sNDA involves the results of *in vitro* receptor binding studies comparing the binding properties of quetiapine with those of norquetiapine. *In vitro* functional assays were also conducted to characterize agonist or antagonist activity of quetiapine and norquetiapine at selected pharmacological targets. In all other respects the nonclinical data provided in NDA 20-639 are hereby cross-referenced to this sNDA. In addition, the nonclinical data provided in IND 74,629 are hereby cross-referenced to this sNDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The quetiapine XR MDD studies supporting the current registration package consists of the following three supplements, S-010, 011 and 012.

Short-term Monotherapy: Studies 1, 2, 3 and 4

Short-term adjunct treatment: Studies 6 and 7

Maintenance treatment: Study 5

The data is presented in the EDR at

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4.2 Tables of Clinical Studies

The quetiapine XR clinical development program for MDD consists of 8 studies, as shown in Table O 1.

Table O 1 Summary of MDD Clinical Development Program

Study number	Study type /	Treatment arms	Duration of treatment
D1448C00001 (Study 1)	Fixed Dose Monotherapy	-Quetiapine XR 50 mg -Quetiapine XR 150 mg -Quetiapine XR 300 mg -Placebo	6 wks
D1448C00002 (Study 2)	Fixed Dose Monotherapy	-Quetiapine XR 150 mg -Quetiapine XR 300 mg -Duloxetine 60 mg -Placebo	6 wks
D1448C00003 (Study 3)	Modified Fixed Dose Monotherapy	-Quetiapine XR 150/300 mg -Placebo	8 wks
D1448C00004 (Study 4)	Modified Fixed Dose Monotherapy	-Quetiapine XR 150/300 mg -Escitalopram 10/20 mg -Placebo	8 wks
D1448C00005 (Study 5)	Maintenance Treatment	-Quetiapine XR 50-300 mg -Placebo	4-8 wks open-label run-in treatment/ at least 16 wks open-label stabilization treatment/ up to 52 wks of randomized treatment
D1448C00006 (Study 6)	Adjunct treatment in inadequate responders	-Quetiapine XR 150, 300 mg -Placebo	6 wks
D1448C00007 (Study 7)	Adjunct treatment in inadequate responders	-Quetiapine XR 150, 300 mg -Placebo	6 wks
D1448C00014 [a] (Study 14)	Flexible Dose Monotherapy Elderly Patients	-Quetiapine XR 50-300 mg -Placebo	9 wks

a Study D1448C00014 was ongoing at the time databases were locked for this application.

4.3 Review Strategy

The review will center on the seven primary studies that support the three indications.

4.4 Data Quality and Integrity

The conduct of the studies in this program appears to be appropriate. No events were noted by the sponsor or reviewers that call into question the data obtained. The DSI review has not yet been recieved.

4.5 Compliance with Good Clinical Practices

AstraZeneca procedures, internal quality control measures and audit programs provide reassurance that the clinical study program was carried out in accordance with the ethical principles and standards that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice.

4.6 Financial Disclosures

I have reviewed the financial disclosure information for the seven studies. There are a few investigators who have received more than $25,000 in fees but the sponsor feels due to the low number of subjects at their sites that no bias overall in the studies would be present. I agree with this.

5 CLINICAL PHARMACOLOGY

Clinical pharmacology findings for quetiapine IR have been described in the original registration dossier and supplemented with the extension of that registration for treatment of acute mania in bipolar disorder and for depressive episodes in bipolar disorder that were subsequently approved (NDA 20-639). Findings for quetiapine XR were described in the dossier for treatment of schizophrenia (NDA 22-047). Additional material is provided regarding 2 issues of pharmacokinetic and pharmacodynamic importance. The first question addressed the potential for pharmacokinetic interaction between quetiapine or its metabolites with various antidepressants and their metabolites. Pooled analysis from Studies 6 and 7 showed that blood concentrations of known antidepressants and their metabolites were not meaningfully altered following administration of quetiapine XR for up to 2 weeks. These results were concordant with the sponsor's review of the literature that revealed little propensity for meaningful interaction via known metabolic pathways. Review of the AstraZeneca post-marketing surveillance database did not reveal any significant concerns regarding potential interactions between quetiapine and antidepressant medications that are not already contained in the quetiapine professional information brochure.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Approval is being sought for the use of quetiapine extended release (XR) for the treatment of major depressive disorder (MDD). This application contains data that supports quetiapine XR in the treatment of major depressive disorder as:

Monotherapy or adjunct therapy to other antidepressants

Maintenance of antidepressant effect

6.1.1 Methods

There were 7 Phase III studies on the safety and efficacy of quetiapine XR when used in the treatment of patients with Major Depressive Disorder (MDD). Studies 1 to 4 were acute monotherapy studies, Studies 6 and 7 were acute adjunct therapy studies (with ongoing antidepressant therapy), and Study 5 was a monotherapy maintenance treatment study.

6.1.2 General Discussion of Endpoints

In short-term Studies 1, 2, 3, 4, 6 and 7 the primary outcome variable was the change from baseline in the MADRS score. All statistical comparisons for quetiapine XR vs placebo for the two outcome variables were alpha-protected.

6.1.3 Study Design

All of the trials were placebo-controlled and two of the trials (Studies 2 and 4) employed active comparators. The active comparators (duloxetine 60 mg daily in Study 2; escitalopram 10-20 mg daily in Study 4) were both standard-of-care treatments for MDD and dosed at standard, known-to-be-effective doses.

In Studies 1 and 2, treatment duration was 6 weeks. In Studies 3 and 4, treatment duration was 8 weeks to allow for assessment of inadequate response after 2 weeks of treatment and a contingent increase in dose. In all 4 studies, the active treatment period was followed by a 2-week period of assessment of withdrawal signs and symptoms following treatment discontinuation via AE reports and the TDSS scale in patients who finished the 6- or 8-week treatment period. The 8- to 10-week duration of placebo treatment was justified by the value of tracking possible withdrawal symptoms in the quetiapine XR-treated patients and the close monitoring of all patients during both the treatment and the post-treatment periods.

The design of Study 5 allowed for a total quetiapine exposure of up to 78 weeks. Patients who responded to open-label treatment in 4 to 8 weeks were admitted to a 12- to 18-week stabilization treatment period. Those maintaining response during the stabilization period were then randomly assigned to continue with quetiapine XR or to switch to placebo treatment for up to 52 weeks. Analysis of time to a depressed event and proportions of patients experiencing such an event were in accord with current scientific and regulatory standards.

Key inclusion criteria (Studies 1, 2, 3, 4, 6, and 7)

The key inclusion criteria for enrollment were as follows:

1. Male and female patients aged 18 to 65 years old, inclusive.

2. Documented clinical diagnosis meeting the DSM-IV criteria for any of the following:

296.2x Major Depressive Disorder, Single Episode, or

296.3x Major Depressive Disorder, Recurrent, as confirmed by MINI

3. HAM-D (17-item) total score and HAM-D Item 1 (depressed mood) score of:

Acute monotherapy studies (Studies 1, 2, 3, and 4): HAM-D total score ≥22,

HAM-D Item 1 score ≥2 at enrolment and randomization

Acute adjunct therapy studies (Studies 6 and 7): HAM-D total score ≥20, HAM-D Item 1 score ≥2 at enrolment and randomization

Maintenance treatment study (Study 5): HAM-D total score ≥20, HAM-D Item 1 score ≥2 at enrolment

4. Outpatient status at enrollment

Quetiapine XR was taken once daily at bedtime in all studies.

Titration schedule for the acute treatment studies (Studies 1,2, 3, 4, 6, and 7)

To maximize tolerability, quetiapine XR was gradually titrated from 50 mg to the final dose. In all studies, patients randomized to quetiapine XR treatment were administered a 50 mg dose for 2 days, with the dose being increased to 150 mg over the next 2 days for the 150 mg/day and 300 mg/day groups, and 300 mg thereafter in the relevant groups.

Concomitant medication for all trials

In all trials, concomitant psychotropic drug use was prohibited with the exception of sleep medications which were permitted only if the patient had been using the agent nightly for 28 days prior to enrollment. Any medication that would induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes was prohibited during and two weeks before the treatment period.

Adjuctive Studies Medications

The following antidepressants were allowed: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine (Studies 6 and 7 only)

In the adjunct treatment trials (Studies 6 and 7), quetiapine XR or placebo treatment was randomly assigned to patients who had been treated with an approved antidepressant but who still exhibited HAM-D total scores of ≥20, with Item 1 of the scale ≥2. Blood samples were taken before the initiation of quetiapine XR treatment and at 2 and 4 weeks after in order to assess any changes in trough antidepressant plasma concentrations consequent to quetiapine exposure. Antidepressants on entry were restricted to amititriptyline, bupropion,

Individual Studies

STUDY 1

A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL®) as Monotherapy in the Treatment of Patients with Major Depressive Disorder (Moonstone Study)

International co-ordinating investigator
Richard Weisler, MD

This study was conducted at 47 centers in the United States.

Study design
This was a 8-week, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled Phase III study of the efficacy and safety of quetiapine XR 50 mg/day, 150 mg (3 × 50 mg) per day, and 300 mg/day as monotherapy in the treatment of patients with MDD. This study consisted of an up to 28-day enrollment period, a 6-week randomized treatment period with 1 of 4 treatment regimens (quetiapine XR 50 mg, quetiapine XR 150 mg, quetiapine XR 300 mg, or placebo), and a 2-week post-treatment period.

Target population and sample size
Male and female patients, 18 to 65 years old inclusive, with documented clinical diagnosis using the Mini-International Neuropsychiatric Interview (MINI) and meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) of either 296.2x Major Depressive Disorder, Single Episode, or 296.3x Major Depressive Disorder, Recurrent. The patients had to have a Hamilton Rating Scale for Depression (HAM-D) score ≥22 to be eligible for the study. The aim of this study was to randomize a patient population with approximately 40% of the patients having a HAM-D score of ≥28.

It was planned to randomly assign 712 patients to obtain a total of 664 evaluable patients (166 per treatment group). The sample size calculation in this study was done to ensure an 80% power in demonstrating superior efficacy of the 150-mg and/or 300-mg quetiapine XR doses over placebo with regard to the primary outcome variable, change in MADRS total score from randomization to Week 6. The appropriate sample size was attained by assuming an anticipated difference of 3.5 unit difference from placebo, with a between-patient variability (standard deviation) of 9 for the change in MADRS total score from baseline to Week 6. Because of multiplicity considerations, a 2-sided test at $\alpha = 0.025$ and a power of 90% for each of the 2 high doses were assumed. This yields a planned sample size of 166 for each of the 4 arms, and 664 in total.

Duration of treatment
An initial washout period of 7 to 28 days (depending on the medications involved) was followed by a double-blind treatment period for up to 6 weeks (42 days). Eligible patients were randomly assigned to blinded treatment in a 1:1:1:1 ratio to the 50-mg/day

quetiapine XR treatment group, the 150-mg/day quetiapine XR treatment group, the 300-mg/day quetiapine XR treatment group, or the placebo treatment group. All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150 mg/day–group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300-mg/day group were uptitrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. Following completion of the 6 week randomization period, patients participated in a 2-week post-treatment period. During the post-treatment period, patients were asked to call in to an Interactive Voice Response System (IVRS) to participate in an assessment of discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale and return to the study center for 2 post-treatment visits.

Figure 3 **Patient disposition (completion or discontinuation)**

Screened	1075
Screen failures	352 (100%)
Eligibility criteria not fulfilled	239 (67.9%)
Patient not willing to continue	53 (15.1%)
Lost to follow-up	49 (13.9%)
Other	6 (1.7%)
Adverse event	3 (0.9%)
Severe non-compliance to the CSP	1 (0.3%)
Development of study-specific discontinuation criteria	1 (0.3%)
Randomized	723

	PLA	QTP50	QTP150	QTP300
Randomized	**184**	**182**	**178**	**179**
Not treated	3 (1.6)	1 (0.5)	2 (1.1)	0
Received drug	**181 (98.4)**	**181 (99.5)**	**176 (98.9)**	**179 (100.0)**
Discontinued study	50 (27.2)	48 (26.4)	55 (30.9)	59 (33.0)
Lost to follow-up	18 (9.8)	14 (7.7)	10 (5.6)	12 (6.7)

	PLA	QTP50	QTP150	QTP300
Adverse event	11 (6.0)	15 (8.2)	25 (14.0)	34 (19.0)
Development of study-specific discontinuation criteria	1 (0.5)	3 (1.6)	0	1 (0.6)
Patient not willing to continue	10 (5.4)	9 (4.9)	9 (5.1)	8 (4.5)
Condition under investigation worsened	4 (2.2)	0	1 (0.6)	0
Severe non-compliance to study protocol	2 (1.1)	6 (3.3)	8 (4.5)	3 (1.7)
Eligibility criteria not fulfilled	1 (0.5)	0	2 (1.1)	0
Other	3 (1.6)	1 (0.5)	0	1 (0.6)
Completed 6-week randomized treatment period	**134 (72.8)**	**134 (73.6)**	**123 (69.1)**	**120 (67.0)**
Completed study[a]	**95 (51.6)**	**103 (56.6)**	**89 (50.0)**	**86 (48.0)**

[a] Patients who completed the randomization phase plus the 2-week follow-up period.

In total, 1075 patients were screened for possible study participation. Of those, 723 qualified and were assigned to randomized treatment on Day 1. Of the 352 patients who did not qualify, 68% (239 patients) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 184 to placebo, 182 to quetiapine XR 50 mg/day, 178 to quetiapine XR 150 mg/day, and 179 to quetiapine XR 300 mg/day.

Overall, the discontinuation rate was highest in the quetiapine XR 300-mg/day group (33%) followed by the quetiapine XR 150-mg/day group (31%), the quetiapine XR 50-mg/day group (26%) and the placebo group (27%). The most common reason for withdrawal was an adverse event. There was a dose-related increase in the rate of discontinuation due to AEs across the quetiapine XR groups. The rates of discontinuation due to AEs were higher in the quetiapine XR 50-mg/day group (19%), 150-mg/day group (14%), and 300-mg/day group (8%) when compared to placebo (6%). Loss to follow-up was the second most common reason for discontinuation and occurred with the highest frequency in the placebo group.

In patients with MDD, all doses of quetiapine XR (50 mg/day, 150 mg/day, and 300 mg/day) were superior to placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant change from randomization to Week 6 in the MADRS total score. Overall, results from the secondary outcome variables supported the primary objective. MADRS total score was improved in all quetiapine groups relative to placebo by Day 4. The quetiapine XR groups demonstrated greater MADRS response, MADRS remission, reduction in the HAM-A total score, CGI-S and CGI-I scores, and improvement in HAM-A psychic anxiety subscale score in comparison to the placebo group. Improvements in MADRS, HAM-D, HAM-A, and PSQI scores indicated improved sleep quality with quetiapine XR treatment. However, in the evaluation of health-related quality of life with Q-LES-Q, the

efficacy of quetiapine XR over placebo was not demonstrated.

Table 17 **MADRS total score change from randomization to Week 6 (LOCF, MITT analysis set)**

		PLA N=178	QTP50 N=178	QTP150 N=168	QTP300 N=176
N[a]		178	178	168	176
Randomization[b]	Mean (SD)	30.5 (5.2)	30.9 (4.5)	30.9 (5.0)	30.6 (4.8)
Week 6	Mean (SD)	19.8 (10.6)	17.6 (10.4)	16.7 (10.2)	16.8 (9.8)
Change	Mean (SD)	-10.7 (10.1)	-13.3 (10.2)	-14.3 (9.9)	-13.8 (10.2)
ANCOVA results	LS mean	-11.07	-13.56	-14.50	-14.18
	95% CI	-12.79 to -9.34	-15.29 to -11.83	-16.26 to -12.74	-15.91 to -12.45

Table 17 **MADRS total score change from randomization to Week 6 (LOCF, MITT analysis set)**

		PLA N=178	QTP50 N=178	QTP150 N=168	QTP300 N=176
Difference vs PLA	Est. difference	NA	-2.50	-3.44	-3.11
	95% CI	NA	-4.48 to -0.51	-5.45 to -1.42	-5.10 to -1.12
	p-value	NA	0.014	<0.001	0.002
	Adjusted p-value[c]	NA	0.042	0.002	0.004

[a] Number of patients with a value at randomization and at least one post-randomization value. The mean value for change from randomization was calculated for these patients.
[b] The mean value at randomization was calculated based on values at randomization for all patients in the MITT analysis set.
[c] P-values were adjusted using the tree-gatekeeping procedure described in Section 5.7.4.1.
ANCOVA Analysis of covariance. CI Confidence interval. Est. Estimated. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. N Number of patients in treatment group. NA Not applicable. PLA Placebo. QTP Quetiapine XR. SD Standard deviation.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

STUDY 2

A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR) as Mono-Therapy in the Treatment of Adult Patients with Major Depressive Disorder (OPAL STUDY)

International co-ordinating investigator
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Study center(s)
This study was conducted at 38 centers in the United States.

Study design

This was an 8-week, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in the treatment of patients with MDD versus placebo and duloxetine 60 mg. This study consisted of an up to 28-day enrollment and washout period, a 6-week randomized treatment period, and a 2-week post-treatment period that included titrated dose decreases during the first post-treatment week for patients randomly assigned to the quetiapine XR 300-mg/day and duloxetine 60-mg dose groups.

Target population and sample size

Male and female patients, 18 to 65 years old inclusive, with documented clinical diagnosis using the Mini-International Neuropsychiatric Interview (MINI) and meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) of either 296.2x Major Depressive Disorder, Single Episode, or 296.3x Major Depressive Disorder, Recurrent.

The patients had to have a Hamilton Rating Scale for Depression (HAM-D) score ≥22 to be eligible for the study. The aim of this study was to randomize a patient population with approximately 40% of the patients having a HAM-D score of ≥28.
The sample size calculation in this study was done to ensure an 80% power in demonstrating superior efficacy of each of the 2 quetiapine XR doses over placebo with regard to the primary outcome variable, change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 6. The appropriate sample size was attained by assuming an anticipated difference of 3.5 units from placebo and a standard deviation of 9 for the change in MADRS total score from randomization to Week 6. Based on a 2-sided test at a 5% significance level (ie, α=0.05), it was planned to randomize a sample size of 140 per treatment group and 560 in total to ensure a power of 90% in each individual comparison and an overall power of at least 80%. Assuming based on earlier studies that 93% of all patients assigned to randomized treatment were expected to be evaluable patients (to be included in the modified intent-to-treat [MITT] group), a total of about 600 patients assigned to randomized treatment were required to obtain 140 evaluable patients per treatment group. A total of 612 patients were assigned to randomized treatment, of whom 610 received treatment and were in the safety analysis set and 587 were included in the MITT analysis set. The study was not powered for a comparison of quetiapine XR versus duloxetine.

Duration of treatment

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by a double-blind treatment period for up to 6 weeks (42 days). During a 2-week post-treatment period, patients randomly assigned to the quetiapine XR 300-mg/day dose

group and the duloxetine 60-mg dose groups took titrated decreased doses of their randomly assigned study medication from Day 43 (final treatment visit) to Post-treatment Day 6. During the 2-week down-titration period, patients assigned to randomized treatment with quetiapine XR 150 mg/day received placebo from Day 43 (Final visit) to Day 49 (Posttreatment Day 6). For all groups, study drugs were stopped after Day 49. All patients randomly assigned to treatment who completed the treatment period and assessments were asked to call in to an Interactive Voice Response System (IVRS) to participate in an assessment of discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale and return to the study center for 2 Post-treatment visits.

Figure 3 **Patient disposition (completion or discontinuation)**

Screened	912
Screen failures	299
Lost to follow-up	36
Adverse event	3
Eligibility criteria not fulfilled	213
Patient not willing to continue	44
Severe noncompliance to protocol	1
Other	2
Randomized	612[a]

	PLA	QTP150	QTP300	DUL
Randomized	**157 (100.0)**	**152 (100.0)**	**152 (100.0)**	**151 (100.0)**
Not treated[b]	0	0	0	2
Received drug	**157**	**152**	**152**	**149**
Discontinued study	33 (21.0)	52 (34.2)	39 (25.7)	46 (30.5)
Adverse event	7 (4.5)	30 (19.7)	23 (15.1)	20 (13.1)
Condition under investigation worsened	3 (1.9)	0	0	2 (1.3)
Death	0	1 (0.7)	0	0
Development of study-specific discontinuation criteria	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.7)
Eligibility criteria not fulfilled	0	1 (0.7)	0	2 (1.3)
Other	1 (0.6)	0	1 (0.7)	2 (1.3)
Severe noncompliance to the protocol	3 (1.9)	2 (1.3)	1 (0.7)	0
Lost to follow-up	9 (5.7)	10 (6.6)	6 (3.9)	7 (4.6)
Not willing to continue	9 (5.7)	7 (4.6)	7 (4.6)	12 (7.9)
Completed 6-week randomized treatment period	**124 (79.0)**	**100 (65.8)**	**113 (74.3)**	**105 (69.5)**
Completed study[c]	**100 (63.7)**	**73 (48.0)**	**92 (60.5)**	**71 (47.0)**

[a] Patient E1009500 was screened for this study but mistakenly assigned to randomized treatment in another study. This patient was counted as screened for this study and was not counted as randomized in this study, but was not counted as a screen failure.
[b] Patients not treated are also included in the discontinued from study treatment analysis set due to development of study-specific discontinuation criteria.
[c] Completed the randomization period and the 2-week follow-up period (TDSS).
DUL Duloxetine. PLA Placebo. QTP Quetiapine XR.

In total, 912 patients were screened for possible study participation. Of those, 612 qualified and were assigned to randomized treatment on Day 1. Of the 299 patients who did not qualify, 71.2% (213 patients) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 157 to placebo, 152 to quetiapine XR 150 mg/day, 152 to quetiapine XR 300 mg/day and 151 to duloxetine 60 mg/day. Of the 612 patients assigned to randomized treatment, 2 did not receive any study medication (both in the duloxetine group).

Overall, 21% of the placebo group, 34.2% quetiapine XR 150-mg/day group, 25.7% of the quetiapine XR 300-mg/day group, and 30.5% of the duloxetine group discontinued the study during randomized treatment. Discontinuations due worsening of the condition under investigation occurred in 1.9% of placebo patients and 1.3% of duloxetine patients. None of the quetiapine XR patients at either dose discontinued for this reason. The rate of discontinuation due to AE was higher in the quetiapine XR 150-mg/day group (19.7%), quetiapine XR 300-mg/day group (15.1%), and the duloxetine group (13.2%) than in the placebo group (4.5%). "Adverse event" was the most common reason for discontinuation in all but the placebo groups. Discontinuations due to loss to follow-up and patient not willing to continue occurred at a similar rate in all of the treatment groups.

Approximately 72% of patients completed the randomized treatment portion of the study. Of those patients who completed randomized treatment, 80.6% of placebo patients, 73.0% of quetiapine XR 150-mg/day patients, 81.4% of quetiapine XR 300-mg/day patients, and 67.6% of duloxetine patients completed the 2-week follow-up (TDSS) period.

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=152	QTP150 N=147	QTP300 N=147	DUL N=141
MADRS LS mean change from randomization	-11.18	-14.81[a]	-15.29[a]	-14.64[a]
Proportion with MADRS response (decrease in MADRS total score ≥50%)	36.2%	54.4%[b]	55.1%[a]	49.6%[c]
Proportion with MADRS remission (total score ≤8)	20.4%	26.5%	32.0%[c]	31.9%[c]
HAM-D LS mean change from randomization	-10.26	-13.12[a]	-14.02[a]	-12.37[c]
HAM-D Item 1 LS mean change from randomization	-1.07	-1.49[a]	-1.56[a]	-1.53[a]
CGI-S LS mean change from randomization	-1.06	-1.43[b]	-1.60[a]	-1.53[a]
Proportion improved on CGI-I	39.5%	54.1%[c]	59.2%[a]	56.7%[b]
Q-LES-Q % maximum total score LS mean change from randomization	11.26	13.68	13.59	16.69[b]
HAM-A total score LS mean change from randomization	-5.55	-7.76[b]	-7.38[b]	-7.83[a]

[a] p≤0.001 comparison with placebo.
[b] p≤0.01 comparison with placebo.
[c] p≤0.05 comparison with placebo.

CGI-S Clinical Global Impression Severity scale. CGI-I Clinical Global Impression Improvement scale. DUL Duloxetine. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

Note: For the analyses of MADRS and Q-LES-Q percent maximum total score change from randomization for the quetiapine XR groups, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy. P-values for the comparison between duloxetine and placebo and between duloxetine and quetiapine XR were not adjusted.

In patients with MDD, quetiapine XR at a dose of 150 mg/day or 300 mg/day was superior to

placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant change from randomization to Week 6 in the MADRS total score. Both quetiapine XR groups showed a greater improvement by Week 1 of treatment (p=0.002 and p=0.004 for 150 mg/day and 300 mg/day, respectively).

The quetiapine XR 150- and 300-mg groups received mean daily doses of 124.7 and 244.8, respectively, and were on treatment for a mean of 37.7 and 40.4 days, respectively, during the 6-week randomized period.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

STUDY 3

A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR) as Mono-Therapy in the Treatment of Adult Patients with Major Depressive Disorder (OPAL STUDY)

International co-ordinating investigator

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Study center(s)

This study was conducted at 35 sites in the United States.

Study design

This was a 10-week, multicenter, double-dummy, randomized, parallel-group, placebo controlled Phase III study of the efficacy and safety of quetiapine XR given as monotherapy in the treatment of patients with MDD. The study consisted of an up to 28-day enrollment period, an 8-week randomized treatment period, and a 2-week post-treatment period. All quetiapine XR patients initiated treatment on quetiapine XR 50 mg/day and were up-titrated to 150 mg/day at Day 3. Placebo patients received matched placebo according to the same treatment plan. After 2 weeks of treatment, patients with an inadequate response (defined as failure to achieve a ≥20% improvement from randomization in MADRS total score) were uptitrated to twice their original dose (300 mg/day quetiapine XR or matching placebo). Investigators were blinded to the criterion defining inadequate response (ie, the criterion for inadequate response was defined in a document separate from the study protocol and not

shared with the investigator) and were blinded to dose increase. At the end of 8 weeks of randomized treatment, all investigational product was discontinued and patients underwent a 2-week post-treatment follow-up period.

Duration of treatment

An initial washout period of up to 28 days (depending on the medications involved) was followed by an 8-week, double-blind randomized treatment period. After 2 weeks of treatment, patients with an inadequate response were treated with double the randomized dose (ie, quetiapine XR 300 mg/day or placebo). The 8-week, double-blind treatment period was followed by a 2-week follow-up period.

Figure 2 **Patient disposition (completion or discontinuation)**

Screened	513
Screen failures	203
Eligibility criteria not fulfilled	154
Other	3
Lost to follow-up	16
Patient not willing to continue	30
Randomized	310

	PLA	QTP
Randomized	**156**	**154**
Not treated[a]	1	2
Received drug	**155 (99.4%)**	**152 (98.7%)**
Adequate response[b]	102 (74.5%)	107 (82.9%)
Inadequate response[b]	35 (25.5%)	22 (17.1%)
Discontinued study	**45 (28.8%)**	**46 (29.9%)**
Adverse event	4 (2.6%)	13 (8.4%)
Eligibility criteria not fulfilled	1 (0.6%)	2 (1.3%)
Lack of therapeutic response	7 (4.5%)	7 (4.5%)
Other	3 (1.9%)	0
Severe noncompliance to the protocol	3 (1.9%)	1 (0.6%)
Did not complete ≥50 days of treatment	1 (0.6%)	0
Lost to follow-up	12 (7.7%)	11 (7.1%)
Not willing to continue with study	14 (9.0%)	12 (7.8%)
Completed 8-week randomized treatment period	**111 (71.2%)**	**108 (70.1%)**
Completed study[c]	**78 (50.0%)**	**81 (52.6%)**

[a] Patients not treated are also included in the discontinued from study treatment analysis set due to development of study-specific discontinuation criteria.

[b] Patients with inadequate response after 2 weeks of treatment (defined as a failure to achieve ≥20% improvement from randomization in MADRS total score) were up-titrated to double their initial dose (300 mg quetiapine XR or double the placebo dose). Those with an adequate response remained at their initial dose (150 mg quetiapine XR or a matching placebo dose). Percentages are based on the numbers of

In total, 513 patients were screened for possible study participation. Of those, 310 qualified and were assigned to randomized treatment on Day 1. Of the 203 patients who did not qualify, 154 patients were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 156 to placebo and 154 to quetiapine XR. Of the 310 randomized patients, 3 patients

(1 and 2 patients in the placebo and quetiapine XR groups, respectively) did not receive any study medication.

Based on the number of patients still receiving randomized treatment at Week 2, a total of 35 of 137 (26%) and 22 of 129 (17%) patients in the placebo and quetiapine XR groups, respectively, met the criterion for inadequate response (ie, were up-titrated to double the initial randomized dose after 2 weeks of treatment for failing to show ≥20% improvement in MADRS total score from randomization).

Overall, 28.8% of the placebo group and 29.9% of the quetiapine XR group discontinued the study during randomized treatment. "Subject not willing to continue with study" was the main reason for withdrawal in placebo-treated patients, and AE was the main reason for discontinuation among quetiapine XR patients. A similar percentage of patients in both treatment groups discontinued the study because they were not willing to continue the study (7.8% and 9.0% in the quetiapine XR and placebo groups, respectively) or were lost to followup (7.1% and 7.7%, respectively). Of patients who completed the randomized treatment period, 70.3% of placebo patients and 75.0% of quetiapine XR patients completed the TDSS follow-up period.

Approximately 71% of patients completed the randomized treatment period of the study, with similar rates of completion in the quetiapine XR group compared to placebo. Of patients who completed the randomized treatment period, 70.3% and 75.0% of placebo and quetiapine XR patients, respectively, completed the 2-week follow-up period (TDSS).

Table S3 Efficacy results at Week 8 (LOCF, MITT analysis set)

Outcome variable	PLA N=152	QTP N=147
MADRS total score LS mean change from randomization	-13.1	-16.49[a]
Proportion with MADRS response (decrease in MADRS total score of ≥50%)	48.0%	61.9%[b]
Proportion with MADRS remission (total score ≤8)	25.0%	34.7%[c]
HAM-D total score LS mean change from randomization	-12.35	-14.75[b]
HAM-D Item 1 LS mean change from randomization	-1.40	-1.71[b]
CGI-S total score LS mean change from randomization	-1.24	-1.64[a]
Proportion improved on CGI-I	52.0%	63.3%[b]
Q-LES-Q % maximum total score LS mean change from randomization	11.93	13.80
HAM-A total score LS mean change from randomization	-7.70	-9.14[b]

[a] p<0.01 comparison with placebo.
[b] p<0.05 comparison with placebo.
[c] p=0.052 comparison with placebo.

In patients with MDD, quetiapine XR was superior to placebo in reducing depressive

symptoms as demonstrated by the statistically significant mean change from randomization to Week 8 in the MADRS total score.

Overall, results from the secondary outcome variables supported the primary objective.

The quetiapine XR group received a mean daily dose of 162.2 mg, reflective of the large percentage of patients (83%) who remained at the 150-mg dose throughout the study.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

STUDY 4

A Multi-Centre, Double-Blind, Randomised, Parallel Group, Placebo-Controlled and Active Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR™) as Mono-Therapy in the Treatment of Adult Patients with Major Depressive Disorder (AMBER STUDY)

International co-ordinating investigator

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Study center(s)

There were 471 patients assigned to randomized treatment at 54 centers in Finland, Spain, Korea, Malaysia, China, Philippines, Canada, Mexico, and South Africa.

Study design

This was a 10-week, multicenter, double-dummy, randomized, parallel-group, placebocontrolled Phase III study of the efficacy and safety of quetiapine XR in the treatment of patients with MDD versus placebo. Escitalopram was added as an active control. This study consisted of an up to 28-day enrollment and washout period, an 8-week randomized treatment period, and a 2-week follow-up (treatment discontinuation signs and symptoms [TDSS]) period. All quetiapine XR patients initiated treatment on quetiapine XR 50 mg/day and were up-titrated to 150 mg/day at Day 3. All escitalopram patients initiated treatment on escitalopram 10 mg/day. After 2 weeks of treatment, patients in each treatment group with an inadequate response (defined as failure to achieve a ≥20% reduction in MADRS total score)

were up-titrated to twice their original dose (300 mg/day quetiapine XR, 20 mg/day escitalopram, or placebo). Investigators were blinded to the criterion defining inadequate response (ie, the criterion for inadequate response was defined in a document separate from the study protocol and not shared with the investigator) and were blinded to actual dose. At the end of the 8 weeks of randomized treatment, patients underwent a 2-week follow-up (TDSS) period including 1 week of down-titration in a blinded fashion. Patients on quetiapine XR 150 mg/day and escitalopram 10 mg/day received placebo for 1 week, whereas patients on quetiapine XR 300 mg/day and escitalopram 20 mg/day underwent a 1-week down-titration of quetiapine XR and escitalopram, to half of the 8-week dose (ie, to 150 mg/day and 10 mg/day, respectively). At the end of Week 9, all investigational product treatment was discontinued.

Duration of treatment

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by an 8-week, double-blind treatment period. After 2 weeks of treatment, patients with an inadequate response were treated with double the randomized dose (ie, quetiapine XR 300 mg/day or escitalopram 20 mg/day). The 8-week, double-blind treatment period was followed by a 2-week follow-up (TDSS) period that included 1 week of down-titration in a blinded fashion.

Figure 2 **Patient disposition (completion or discontinuation)**

Screened	660
Screen failures	189
Eligibility criteria not fulfilled	107 (16.2%)
Patient not willing to continue	48 (7.3%)
Lost to follow-up	27 (4.1%)
Adverse event	1 (0.2%)
Death	1 (0.2%)
Severe noncompliance	1 (0.2%)
Other	4 (0.6%)
Randomized	471

	PLA	QTP	ESC
Randomized	**157**	**157**	**157**
Not treated[a]	2 (1.3%)	0	1 (0.6%)
Received drug	**155 (98.7%)**	**157 (100.0%)**	**156 (99.4%)**
Patients with inadequate response[b,c]	40 (26.1%)	20 (13.0%)	36 (23.7%)
Patients with adequate response[c]	113 (73.9%)	134 (87.0%)	116 (76.3%)
Discontinued study	40 (25.5%)	50 (31.8%)	39 (24.8%)
Adverse event	7 (4.5%)	24 (15.3%)	9 (5.7%)
Condition under investigation not improved	7 (4.5%)	4 (2.5%)	6 (3.8%)
Eligibility criteria not fulfilled	2 (1.3%)	0	1 (0.6%)
Severe non-compliance with the protocol	2 (1.3%)	2 (1.3%)	2 (1.3%)
Patient lost to follow-up	9 (5.7%)	4 (2.5%)	5 (3.2%)
Patient not willing to continue	12 (7.6%)	14 (8.9)	12 (7.6%)
Other	1 (0.6%)	2 (1.3%)	4 (2.5%)
Completed 8-week randomized treatment period	**117 (74.5%)**	**107 (68.2%)**	**118 (75.2%)**
Completed study[d]	**73 (46.5%)**	**81 (51.6%)**	**69 (43.9%)**

[a] Patients not treated are also included in the discontinued from study treatment analysis set due to development of study-specific discontinuation criteria.
[b] Patients who failed to meet the criterion of adequate response (≥20% reduction in MADRS total score after 2 weeks of treatment) were up-titrated to double the initial randomized dose for the remaining 6 weeks of randomized treatment.
c Percentages based on MITT analysis set
[c] Completed the randomization period and the 2-week follow-up (TDSS) period.
ESC Escitalopram. PLA Placebo. QTP Quetiapine XR.

In total, 660 patients were screened for possible study participation. Of those, 471 qualified and were assigned to randomized treatment on Day 1. Of the 189 patients who did not qualify, 107 patients were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 157 to placebo, 157 to quetiapine XR 150 mg/day, and 157 to escitalopram 10 mg/day. Of the 471 patients assigned to randomized treatment, 3 patients (2 patients in the placebo group and 1 patient in the escitalopram group) did not receive any study medication. The number of patients assigned to randomized treatment categorized by country include:

Canada, 100; China, 40; Finland, 39; Korea, 31; Malaysia, 24; South Africa, 108; Spain, 17; Philippines, 38; and Mexico, 74 (see Table 11.1.1.2, Section 11.1). For each country, the proportions of patients assigned to each treatment group were generally well-balanced with the exception of Mexico (15%, 20%, and 12% of patients were randomized to the placebo, quetiapine XR, and escitalopram groups, respectively).

A total of 26.1%, 13.0%, and 23.7% of patients in the placebo, quetiapine XR, and escitalopram groups, respectively, met the criterion for inadequate response (ie, failed to achieve a ε20% reduction in MADRS total score after 2 weeks of randomized treatment). Those patients having an inadequate response were up-titrated to double the initial dose. Overall, 25.5% of the placebo group, 31.8% of the quetiapine XR group, and 24.8% of the escitalopram group discontinued the study during randomized treatment. Discontinuations due to lack of improvement in condition under investigation occurred less frequently in the quetiapine XR group (2.5%) than either the placebo or escitalopram groups (4.5% and 3.8%, respectively). The rate of discontinuation due to AEs was higher in the quetiapine XR group (15.3%) compared to the placebo and escitalopram groups (4.5% and 5.7%, respectively). A total of 5.7%, 2.5%, and 3.2% of patients in the placebo, quetiapine XR, and escitalopram groups were lost to follow-up.

Approximately 73% of patients completed the randomized treatment period of the study, with the lowest rate of completion occurring in the quetiapine XR group (68.2% vs. 74.5% in the placebo group and 75.2% in the escitalopram group. Of patients who completed the randomized treatment phase of the study, 62.4%, 75.7%, and 58.5% of placebo, quetiapine XR, and escitalopram patients, respectively, completed the 2-week follow-up (TDSS) period.

Table S3 Efficacy results at Week 8 (LOCF, MITT analysis set)

Outcome variable	PLA N=153	QTP N=154	ESC N=152
MADRS total score, LS mean change from randomization	-15.61	-17.21	-16.73
Proportion with MADRS response (total score ≥50% reduction from baseline)	51.0%	60.4%	59.9%
Proportion with MADRS remission (total score ≤8)	35.3%	35.7%	40.8%
HAM-D total score, LS mean change from randomization	-13.75	-14.99	-14.70
HAM-D Item 1 score, LS mean change from randomization	-1.41	-1.57	-1.65
HAM-A total score, LS mean change from randomization	-8.28	-9.44	-9.67
CGI-S score, LS mean change from randomization	-1.76	-1.83	-1.85
Proportion improved on CGI-I	58.8%	61.4%	64.2%
Q-LES-Q % maximum total score, LS mean change from randomization	13.55	13.46	16.00

CGI-I Clinical Global Impression - Improvement scale. CGI-S Clinical Global Impression - Severity scale. ESC Escitalopram. MADRS Montgomery-Åsberg Depression Rating Scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

The quetiapine XR group showed a greater mean change in MADRS total score at Week 8 compared with placebo; however, superiority over placebo was not demonstrated based on the nominal p-value when using the primary analysis method (least square [LS] mean change from randomization for quetiapine XR versus placebo of -1.6, p=0.174). Similar results were observed for the escitalopram group in mean change in MADRS total score at Week 8 when compared with placebo (LS mean change from randomization for escitalopram versus placebo of -1.1, p=0.346). Similar results were also observed for quetiapine XR versus placebo when using the PP analysis set (LOCF) (LS mean change from randomization for quetiapine XR versus placebo of -1.7, p=0.175).

The quetiapine group received a mean daily dose of 139.8 mg, reflective of the large percentage of patients (87.0%) who remained at the 150-mg dose throughout the study.

This study was not significant.

STUDY 6

A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL XR™) in Combination with an Antidepressant in the Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (Pearl Study)

Co-ordinating investigator

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Study center(s)

This study was conducted in the USA (56 centers).

Study design

This was an 8-week, multicenter, double-blind, randomized, parallel-group, placebocontrolled, double-dummy, Phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to antidepressant monotherapy. The study comprised 3 periods: an enrollment and washout period of up to 14 days (for the discontinuation of all prohibited medications), a 6-week randomized treatment period, and a 2-week follow-up period. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment.

Duration of treatment

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio to 150 mg/day quetiapine XR, 300 mg/day quetiapine XR, or placebo (each in combination with the ongoing antidepressant treatment). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150-mg/day group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300-mg/day group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study. During the 2-week follow-up period, no down-titration of quetiapine XR was performed since the dose of antidepressant was maintained.

In total, 659 patients were screened for possible study participation. Of those, 446 qualified and were assigned to randomized treatment on Day 1. Of the 213 patients who did not qualify, 158 patients (74%) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 148 to placebo, 148 to quetiapine XR 150 mg/day, and 150 to quetiapine XR 300 mg/day. Of the 446 patients assigned to randomized treatment, 1 patient (assigned to the quetiapine XR 300-mg/day group) did not receive any study medication.

Overall, the discontinuation rate during the 6-week randomized treatment period was highest in the quetiapine XR 300-mg/day group (30.0%) followed by the quetiapine XR 150-mg/day group (23.0%), and the placebo group (15.5%). Discontinuations due to lack of therapeutic response were more frequent in the placebo group (2.7%) than in the quetiapine XR groups (1.4% in the 150-mg/day group, and 0% in the 300-mg/day group). The percentages of patients lost to follow-up or not willing to continue were low (<7%); these 2 reasons for discontinuation were more prevalent among placebo patients compared with those treated with either dose of quetiapine XR. There was an apparent dose-related increase in the rate of discontinuation due to AEs across the quetiapine XR groups. The rate of discontinuation due to AEs was 18.0% and 10.8% in the quetiapine XR 300-mg/day and 150-mg/day groups, respectively, compared with 0.7% in the placebo group.

Approximately 77% of patients completed the randomized treatment period of the study, with higher rates of completion in the placebo group (85%) compared with the quetiapine XR groups (77% in the 150-mg/day group and 70% in the 300-mg/day group). Of those patients who completed the randomized treatment period, approximately 79% of patients in the placebo group, 81% of patients in the quetiapine XR 150-mg/day group, and 65% of those in the quetiapine XR 300-mg/day group completed the 2 week follow-up (TDSS) period. The overall completion rate for the study—through the end of the 2-week follow-up (TDSS) period—was approximately 67%, 62%, and 45% for patients in the placebo, quetiapine XR 150-mg/day, and quetiapine XR 300-mg/day groups, respectively.

Figure 3 **Patient disposition (completion or discontinuation)**

Screened	659
Screen failures	213
Lost to follow-up	6
Adverse event	3
Eligibility criteria not fulfilled	158
Development of study-specific discontinuation criteria	1
Patient not willing to continue	43
Other	2
Randomized	446

	PLA	QTP150	QTP300
Randomized	**148**	**148**	**150**
Not treated	0	0	1
Received drug	**148 (100%)**	**148 (100%)**	**149 (99.3%)**
Discontinued study[a]	**23 (15.5%)**	**34 (23.0%)**	**45 (30.0%)**
Adverse event	1 (0.7%)[b]	16 (10.8%)[c]	27 (18.0%)
Eligibility criteria not fulfilled	0	1 (0.7%)	1 (0.7%)
Lack of therapeutic response	4 (2.7%)	2 (1.4%)	0
Severe non-compliance with the study protocol	0	2 (1.4%)	0
Did not complete ≥36 days of study treatment	0	1 (0.7%)	1 (0.7%)
Lost to follow-up	10 (6.8%)	8 (5.4%)	7 (4.7%)
Patient not willing to continue	8 (5.4%)	4 (2.7%)	6 (4.0%)
Other	0	0	3 (2.0%)
Completed 6-week randomized treatment period	**125 (84.5%)**	**114 (77.0%)**	**105 (70.0%)**
Discontinued during post–Week 6 TDSS period[a]	**26 (17.6%)**	**22 (14.9%)**	**37 (24.7%)**
Adverse event	0	0	3 (2.0%)
Severe non-compliance with the study protocol	1 (0.7%)	1 (0.7%)	1 (0.7%)
Patient did not complete Day 14 TDSS assessment	6 (4.1%)	7 (4.7%)	9 (6.0%)
Lost to follow-up	3 (2.0%)	2 (1.4%)	4 (2.7%)
Patient not willing to continue	5 (3.4%)	3 (2.0%)	2 (1.3%)
Other	11 (7.4%)	9 (6.1%)	18 (12.0%)
Completed study[d]	**99 (66.9%)**	**92 (62.2%)**	**68 (45.3%)**

[a] For reasons for withdrawal for individual patients, see Listing 12.2.1.2, Appendix 12.2.
[b] The 1 placebo patient (E1605429) had an onset of AE (ECG abnormalities) prior to randomization, but was discontinued due to this AE during the randomized treatment period.

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=143	QTP150 N=143	QTP300 N=146
MADRS total score, LS mean change from baseline	-11.70	-13.60	-14.70[b]
Proportion with ≥50% MADRS response	46.2%	51.7%	58.9%[a]
Proportion with MADRS remission (total score ≤8)	24.5%	35.0%	42.5%[b]
HAM-D total score, LS mean change from baseline	-10.80	-12.63[a]	-13.53[b]
HAM-D Item 1 score, LS mean change from baseline	-1.35	-1.53	-1.60
HAM-A total score, LS mean change from baseline	-6.67	-7.43	-8.50[a]
CGI-S score, LS mean change from baseline	-1.23	-1.47	-1.52[a]
Proportion improved on CGI-I	46.9%	58.0%	58.2%[a]
Q-LES-Q percent maximum total score, LS mean change from baseline	11.32	10.37	11.82

[a] p<0.05 comparison with placebo.
[b] p<0.01 comparison with placebo.
CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.
Note: For the analyses of MADRS total score and Q-LES-Q % maximum total score change from baseline, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy.

The mean change from baseline for both quetiapine XR treatment groups was superior to placebo at Week 1 (-5.95 in the placebo group; -9.06 for quetiapine XR 150 mg/day [p<0.001 vs placebo]; and -8.20 in the quetiapine XR 300 mg/day group [p=0.002 vs placebo]). Patients in the 300-mg/day group continued to demonstrate a statistically significant greater change in the MADRS total score compared with placebo throughout the 6 weeks of randomized treatment.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

STUDY 7

A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL XR™) in Combination with an Antidepressant in the Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (Onyx Study)

International co-ordinating investigator

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Study center(s)

Five hundred seventy-two patients were enrolled to obtain 493 patients assigned to randomized treatment in Europe, South Africa, North America, and Australia to yield 420 evaluable patients at 87 study sites.

Study design

This was a 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy, phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to an antidepressant treatment. The randomized treatment period was preceded by a washout period of up to 14 days. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment.

Duration of treatment

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio to 150 mg/day quetiapine XR, 300 mg/day quetiapine XR, or placebo (each in combination with the ongoing antidepressant treatment). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150 mg/day–group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300 mg/day–group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study.

A total of 1854 patients received open-label treatment with quetiapine XR during the open-label phase. Of these, 776 patients continued in the study and received randomized study treatment: 391 received quetiapine XR and 385 received placebo. The mean daily dose of study drug at randomization was similar for the quetiapine XR group (176.6 [95.5] mg) and the placebo group (177.9 [90.8] mg). The mean and median daily doses during the randomized phase did not change considerably from the mean daily dose at randomization. Table 11.3.1.6 summarizes treatment exposure by last open-label dose and confirms that the last dose taken during the open-label phase reflects the mean daily dose of quetiapine XR taken during the randomized phase: 57.1 [27.5] mg for the 50 mg dose group; 154.4 [34.5] mg for the 150 mg dose group; 296.1 [22.1] mg for the 300 mg dose group.

During the open-label phase, mean duration of exposure was 51 days for the open-label only population, 131 days for the patients randomized to placebo, and 131 days for the patients randomized to quetiapine XR. During the randomized phase, mean duration of exposure was higher for the quetiapine XR group (167 days) compared with the placebo group (126 days), which is reflective of the higher rate of discontinuation for the placebo group. Total exposure to study drug over the entire study was 257 days for patients randomized to placebo and 298 days for patients randomized to quetiapine XR. A total of 787 patients completed the open-label phase and received up to 16 weeks of open-label quetiapine XR (Figure 2). A total of 776 patients were randomized to and received either quetiapine XR or placebo. Of the 391 patients who were randomized to receive quetiapine XR, 173 patients received at least 24 weeks of randomized treatment with quetiapine XR, 88 received at least 36 weeks of randomized treatment with quetiapine XR, and 46 received at least 44 weeks of randomized treatment with quetiapine XR.

Figure 3 **Patient disposition (completion or discontinuation)**

Screened	572
Screen failures	79
Lost to follow-up	1 (1.3%)
Adverse event	1 (1.3%)
Eligibility criteria not fulfilled	62 (78.5%)
Patient not willing to continue	13 (16.5%)
Death	1 (1.3%)
Other	1 (1.3%)
Randomized	493

	PLA	QTP150	QTP300
Randomized	**163**	**167**	**163**
Not treated	2 (1.2%)	0	0
Received drug	**161 (98.8%)**	**167 (100%)**	**163 (100%)**
Discontinued study	**18 (11.0%)**	**21 (12.6%)**	**30 (18.4%)**
Lost to follow-up	0	3 (1.8%)	0
Adverse event	5 (3.1%)	11 (6.6%)	19 (11.7%)
Development of study-specific discontinuation criteria	0	0	2 (1.2%)
Patient not willing to continue	5 (3.1%)	7 (4.2%)	3 (1.8%)
Lack of therapeutic response	5 (3.1%)	0	1 (0.6%)
Eligibility criteria not fulfilled	1 (0.6%)	0	2 (1.2%)
Severe non-compliance to protocol	1 (0.6%)	0	3 (1.8%)
Other	1 (0.6%)	0	0
Completed study	**145 (89.0%)**	**146 (87.4%)**	**133 (81.6%)**

PLA Placebo, QTP Quetiapine XR.

In total, 572 patients were screened for possible study participation. Of those, 493 qualified and were assigned to randomized treatment on Day 1. Of the 79 patients who did not qualify, 78.5% (62 patients) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 163 to placebo, 167 to quetiapine XR 150 mg/day, and 163 to quetiapine XR 300 mg/day.

Overall, the discontinuation rate was highest in the quetiapine XR 300-mg/day group (18.4%) followed by the quetiapine XR 150-mg/day group (12.6%), and the placebo group (11.0%). Discontinuations due to lack of efficacy were more frequent in the placebo group (3.1%) than in any of active treatment groups (0% in the quetiapine XR 150-mg/day group, and 0.6% in the quetiapine XR 300-mg/day group). There was a dose-related increase in the rate of discontinuation due to AEs across the quetiapine XR groups. The rates of discontinuation due

to AEs were higher in the quetiapine XR 150-mg/day group (6.6%) and 300-mg/day group (11.7%) when compared to placebo (3.1%).

Approximately 86% of patients completed the study, with higher rates of completion in the placebo group (89%) in comparison to the quetiapine XR groups (87.4% in the quetiapine XR 150-mg/day group and 81.6% in the quetiapine XR 300-mg/day group).

Quetiapine XR doses of 150 mg/day and 300 mg/day were statistically superior to placebo as demonstrated by the mean change from randomization to Week 6 in the MADRS total score (LOCF, MITT analysis set), with adjustment for multiplicity (quetiapine XR 150 mg vs placebo: p=0.003; quetiapine XR 300 mg vs placebo: p=0.005).

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=160	QTP150 N=166	QTP300 N=161
MADRS total score, LS mean change from baseline	-12.21	-15.26[a]	-14.94[a]
Proportion with ≥50% MADRS response	46.3%	55.4%	57.8%[b]
Proportion with MADRS remission (total score ≤8)	23.8%	36.1%[b]	31.1%
HAM-D total score, LS mean change from baseline	-11.13	-13.81[c]	-13.56[a]
HAM-D Item 1 score, LS mean change from baseline	-1.35	-1.56	-1.57
HAM-A total score, LS mean change from baseline	-7.92	-10.27	-9.70
CGI-S score, LS mean change from baseline	-1.25	-1.72[c]	-1.64[b]
Proportion improved in CGI-I	52.5%	64.5%[b]	62.7%

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=160	QTP150 N=166	QTP300 N=161
Q-LES-Q % maximum total score, LS mean change from baseline	12.58	14.70	12.81

[a] p<0.01 comparison with placebo.
[b] p<0.05 comparison with placebo.
[c] p<0.001 comparison with placebo.

CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

Note: For the analyses of MADRS and Q-LES-Q change from baseline, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

STUDY 5

A Multicenter, Double-blind, Randomized-withdrawal, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR™) as Monotherapy in the Maintenance Treatment of Patients with Major Depressive Disorder Following an Open-Label Stabilization Period (AMETHYST STUDY)

International co-ordinating Investigator

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Study centers

A total of 1876 patients were enrolled

Study design

This was a multicenter, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy (time to depressed event) and safety of quetiapine XR for up to 52 weeks of maintenance treatment in adult patients with MDD. The study comprised 4 periods: an enrollment period of up to 28 days; an open-label run-in period of 4 to 8 weeks, an open-label stabilization treatment period of at least 12 weeks (which could have been extended 6 additional weeks to meet eligibility criteria for randomization), and a randomized treatment period of up to 52 weeks.

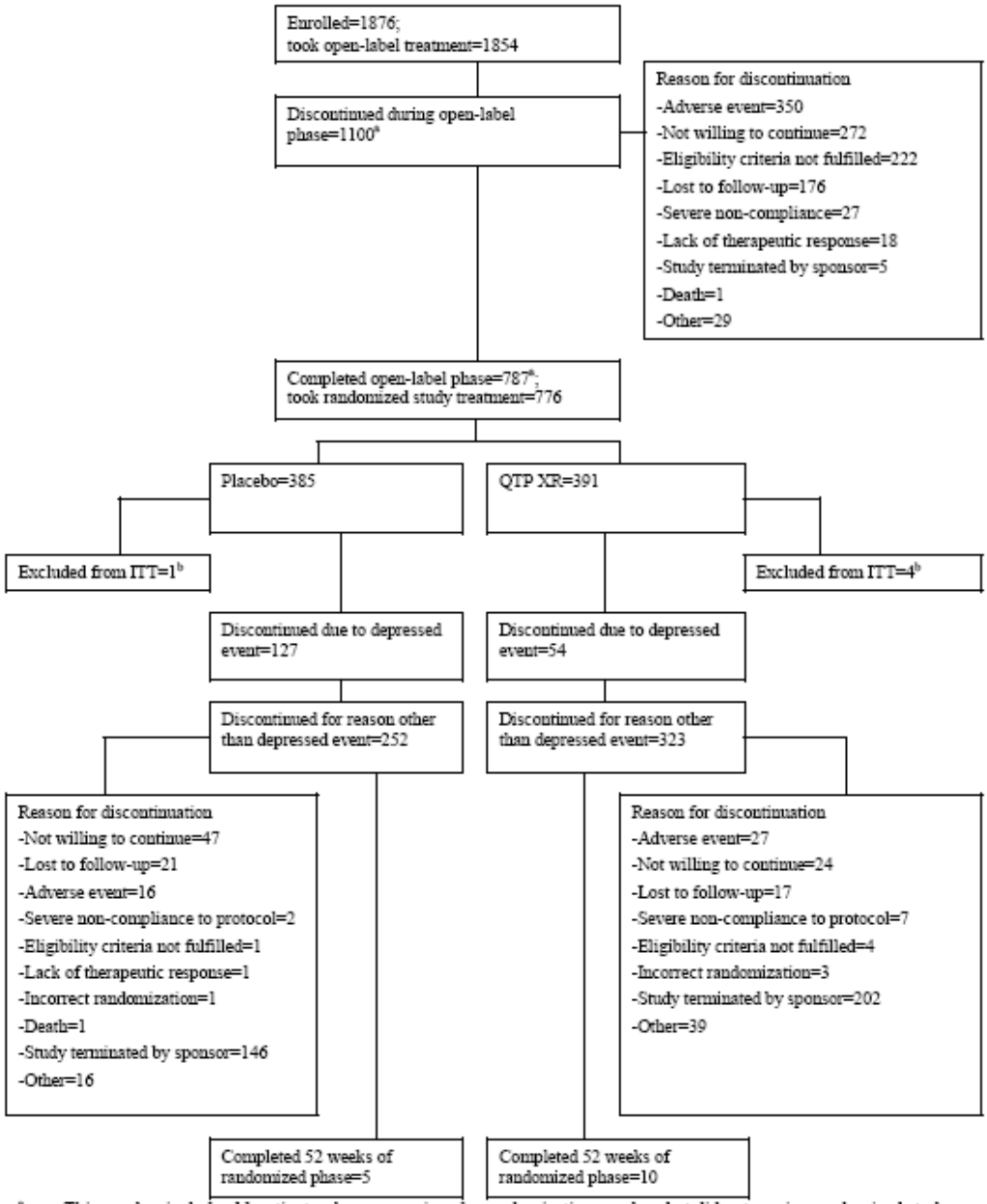
Duration of treatment

This study consisted of an open-label run-in treatment period of 4 to 8 weeks and an open-label stabilization treatment period of at least 12 weeks (patients were permitted to return to the clinic for up to 3 more visits [ie, for up to 6 more weeks] to meet eligibility criteria for randomization), followed by a randomized treatment period of up to 52 weeks.

A total of 1854 patients received quetiapine XR during the open-label phase of the study; 776 patients received randomized study treatment. The most common reasons for discontinuation during the open-label phase were AE (19%) and not willing to continue (15%). Discontinuations due to a depressed event during randomized treatment were less common in the quetiapine XR group (14%) than in the placebo group (33%). Other than

depressed events and termination of the study by the sponsor, the most frequent reason for discontinuation was AE in the quetiapine XR group (7%) and not willing to continue in the placebo group (12%). During randomized treatment, exposure to study drug was greater in the quetiapine XR group than in the placebo group (167 days vs 126 days). A total of 787 patients completed the open-label phase and received up to 16 weeks of open-label quetiapine XR. A total of 776 patients were randomized to and received either quetiapine XR or placebo. Of the 391 patients who were randomized to receive quetiapine XR, 173 patients received at least 24 weeks of randomized treatment with quetiapine XR, 88 received at least 36 weeks of randomized treatment with quetiapine XR, and 46 received at least 44 weeks of randomized treatment with quetiapine XR.

Figure 2 Patient disposition (completion or discontinuation)



[a] This number includes 11 patients who were assigned a randomization number, but did not receive randomized study treatment.

At the time of randomization, patients had been stabilized during an open–label treatment period of at least 12 weeks using the effective quetiapine XR dose range, with 21% receiving 50 mg/day, 46% receiving 150 mg/day, and 32% receiving 300 mg/day.

During the randomized phase, 90% of 91 patients who started at 50 mg/day finished on the same dose, 85% of 170 patients who started on 150 mg/day, and 94% of 130 starting on 300 mg/day finished on their starting dose.

Maintenance treatment with quetiapine XR at flexible doses of 50 mg/day, 150 mg/day, or 300 mg/day statistically significantly increased the time to a depressed event in patients with MDD, with an apparent dose response relationship.

In the maintenance trial (Study 5), a total of 1854 patients received open-label treatment with quetiapine XR during the open label phase. Of these, 776 patients continued in the study and received randomized study treatment: 391 received quetiapine XR and 385 received placebo. The mean daily dose of study drug at randomization was similar for the quetiapine XR group (176.6 [SD=95.5] mg) and the placebo group (177.9 [SD=90.8] mg). Mean duration of exposure was highest for the quetiapine XR group (167 days) compared with the placebo group (126 days) and patients in the open-label phase (51 days), which is reflective of the higher rates of discontinuation for the 2 latter groups. Total exposure during the open-label phase was 151 patient-years. During the randomized phase, total exposure was 133 patientyears for the placebo group and 179 patient-years for the quetiapine XR group. Of the 391 patients who received quetiapine XR in the randomized phase, 173 patients received it for at least 24 weeks, 88 for at least 36 weeks, and 46 for at least 44 weeks.

Table 36 Overview of exposure

Analysis set	Open-label only	Randomized safety	
	QTP XR N=1078	PLA N=385	QTP XR N=391
Daily dose at randomization (mg)[a]			
N[b]	NA	385	391
Mean (SD)	NA	177.9 (90.8)	176.6 (95.5)
Median	NA	150	150
Min to max	NA	25 to 300	50 to 300
Mean daily dose (mg)[c]			
N[b]	1078	385	391
Mean (SD)	151.8 (80.6)	182.1 (91.5)	177.1 (95.6)
Median	143	150	150
Min to max	38 to 628	49 to 300	47 to 300
Median daily dose (mg)[c]			
N[b]	1078	385	391
Mean (SD)	159.2 (95.9)	182.6 (92.9)	176.7 (97.4)
Median	150	150	150
Min to max	38 to 300	50 to 300	50 to 300
Minimum daily dose (mg)[c]			
N[b]	1078	385	391
Mean (SD)	49.8 (10.4)	172.3 (93.8)	166.9 (98.5)
Median	50	150	150
Min to max	0 to 300	0 to 300	0 to 300
Maximum daily dose (mg)[c]			
N[b]	1078	385	391
Mean (SD)	215.0 (333.6)	187.7 (95.0)	186.3 (96.7)
Median	150	150	150
Min to max	50 to 9300	50 to 600	50 to 300
Duration of exposure (days)[c]			
N[b]	1078	385	391
Mean (SD)	51.1 (41.8)	126.3 (103.0)	167.0 (103.0)
Median	45	116	158
Min to max	1 to 217	1 to 372	1 to 371
Total exposure (patient-years)	151.1	133.2	178.8

[a] Last prescribed dose during open-label phase.

Figure S1 Time to a depressed event, Kaplan Meier curves (ITT population)

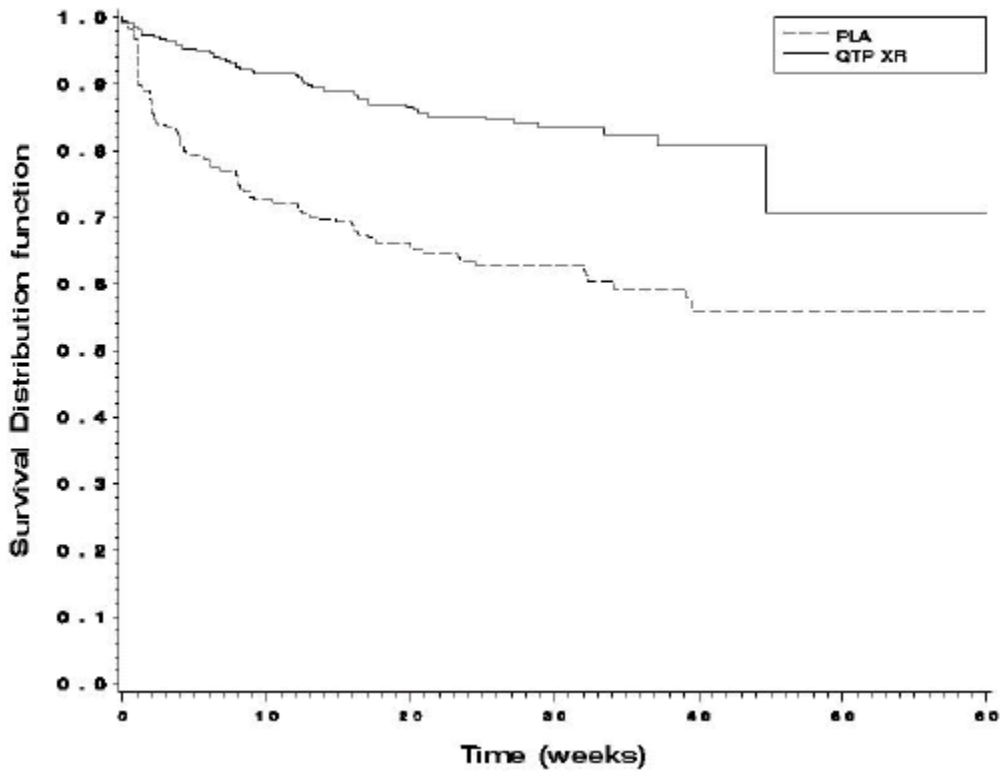


Table S3 Efficacy results, randomized treatment period (ITT population)

Outcome variable		PLA	QTP XR	Hazard ratio / estimated difference (95% CI)	p-value
Primary analysis	N	384	387		
Time to depression relapse	Number of relapses (%)	132 (34.4%)	55 (14.2%)	0.34 / (0.25, 0.46)[a]	<0.001[b]
Secondary analyses					
MADRS total score[c]	LS mean[b] (SE)	2.03 (0.21)	0.15 (0.20)	Diff: 1.88 (0.28) / (1.61, 2.44)	<0.001
CGI-S score[c]	LS mean[b] (SE)	0.23 (0.04)	-0.03 (0.03)	Diff: 0.26 (0.05) / 0.16, 0.35)	<0.001
HAM-A total score[c]	LS mean[b] (SE)	1.58 (0.18)	0.20 (0.17)	Diff: 1.37 (0.25) / (0.89, 1.86)	<0.001
HAM-A psychic anxiety factors score[c]	LS mean[b] (SE)	1.23 (0.12)	0.16 (0.11)	Diff: 1.07 (0.16) / (0.76, 1.38)	<0.001
HAM-A somatic anxiety factors score[c]	LS mean[b] (SE)	0.33 (0.09)	0.06 (0.09)	Diff: 0.27 (0.13) / (0.03, 0.52)	0.031
SDS total score[c]	LS mean[b] (SE)	0.44 (0.28)	-0.45 (0.25)	Diff: 0.89 (0.37) / (0.16, 1.61)	0.016
Q-LES-Q percentage of the maximum total score[c]	LS mean[b] (SE)	-0.36 (0.65)	0.52 (0.59)	Diff: -0.88 (0.86) / (-2.57, 0.80)	0.303
Q-LES-Q Item 15	LS mean[b] (SE)	-0.24 (0.04)	-0.13 (0.04)	Diff: -0.12 (0.06) / (-0.23, -0.01)	0.039
Q-LES-Q Item 16	LS mean[b] (SE)	-0.12 (0.04)	0.02 (0.03)	Diff: -0.14 (0.05) / (-0.23, -0.04)	0.004
PSQI global score[c]	LS mean[b] (SE)	1.35 (0.17)	0.06 (0.15)	Diff: 1.30 (0.22) / (0.87, 1.73)	<0.001

[a] Hazard ratio estimated by Cox proportional hazards model.
[b] Estimate of LS mean change during randomized period from an ANCOVA of the average of all post-baseline measurements from randomization up to, but not including, the relapse; the score at randomization was a covariate, and treatment and region were fixed effects.
[c] Change from randomization

ANCOVA Analysis of covariance. CGI-S Clinical Global Impression-Severity of Illness. CI Confidence interval. HAM-A Hamilton Rating Scale for Anxiety. ITT Intention to treat. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. PLA Placebo. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. QTP XR Quetiapine extended release. N Number of patients in treatment group. SDS Sheehan Disability Scale. SE Standard error.

Quetiapine XR at flexible doses of 50 mg, 150 mg, or 300 mg significantly increases the time to a depressed event compared with placebo when used as monotherapy in the maintenance treatment of patients with MDD.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

6.1.4 Efficacy Findings

Quetiapine XR at doses of 50 mg/day, 150 mg/day, and 300 mg/day was superior to placebo as monotherapy in reducing the level of depressive symptoms through Week 6 or 8 in patients with MDD, as assessed by evaluation of Montgomery-Åsberg Depression Rating Scale (MADRS) total score in studies 1, 2 and 3. Study 4 was not significant..

Quetiapine XR at doses of 150 mg/day and 300 mg/day as adjunct to an antidepressant was superior to antidepressant therapy as adjunct to placebo in reducing the level of depressive symptoms at Week 6 in patients with MDD who had an inadequate response to previous antidepressant treatment, as assessed by evaluation of MADRS total score. See studies 6 and 7. More consistent findings supporting efficacy across primary and secondary variables were noted for the 300 mg/day dose.

Maintenance treatment with quetiapine XR at flexible doses of 50 mg/day, 150 mg/day, or 300 mg/day statistically significantly increased the time to a depressed event in patients with MDD, with an apparent dose response relationship in study 5.

Table E7 Efficacy results from Studies 1 and 2 at Week 6 (LOCF, MITT analysis set)

Outcome variable	Study 1				Study 2			
	PLA N=179	QTP 50 N=168	QTP 150 N=179	QTP 300 N=176	PLA N=152	QTP 150 N=147	QTP 300 N=147	DUL N=141
MADRS total score, LS mean change from randomization	-11.07	-13.56c	-14.50b	-14.18b	-11.18	-14.81a	-15.29a	-14.64a
Proportion with MADRS response (total score ≥50% reduction from randomization)	30.3%	42.7%b	51.2%a	44.9%a	36.2%	54.4%b	55.1%a	49.6%c
Proportion with MADRS remission (total score ≤8)	18.5%	25.8%	20.8%	26.1%	20.4%	26.5%	32.0%c	31.9%c
HAM-D total score, LS mean change from randomization	-10.93	-12.35	-12.84c	-12.65c	-10.26	-13.12a	-14.02a	-12.37c
HAM-D Item 1, LS mean change from randomization	-1.18	-1.34	-1.45c	-1.48c	-1.07	-1.49a	-1.56a	-1.53a
HAM-A total score, LS mean change from randomization	-6.64	-8.11c	-8.34b	-8.20c	-5.55	-7.76b	-7.38b	-7.83a
CGI-S score, LS mean change from randomization	-1.11	-1.43c	-1.50b	-1.49b	-1.06	-1.43b	-1.60a	-1.53a
Proportion improved on CGI-I	39.3%	52.8%b	54.2%b	54.0%b	39.5%	54.1%c	59.2%a	56.7%b
Q-LES-Q, LS mean change from	12.59	12.50	12.30	11.56	11.26	13.68	13.59	16.69b

randomization

a p<0.001 comparison with placebo. b p<0.01 comparison with placebo. c p<0.05 comparison with placebo. Note: For the analyses of MADRS and Q-LES-Q change from randomization, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy. CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. DUL Duloxetine. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LS Least square LOCF Last observation carried forward. MADRS Montgomery-Asberg Depression Rating Scale. MITT Modified intention-to-treat. N Number of patients in treatment group. PLA Placebo. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. QTP Quetiapine extended release. Corresponds to Appendix Table EA001a in Module 5.3.5.3 Pooled Efficacy Data Tables and Table S3 in CSR 1 and Table S3 in CSR 2.

Table E8 Efficacy results from Studies 3 and 4 at Week 8 (LOCF, MITT analysis set)

	Study 3		Study 4		
Outcome variable	**PLA N=152**	**QTP N=147**	**PLA N=153**	**QTP N=154**	**ESC N=152**
MADRS total score, LS mean change from randomization	-13.1	-16.49b	-15.61	-17.21	-16.73
Proportion with MADRS response (total score ≥50% reduction from randomization)	48.0%	61.9%c	51.0%	60.4%	59.9%
Proportion with MADRS remission (total score ≤8)	25.0%	34.7%d	35.3%	35.7%	40.8%
HAM-D total score, LS mean change from randomization	-12.35	-14.75c	-13.75	-14.99	-14.70
HAM-D Item 1, LS mean change from randomization	-1.40	-1.71c	-1.41	-1.57	-1.65
HAM-A total score, LS mean change from randomization	-7.70	-9.14c	-8.28	-9.44	-9.67
CGI-S score, LS mean change from randomization	-1.24	-1.64b	-1.76	-1.83	-1.85
Proportion improved on CGI-I	52.0%	63.3%c	58.8%	61.4%	64.2%
Q-LES-Q, LS mean change from randomization	11.93	13.80	13.55	13.46	16.00

a p<0.001 comparison with placebo b p<0.01 comparison with placebo c p<0.05 comparison with placebo d p=0.052 comparison with placebo. Note: For the analyses of MADRS and Q-LES-Q change from randomization, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy. CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. ESC Escitalopram. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Asberg Depression Rating Scale. MITT Modified intention-to-treat. N Number of patients in treatment group. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. QTP Quetiapine extended release. PLA Placebo. Corresponds to Appendix Table EA001b in Module 5.3.5.3 Pooled Efficacy Data Tables, Table S3 in CSR 3, and Table S3 in CSR 4.

Table E9 Efficacy results from Studies 6 and 7 at Week 6 (LOCF, MITT analysis set)

	Study 6			Study 7		
Outcome variable	**PLA N=143**	**QTP150 N=143**	**QTP300 N=146**	**PLA N=160**	**QTP150 N=166**	**QTP300 N=161**
MADRS total score, LS mean change from randomization	-11.70	-13.60	-14.70b	-12.21	-15.26b	-14.94b
Proportion with MADRS response (total score ≥50% reduction from randomization)	46.2%	51.7%	58.9%c	46.3%	55.4%	57.8%c
Proportion with MADRS remission (total score ≤8)	24.5%	35.0%	42.5%b	23.8%	36.1%c	31.1%
HAM-D total score, LS mean change from randomization	-10.80	-12.63c	-13.53b	-11.13	-13.81a	-13.56b
HAM-D Item 1, LS mean change from randomization	-1.35	-1.53	-1.60	-1.35	-1.56	-1.57
HAM-A total score, LS mean change from randomization	-6.67	-7.43	-8.50c	-7.92	-10.27	-9.70
CGI-S score, LS mean change from randomization	-1.23	-1.47	-1.52c	-1.25	-1.72a	-1.64c
Proportion improved on CGI-I	46.9%	58.0%	58.2%c	52.5%	64.5%c	62.7%
Q-LES-Q, LS mean	11.32	10.37	11.82	12.58	14.70	12.81

change from randomization					

a p<0.001 comparison with placebo. b p<0.01 comparison with placebo. c p<0.05 comparison with placebo. Note: For the analyses of MADRS and Q-LES-Q change from randomization, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy. CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Asberg Depression Rating Scale. N Number of patients in treatment group. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. LOCF Last observation carried forward. MITT Modified intention-to-treat. LS Least square. QTP Quetiapine extended release. PLA Placebo. Corresponds to Appendix Table EA001c in Module 5.3.5.3 Pooled Efficacy Data Tables, Table S3 in CSR 6, and Table S3 in CSR 7. .

Table E10 Efficacy results for Study 5, randomized treatment period (ITT population)

Outcome variable		PLA	QTP	Hazard ratioa (95% CI)	p-value
	N	384	387		
Time to recurrence of a depressed event (all events)	Number of relapses (%)	132 (34.4)	55 (14.2)	0.34 (0.25, 0.46)	<0.0001
Time to recurrence of a late depressed event (randomized >30 days)	Number of relapses (%)	59 (20.7)	39 (11.0)	0.49 (0.32, 0.73)	0.0005

a Hazard ratio estimated by Cox proportional hazards model. CI Confidence interval. ITT Intention-to-treat. PLA Placebo. QTP Quetiapine extended release. N Number of patients in treatment group.

Corresponds to Table 11.2.1.1.1, Section 11.2 in CSR 5.

Phillip Dinh, Ph.D. , the FDA statistical reviewer summarized his findings as follows below.

"All six studies were positive on the primary efficacy variable on at least one dose under investigation. Among five studies that had the key secondary endpoint (Q-LES-Q percent maximum score), none of the studies was positive on the key secondary endpoint. The HAM-A was not a pre-specified endpoint, thus it cannot be used to support labeling claims. Although the numerical evidence suggested that patients who took quetiapine XR benefited from the treatment early in the course of the trials, no appropriate statistical methods were pre-specified to assess this claim formally. Thus the claim that a significant improvement was observed within the first week and continuing throughout the study was not justified

and could only be used descriptively."

6.1.5 Clinical Microbiology

n/a

6.1.6 Efficacy Conclusions

I believe Seroquel XR is effective in all 3 indications.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Patients providing safety information in this clinical trial program included 3337 treated with quetiapine XR and 957 treated with placebo.

7.1.1 Deaths

Acute monotherapy

There was one death during these studies, Patient E1013573 in Study 2. The patient was a 42-year-old male who died due to homicide (gun shot wound to the chest) on Day 9 of the study.

Acute adjunct therapy

There were no deaths during the acute adjunct therapy studies (6 and 7).

Maintenance therapy

Three (0.3%) patients had SAEs leading to death in the open-label phase, and 1 (0.3%) patient in the placebo group had a fatal SAE during the randomized phase. For one patient during the open-label phase, death occurred approximately 2 months after discontinuation from the study.

Table S 39 Listing of deaths during entire study (Study 5)

Treatment	Patient No.	Sex/ Age[a] (years)	Treatment duration OLT + RTP (days)[b]	AE (preferred term)	AE (investigators text)	Onset of AE (day)[c]	Causality[d]
Open-label phase							
QTP XR	1018012	F/55	50	Death	Death	63	No
QTP XR	3708006	M/60	23	Metastatic neoplasm	Searing paravertebral tumor	26	No
QTP XR	5407001	M/54	20	Myocardial infarction	Myocardial infarction	21	No
Randomized phase, PLA							

Narratives are provided in the study reports for the following patients: patients who died, patients with serious adverse events, and patients who discontinued treatment because of AEs. I have reviewed the narratives.

7.1.2 Other Serious Adverse Events

The incidence of SAEs in the pooled studies is shown below and tended to increase with dose. The most frequently reported non-fatal SAE in the quetiapine XR groups was depression. There are no unusual or unexpected events in this NDA.

Table S 40 Non-fatal serious adverse events - safety population (Studies 1, 2, 3 and 4)

		PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
System organ class	Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
TOTAL	TOTAL	5 (0.8)	13 (1.1)	1 (0.6)	4 (0.7)	8 (2.1)
Cardiac disorders	TOTAL	1 (0.2)	0	0	0	0
	Angina pectoris	1 (0.2)	0	0	0	0
General disorders and administration site conditions	TOTAL	1 (0.2)	0	0	0	0
	Chest pain	1 (0.2)	0	0	0	0
Hepatobiliary disorders	TOTAL	0	1 (0.1)	0	0	1 (0.3)
	Cholecystitis acute	0	1 (0.1)	0	0	1 (0.3)
Infections and infestations	TOTAL	1 (0.2)	2 (0.2)	1 (0.6)	0	1 (0.3)
	Cellulitis	1 (0.2)	0	0	0	0
	Diverticulitis	0	1 (0.1)	0	0	1 (0.3)
	Pneumonia	0	1 (0.1)	1 (0.6)	0	0
Injury, poisoning and procedural complications	TOTAL	0	2 (0.2)	0	1 (0.2)	1 (0.3)
	Fall	0	1 (0.1)	0	1 (0.2)	0
	Overdose	0	1 (0.1)	0	0	1 (0.3)
Pregnancy, puerperium and perinatal conditions	TOTAL	1 (0.2)	0	0	0	0
	Abortion spontaneous	1 (0.2)	0	0	0	0
Psychiatric disorders	TOTAL	1 (0.2)	8 (0.7)	0	3 (0.5)	5 (1.3)
	Depression	0	6 (0.5)	0	3 (0.5)	3 (0.8)
	Panic attack	0	1 (0.1)	0	0	1 (0.3)
	Suicidal behaviour	0	1 (0.1)	0	0	1 (0.3)
	Suicidal ideation	0	1 (0.1)	0	0	1 (0.3)
	Suicide attempt	1 (0.2)	2 (0.2)	0	1 (0.2)	1 (0.3)

The incidence of SAEs in the adjunct therapy studies was 1.3% in the placebo group and 1.0% in both quetiapine XR groups. The most frequently reported non-fatal SAE was depression.

Table S 41 Non-fatal serious adverse events - safety population (Studies 6 and 7)

		PLA (N=309)	QTP 150 (N=315)	QTP 300 (N=312)
System organ class	Preferred term	n (%)	n (%)	n (%)
TOTAL	TOTAL	4 (1.3)	3 (1.0)	3 (1.0)
Injury, poisoning and procedural complications	TOTAL	1 (0.3)	1 (0.3)	1 (0.3)
	Drug toxicity	0	0	1 (0.3)
	Fall	0	1 (0.3)	0
	Lower limb fracture	0	1 (0.3)	0
	Overdose	1 (0.3)	0	0
Musculoskeletal and connective tissue disorders	TOTAL	0	1 (0.3)	0
	Spondylitis	0	1 (0.3)	0
Nervous system disorders	TOTAL	1 (0.3)	1 (0.3)	0
	Syncope	0	1 (0.3)	0
	Transient ischaemic attack	1 (0.3)	0	0

Table S 41 Non-fatal serious adverse events - safety population (Studies 6 and 7)

		PLA (N=309)	QTP 150 (N=315)	QTP 300 (N=312)
System organ class	Preferred term	n (%)	n (%)	n (%)
Psychiatric disorders	TOTAL	3 (1.0)	0	2 (0.6)
	Depression	2 (0.6)	0	2 (0.6)
	Suicide attempt	1 (0.3)	0	0

PLA Placebo. QTP Quetiapine XR.
MedDRA Medical Dictionary for Regulatory Affairs, version 10.
Corresponds to Table SA020d in Module 5.3.5.3 Pooled Safety Data Tables.

The incidence of non-fatal SAEs during the randomized treatment phase of study 5 was 2.0% and 1.8% in the quetiapine XR and placebo groups, respectively.

Quetiapine Fumarate Extended Release D1448C00005

Table 11.3.4.1.1.3 Serious adverse Events not leading to death by Preferred Term
Ongoing or during randomized treatent phase
Randomized safety analysis set

	ACTUAL TREATMENT GROUP		
PREFERRED TERM	PLA (N=385) n (%)	QTP XR (N=391) n (%)	Total (N=776) n (%)
TOTAL	7 (1.8)	8 (2.0)	15 (1.9)
CHEST PAIN	1 (0.3)	0	1 (0.1)
CHOLELITHIASIS	0	3 (0.8)	3 (0.4)
DIVERTICULITIS	0	1 (0.3)	1 (0.1)
GASTRITIS	0	1 (0.3)	1 (0.1)
GASTRODUODENITIS	1 (0.3)	0	1 (0.1)
GASTROENTERITIS	1 (0.3)	0	1 (0.1)
MENTAL STATUS CHANGES	1 (0.3)	0	1 (0.1)
MUSCULOSKELETAL CHEST PAIN	1 (0.3)	0	1 (0.1)
NON-CARDIAC CHEST PAIN	0	1 (0.3)	1 (0.1)
OESOPHAGEAL FOOD IMPACTION	0	1 (0.3)	1 (0.1)
REFLUX OESOPHAGITIS	0	1 (0.3)	1 (0.1)
SUICIDAL IDEATION	1 (0.3)	0	1 (0.1)
WEST NILE VIRAL INFECTION	1 (0.3)	0	1 (0.1)

All AEs ongoing at randomization or occurred during randomized treatment phase.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

MONOTHERAPY

Table S 13 Discontinuations - safety population (Studies 1, 2, 3 and 4)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
CATEGORY	n %	n %	n %	n %	n %
Total number of randomized patients	648 (100.0)	1149 (100.0)	181 (100.0)	595 (100.0)	373 (100.0)
Completed 6/8 weeks of treatment	486 (75.0)	805 (70.1)	134 (74.0)	404 (67.9)	267 (71.6)
Withdrawals	162 (25.0)	344 (29.9)	47 (26.0)	191 (32.1)	106 (28.4)
--Adverse event	29 (4.5)	164 (14.3)	15 (8.3)	89 (15.0)	60 (16.1)
--Condition under investigation worsened	7 (1.1)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)

Table S 13 Discontinuations - safety population (Studies 1, 2, 3 and 4)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
CATEGORY	n %	n %	n %	n %	n %
--Death	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
--Development of study-specific discontinuation criteria	2 (0.3)	6 (0.5)	3 (1.7)	1 (0.2)	2 (0.5)
--Eligibility criteria not fulfilled	2 (0.3)	3 (0.3)	0 (0.0)	3 (0.5)	0 (0.0)
--Lack of therapeutic response	14 (2.2)	11 (1.0)	0 (0.0)	10 (1.7)	1 (0.3)
--Other	8 (1.2)	5 (0.4)	1 (0.6)	2 (0.3)	2 (0.5)
--Severe non-compliance to the CSP	9 (1.4)	22 (1.9)	6 (3.3)	12 (2.0)	4 (1.1)
--Subject did not complete >=50 days study treatment	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
--Subject lost to follow-up	47 (7.3)	66 (5.7)	14 (7.7)	33 (5.5)	19 (5.1)
--Subject not willing to continue study	43 (6.6)	65 (5.7)	8 (4.4)	39 (6.6)	18 (4.8)
Completed TDSS follow-up	346 (53.4)	605 (52.7)	103 (56.9)	298 (50.1)	204 (54.7)
Withdrawals during TDSS follow-up	140 (21.6)	200 (17.4)	31 (17.1)	106 (17.8)	63 (16.9)
--Adverse event	0 (0.0)	6 (0.5)	1 (0.6)	3 (0.5)	2 (0.5)
--Condition under investigation worsened	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
--Development of study-specific discontinuation criteria	1 (0.2)	1 (0.1)	1 (0.6)	0 (0.0)	0 (0.0)
--Eligibility criteria not fulfilled	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)
--Lack of therapeutic response	2 (0.3)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
--Other	5 (0.8)	3 (0.3)	0 (0.0)	3 (0.5)	0 (0.0)
--Severe non-compliance to the CSP	3 (0.5)	5 (0.4)	1 (0.6)	2 (0.3)	2 (0.5)
--Subject did not complete day 14 TDSS assessment	94 (14.5)	115 (10.0)	15 (8.3)	66 (11.1)	34 (9.1)
--Subject lost to follow-up	21 (3.2)	49 (4.3)	10 (5.5)	19 (3.2)	20 (5.4)
--Subject not willing to continue study	13 (2.0)	19 (1.7)	3 (1.7)	12 (2.0)	4 (1.1)

N Number of patients in treatment group. n Number of patients in analysis subgroup. PLA Placebo. QTP Quetiapine XR.
Randomized treatment period was 6 weeks for Studies1 and 2 and 8 weeks for Studies 3 and 4.

The proportion of patients that discontinued from the acute monotherapy studies was greater in the quetiapine XR treatment groups (29.9%) than in the placebo group (25.0%). The

greater number of withdrawals in the quetiapine XR groups can be attributed to the incidences of withdrawal due to adverse events (4.5% in the placebo group and 14.3% in the quetiapine XR groups). There were fewer withdrawals due to adverse events in the 50 mg/day quetiapine group (8.3%) than in the 150 mg/day or 300 mg/day quetiapine groups (15.0% and 16.1%, respectively). The incidence of withdrawal due to 'condition under investigation worsened' was 1.1% in the placebo group and 0.1% in the quetiapine XR groups. The other reasons for withdrawal were similar between the placebo and quetiapine XR treatment groups.

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Table S 14 Discontinuations - safety population (Studies 6 and 7)

	PLA (N=309)	QTP 150 (N=315)	QTP 300 (N=312)
CATEGORY	n %	n %	n %
Total number of randomized patients	309 (100.0)	315 (100.0)	312 (100.0)
Completed 6 weeks of treatment	270 (87.4)	260 (82.5)	238 (76.3)
Withdrawals	39 (12.6)	55 (17.5)	74 (23.7)
--Adverse event	6 (1.9)	27 (8.6)	46 (14.7)
--Development of study-specific discontinuation criteria	0 (0.0)	0 (0.0)	2 (0.6)
--Eligibility criteria not fulfilled	0 (0.0)	1 (0.3)	3 (1.0)
--Lack of therapeutic response	9 (2.9)	2 (0.6)	1 (0.3)
--Other	1 (0.3)	0 (0.0)	3 (1.0)
--Severe non-compliance to the CSP	1 (0.3)	2 (0.6)	3 (1.0)
--Subject did not complete >=36 days study treatment	0 (0.0)	1 (0.3)	1 (0.3)
--Subject lost to follow-up	10 (3.2)	11 (3.5)	7 (2.2)
--Subject not willing to continue study	12 (3.9)	11 (3.5)	8 (2.6)
Completed TDSS follow-up	99 (32.0)	92 (29.2)	68 (21.8)
Withdrawals during TDSS follow-up	26 (8.4)	22 (7.0)	37 (11.9)
--Adverse event	0 (0.0)	0 (0.0)	3 (1.0)
--Other	11 (3.6)	9 (2.9)	18 (5.8)
--Severe non-compliance to the CSP	1 (0.3)	1 (0.3)	1 (0.3)
--Subject did not complete day 14 TDSS assessment	6 (1.9)	7 (2.2)	9 (2.9)
--Subject lost to follow-up	3 (1.0)	2 (0.6)	4 (1.3)
--Subject not willing to continue study	5 (1.6)	3 (1.0)	2 (0.6)

N Number of patients in treatment group. n Number of patients in analysis subgroup. PLA Placebo.
QTP Quetiapine XR.

The proportion of patients that discontinued from the acute adjunct studies was greater in the quetiapine XR treatment groups (17.5% and 23.7% in the 150 mg/day and 300 mg/day quetiapine XR groups, respectively) than in the placebo group (12.6%). This can be attributed to the increased incidences of withdrawal due to adverse events in the quetiapine XR groups, which increased by dose (1.9% in the placebo group; 8.6% and 14.7% in the 150 mg/day and 300 mg/day quetiapine XR groups, respectively). The incidence of withdrawal due to 'lack of therapeutic response' was 2.9% in the placebo group, 0.6% in the 150 mg/day quetiapine XR

group, and 0.3% in the quetiapine XR treatment group. The other reasons for withdrawal were similar between the placebo and quetiapine XR treatment groups.

Table S 16 Discontinuation from randomized treatment phase (Study 5, ITT population)

	PLA N=384 n (%)	QTP N=387 n (%)
Discontinuation due to a depressed event	127 (33.1)	54 (14.0)
Discontinuation due to reason other than depressed event	252 (65.6)	323 (83.5)
-Eligibility criteria not fulfilled	1 (0.3)	4 (1.0)
-Adverse event	16 (4.2)	27 (7.0)
-Lack of therapeutic response	1 (0.3)	0
-Subject not willing to continue	47 (12.2)	24 (6.2)
-Subject lost to follow-up	21 (5.5)	17 (4.4)
-Incorrect randomization	1 (0.3)	3 (0.8)
-Severe non-compliance to protocol	2 (0.5)	7 (1.8)
-Death	1 (0.3)	0
-Terminated by sponsor[a]	146 (38.0)	202 (52.2)
-Other	16 (4.2)	39 (10.1)
Completed randomized treatment phase[b]	5 (1.3)	10 (2.6)

[a] Terminated by sponsor was due to study reaching criterion number of depressed events in entire population.
[b] Treated for up to 52 weeks or not discontinued until study termination.
Note: Patients discontinued due to a depressed event had "Development of study-specific discontinuation criteria" marked in the CRF module for study termination.
ITT Intention-to-treat. PLA Placebo. n Number of patients in analysis set. QTP Quetiapine extended release.

Of the 387 patients in the quetiapine XR group participating in the randomized phase, the most frequent reason for discontinuation (due to a reason other than a depressed event or terminated by sponsor) was "Other" (10.1%), followed by "adverse event (7.0%), and subject not willing to continue (6.2%). Of the 387 patients in the placebo group participating in the randomized phase, the most frequent reason for discontinuation (due to a reason other than a depressed event or terminated by sponsor) was not willing to continue (12.2%), followed by "adverse event and "Other" (both 4.2%). When the required number of depressed events had occurred and the study was terminated by the sponsor, 15 patients had completed the maximum 52 weeks of randomized treatment (10 in the quetiapine XR group and 5 in the placebo group); 348 patients were still participating in the randomized phase (202 patients in the quetiapine XR group and 146 patients in the placebo group).

The number of patients who discontinued due to an adverse events was greater in the quetiapine XR group (27 of the 323 patients not discontinued due to a depressed event) compared to the placebo group (16 of the 252 patients not discontinued due to a depressed

event). However, during the randomized treatment phase, the quetiapine XR group had considerably longer exposure to study drug than the placebo group due to the efficacy of quetiapine in preventing or delaying depressed events. The mean duration of exposure to quetiapine XR was approximately 32% longer (167 days) compared to the exposure to placebo (126 days).

7.1.3.2 Adverse events associated with dropouts

Monotherapy

In the acute monotherapy pool (Studies 1, 2, 3 & 4), the incidence of AEs leading to discontinuation was higher in quetiapine XR treated patients (14.9%) compared with placebotreated patients (5.2%). Of the quetiapine XR groups, the incidence of AEs leading to discontinuation was lowest in the 50 mg/day group. Sedation (6.1%), somnolence (2.4%), dizziness (1.1%), and fatigue (1.0%) were the most common AEs leading to discontinuation in quetiapine XR patients.

Adductive therapy

In the pooled adjunct therapy studies, the incidence of AEs leading to discontinuation was 1.9% in the placebo groups, 8.9% in the 150 mg/day quetiapine XR groups, and 15.4% in the 300 mg/day quetiapine XR groups. Somnolence, sedation, dizziness, and fatigue were the most common reasons for discontinuation in quetiapine XR patients.

Maintenance therapy

The overall incidence of AEs leading to discontinuation during the open-label treatment phase was 19.8%. The most common AEs leading to discontinuation during the open label phase were somnolence (4.5%), sedation (3.1%), and fatigue (2.0%), most of which were considered drug-related. During the open-label phase, most AEs leading to discontinuation were reported during the first 12 weeks of open-label treatment with quetiapine XR.

The proportion of patients with AEs leading to discontinuation during the randomized phase was comparable for the two treatment groups: 6.4% in the quetiapine XR group and 5.2% in the placebo group.

7.1.4 Other Search Strategies

Safety in special groups defined by sex, age and race was explored by tabulating adverse event incidence by those factors. The incidence of common AEs in patients was generally consistent across gender, age from 18 to 65 and race in both monotherapy and adjunct treatment trials, and did not give rise to any new safety issues regarding the use of quetiapine XR in special groups and situations.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited weekly in most studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The MedDRA-encoded adverse events were appropriate.

7.1.5.3 Incidence of common adverse events

The incidence of patients experiencing at least one AE was greater in the quetiapine XR groups (81.7%) than in the placebo group (58.8%). Of the 3 quetiapine XR dose groups, the incidence of common AEs was lowest in the 50 mg/day group.

7.1.5.4 Common adverse event tables

The incidence of common AEs is presented below. The incidence increases generally with study drug dose.

Table S 32 Common adverse events (>=2%) by decreasing incidence - safety population (Studies 1, 2, 3 and 4)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Dry mouth	53 (8.2)	401 (34.9)	40 (22.1)	214 (36.0)	147 (39.4)
Sedation	29 (4.5)	335 (29.2)	49 (27.1)	167 (28.1)	119 (31.9)
Somnolence	45 (6.9)	286 (24.9)	33 (18.2)	149 (25.0)	104 (27.9)
Dizziness	56 (8.6)	174 (15.1)	16 (8.8)	99 (16.6)	59 (15.8)
Headache	112 (17.3)	175 (15.2)	22 (12.2)	104 (17.5)	49 (13.1)
Nausea	68 (10.5)	128 (11.1)	14 (7.7)	77 (12.9)	37 (9.9)
Constipation	24 (3.7)	96 (8.4)	13 (7.2)	49 (8.2)	34 (9.1)
Fatigue	17 (2.6)	80 (7.0)	11 (6.1)	45 (7.6)	24 (6.4)
Vomiting	14 (2.2)	50 (4.4)	3 (1.7)	27 (4.5)	20 (5.4)
Diarrhoea	47 (7.3)	77 (6.7)	12 (6.6)	46 (7.7)	19 (5.1)
Increased appetite	18 (2.8)	61 (5.3)	8 (4.4)	34 (5.7)	19 (5.1)
Insomnia	53 (8.2)	85 (7.4)	9 (5.0)	57 (9.6)	19 (5.1)
Vision blurred	10 (1.5)	41 (3.6)	3 (1.7)	19 (3.2)	19 (5.1)
Dyspepsia	21 (3.2)	49 (4.3)	4 (2.2)	28 (4.7)	17 (4.6)
Irritability	24 (3.7)	56 (4.9)	11 (6.1)	28 (4.7)	17 (4.6)
Back pain	11 (1.7)	38 (3.3)	3 (1.7)	19 (3.2)	16 (4.3)
Weight increased	3 (0.5)	32 (2.8)	2 (1.1)	16 (2.7)	14 (3.8)
Upper respiratory tract infection	30 (4.6)	31 (2.7)	6 (3.3)	12 (2.0)	13 (3.5)
Anxiety	15 (2.3)	32 (2.8)	2 (1.1)	19 (3.2)	11 (2.9)
Dysarthria	0	14 (1.2)	1 (0.6)	2 (0.3)	11 (2.9)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Myalgia	13 (2.0)	49 (4.3)	8 (4.4)	30 (5.0)	11 (2.9)
Nasal congestion	10 (1.5)	29 (2.5)	1 (0.6)	17 (2.9)	11 (2.9)
Arthralgia	17 (2.6)	37 (3.2)	3 (1.7)	24 (4.0)	10 (2.7)
Musculoskeletal stiffness	7 (1.1)	25 (2.2)	5 (2.8)	10 (1.7)	10 (2.7)
Nasopharyngitis	31 (4.8)	31 (2.7)	3 (1.7)	18 (3.0)	10 (2.7)
Abnormal dreams	11 (1.7)	26 (2.3)	3 (1.7)	15 (2.5)	8 (2.1)
Disturbance in attention	3 (0.5)	18 (1.6)	1 (0.6)	9 (1.5)	8 (2.1)
Pharyngolaryngeal pain	2 (0.3)	22 (1.9)	3 (1.7)	11 (1.8)	8 (2.1)
Sluggishness	3 (0.5)	16 (1.4)	4 (2.2)	4 (0.7)	8 (2.1)
Palpitations	15 (2.3)	20 (1.7)	2 (1.1)	11 (1.8)	7 (1.9)
Asthenia	6 (0.9)	16 (1.4)	7 (3.9)	3 (0.5)	6 (1.6)
Tremor	7 (1.1)	20 (1.7)	5 (2.8)	9 (1.5)	6 (1.6)
Decreased appetite	5 (0.8)	21 (1.8)	3 (1.7)	13 (2.2)	5 (1.3)
Influenza	9 (1.4)	20 (1.7)	3 (1.7)	12 (2.0)	5 (1.3)
Cough	8 (1.2)	18 (1.6)	5 (2.8)	9 (1.5)	4 (1.1)
Hypersomnia	1 (0.2)	18 (1.6)	1 (0.6)	13 (2.2)	4 (1.1)
Abdominal pain upper	11 (1.7)	18 (1.6)	1 (0.6)	14 (2.4)	3 (0.8)
Tachycardia	2 (0.3)	17 (1.5)	1 (0.6)	13 (2.2)	3 (0.8)
Blood pressure increased	2 (0.3)	10 (0.9)	4 (2.2)	5 (0.8)	1 (0.3)

Patients with multiple events falling under the same preferred term are counted only once in that term.
Note: Common AEs: AEs occurring at an incidence of =2% in any treatment group.
PLA Placebo. QTP Quetiapine XR.
MedDRA Medical Dictionary for Regulatory Affairs, version 10.

7.1.5.5 Identifying common and drug-related adverse events

The incidence of common AEs associated with quetiapine treatment (those observed at an incidence of >2% and at least twice that of placebo) is summarized by treatment for the acute monotherapy pool (Studies 1, 2, 3, & 4) in Table S 34.

Table S 34 Common adverse events associated with quetiapine XR in patients with MDD - safety population (Studies 1, 2, 3 and 4)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Dry mouth	53 (8.2)	401 (34.9)	40 (22.1)	214 (36.0)	147 (39.4)
Sedation	29 (4.5)	335 (29.2)	49 (27.1)	167 (28.1)	119 (31.9)
Somnolence	45 (6.9)	286 (24.9)	33 (18.2)	149 (25.0)	104 (27.9)
Constipation	24 (3.7)	96 (8.4)	13 (7.2)	49 (8.2)	34 (9.1)
Fatigue	17 (2.6)	80 (7.0)	11 (6.1)	45 (7.6)	24 (6.4)
Vomiting	14 (2.2)	50 (4.4)	3 (1.7)	27 (4.5)	20 (5.4)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Increased appetite	18 (2.8)	61 (5.3)	8 (4.4)	34 (5.7)	19 (5.1)
Vision blurred	10 (1.5)	41 (3.6)	3 (1.7)	19 (3.2)	19 (5.1)
Myalgia	13 (2.0)	49 (4.3)	8 (4.4)	30 (5.0)	11 (2.9)

MedDRA-encoded adverse events occurring at an incidence of =5% in any active treatment group and observed at a rate of at least twice that of placebo. PLA Placebo. QTP Quetiapine XR.

7.1.5.6 Additional analyses and explorations

The uniformity of treatment effects of quetiapine XR in MDD across patient subgroups of sex, race, age and baseline severity of illness were analyzed for change from baseline in MADRS total score at last visit. Differences by geographic region were tabulated for Study 5 and Study 7.

The sponsoor's subgroup analysis of pooled data showed that all subgroups changed in the same direction, that no subgroup drove the differences between placebo and quetiapine XR and that no subgroup was excluded from therapeutic effects.

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

As this drug has been reviewed on several previous occasions I will highlight only selected laboratory findings found in this submission.

THYROID:

MONO

In the acute monotherapy pool (Studies 1, 2, 3 & 4), thyroid stimulating hormone increased in the quetiapine XR group (0.129 uIU/mL) and decreased in the placebo group (-0.077 uIU/mL). Free thyroxine decreased more in the quetiapine XR group (-0.070 ng/dL) than in the placebo group (-0.015 ng/dL). Free triiodothyronine decreased in the quetiapine XR group (-0.49 pg/mL) and increased in the placebo group (0.18 pg/mL).

ADJUNCTIVE

In the adjunct therapy studies (Studies 6 & 7), thyroid stimulating hormone increased more in the quetiapine XR groups (0.222 and 0.184 uIU/mL in the 150 mg/day and 300 mg/day

groups, respectively) than in the placebo group 0(.077 uIU/mL). Free thyroxine decreased more in the quetiapine XR groups (-0.74 and –0.123 ng/dL in the 150 mg/day and 300 mg/day groups, respectively) than in the placebo group (-0.006 ng/dL). Free triiodothyronine decreased in the quetiapine XR groups (-0.071 and –0.159 pg/mL in the 150 mg/day and 300 mg/day groups, respectively) and increased in the placebo group (0.002 pg/mL).

MAINTAINENCE

During the randomized treatment phase, the mean TSH values decreased in both treatment groups. During the randomised treatment phase, the mean free thyroxine values increased more in the placebo group than in the quetiapine XR group, while the mean free triiodothyronine value increased in the placebo group and decreased in the quetiapine XR group.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), few patients had clinically important thyroid laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), no patients had both high TSH and low total/free thyroxine shifts to clinically important values at end of treatment

In the adjunct therapy pool (Studies 6 & 7), few patients had clinically important thyroid laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.
In the acute adjunct therapy pool (Studies 6 & 7), no patients had both high TSH and low total/free thyroxine shifts to clinically important values at end of treatment

At the end of open-label treatment, no patients in the open-label only population had both a clinically important low free thyroxine value and a clinically important high TSH value.
Only 1 patient (in the quetiapine XR group) had both a clinically significant low free thyroxine value and a clinically significant high TSH value at end of treatment. Although hypothyroidism was not reported as an AE for this patient, the clinically significant laboratory values were reported as AEs, as were weight increased and increased appetite.
Only 1 patient (in the quetiapine XR group) had a clinically important low free triiodothyronine value and a clinically important high TSH value. This patient had AEs of weight increased and increased appetite. Blood thyroid stimulating hormone increased was also reported as a post-treatment AE (occuring within 30 days of last dose of study drug). No major differences between randomized treatment groups were observed.

Hemotology:

In the acute monotherapy pool (Studies 1, 2, 3 & 4), there were no clinically relevant differences in mean change from randomization between treatment groups for any hematology assessments.

In the adjunct therapy pool (Studies 6 & 7), there were no clinically relevant differences in mean change from randomization between treatment groups for any hematology assessments.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), few patients had clinically important hematology laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the acute adjunct therapy pool (Studies 6 & 7), few patients had clinically important hematology laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the maintenance (Study 5), few patients had clinically important hematology laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

Leukocytes:

In the acute monotherapy pool (Studies 1, 2, 3 & 4) there were no clinically relevant differences in mean change from randomization between treatment groups for any leukocyte differential assessments.

In the acute adjunct therapy pool (Studies 6 & 7) there were no clinically relevant differences in mean change from randomization between treatment groups for any leukocyte differential assessments.

In Study 5, there were no remarkable changes in mean leukocyte differential parameters during the open-label treatment phase. Also, there were no clear systematic differences in mean change from randomization between treatment groups for any leukocyte differential parameters.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), few patients had clinically important leukocyte differential laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the adjunct therapy pool (Studies 6 & 7), few patients had clinically important leukocyte differential laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the maintenance study (Study 5), few patients had clinically important leukocyte differential laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

Table S 69 Leukocyte shifts to clinical importance at any time - safety population (Studies 1, 2, 3 and 4)

PLA (N=648)				ALL QTP (N=1149)			QTP 50 (N=181)			QTP 150 (N=595)			QTP 300 (N=373)		
N	**n**		**(%)**	**N**	**n**	**(%)**	**N**	**n**	**(%)**	**N**	**n**	**(%)**	**N**	**n**	**(%)**
Basophils, (109 cells/L)															
≥0.5 x 10E9 cells/L	578	0	(0.0)	1005	0	(0.0)	156	0	(0.0)	524	0	(0.0)	325	0	(0.0)
Eosinophils, (109 cells/L)															
≥1x10E9 cells/L	577	0	(0.0)	1003	3	(0.3)	155	0	(0.0)	523	3	(0.6)	325	0	(0.0)
Leucocytes, (109 cells/L)															
≤3 x 109 cells/L	578	3	(0.5)	1009	7	(0.7)	156	1	(0.6)	525	4	(0.8)	328	2	(0.6)
≥16 x 109 cells/L	578	0	(0.0)	1008	5	(0.5)	155	0	(0.0)	525	4	(0.8)	328	1	(0.3)
Lymphocytes, (109 cells/L)															
≤0.5 x 109 cells/L	577	1	(0.2)	1004	0	(0.0)	155	0	(0.0)	524	0	(0.0)	325	0	(0.0)
≥6 x 109 cells/L	578	0	(0.0)	1005	0	(0.0)	156	0	(0.0)	524	0	(0.0)	325	0	(0.0)
Monocytes, (109 cells/L)															
≥1.4 x 109 cells/L	578	0	(0.0)	1005	3	(0.3)	156	0	(0.0)	524	3	(0.6)	325	0	(0.0)
Neutrophils, (109 cells/L)															
<0.5 x 109 cells/L	578	0	(0.0)	1005	0	(0.0)	156	0	(0.0)	524	0	(0.0)	325	0	(0.0)
≥10 x 109 cells/L	576	7	(1.2)	999	11	(1.1)	154	0	(0.0)	523	9	(1.7)	322	2	(0.6)
Neutrophils, (109 cells/L)															
<1.5 x 109 cells/L	578	12	(2.1)	1005	23	(2.3)	156	4	(2.6)	524	11	(2.1)	325	8	(2.5)
≥10 x 109 cells/L	576	7	(1.2)	999	11	(1.1)	154	0	(0.0)	523	9	(1.7)	322	2	(0.6)

N is number of patients at risk, i.e. not fulfilling the criteria at randomization. PLA Placebo. QTP Quetiapine XR.

MONOTHERAPY

The incidence of AEs potentially associated with neutropenia and agranulocytosis was 0.0% in the placebo group and 0.2% in the quetiapine XR group. The 2 AEs potentially associated with neutropenia and agranulocytosis occurred in studies 2 and 3.

In Study 2, a non-serious AE (neutrophil count decreased) associated with neutropenia or agranulocytosis was reported for 1 patient in the 150 mg/day quetiapine XR group (Patient E1040517). This patient had an AE of neutrophil count decreased, with a neutrophil particle concentration of 4.20×10^9 cells/L at baseline (Visit 1) and 1.12×10^9 cells/L at Week 4. The event was considered by the investigator to be drug-related, although no action was taken with regard to study drug. Neutrophil particle concentration increased to 4.88×10^9 cells/L at an unscheduled visit at Week 4 and remained normal at Week 6 (End of Treatment) (3.76×10^9 cells/L) (see Tables 11.3.6.2.5 in Study 2 CSR and 11.3.7.2.1.4 in Study 2 CSR). There were no AEs related to agranulocytosis.

In Study 3, a non-serious AE (neutropenia) associated with neutropenia or agranulocytosis was reported for 1 patient in the quetiapine XR group (Patient E1099220). This patient had a low neutrophil count (not clinically important) at randomization (1.69×10^9/L), which decreased to 1.11×10^9/L by Week 4 and 0.75×10^9/L at an unscheduled visit. At the scheduled Week 8 visit (End of Treatment), values had increased to 1.54×10^9/L. Overall, there were 3 placebo patients and 4 quetiapine XR patients with shifts to clinically important low neutrophil values at the end of treatment.

There were no cases of agranulocytosis.

ADJUCTIVE THERAPY:

There were only two AEs potentially associated with neutropenia and agranulocytosis, both in the quetiapine XR 150 mg/day group.

In Study 6, there was 1 AE (neutropenia) associated with neutropenia or agranulocytosis. This event was reported on Day 28 (Week 4) in a patient in the quetiapine XR 150 mg/day group (Patient E1338403). The patient had a normal neutrophil value at baseline (4.21 x 10^9/L) and a potentially clinically important low value at Week 4 (0.82 x 10^9/L). A repeat measurement taken 15 days after Week 4 (but 5 days before the Week 6 visit) showed a neutrophil value of 0.64 x 10^9/L. The neutrophil level had returned to normal at Week 6 of randomized treatment (2.05 x 10^9/L). The patient's WBC count was normal at baseline and at Week 6 (7.2 x 10^9/L and 4.4 x 10^9/L, respectively), but was below the lower limit of normal at Week 4 (3.9 x 10^9/L). The AE of neutropenia was of moderate intensity and was not an SAE, but it did result in the discontinuation of the patient from the study and was considered by the investigator to be possibly related to study medication. The other AEs reported for this patient were headache, constipation, dysphagia, nausea, fatigue, and vomiting.

In Study 7, there was 1 AE (neutrophil count decreased) associated with neutropenia or agranulocytosis. This event occurred in a patient in the quetiapine XR 150 mg/day group (Patient E3005406); the investigator noted that the percent neutrophils was 23.4% at Week 4

(normal range, 40.9% to 77.0%). The patient had a normal neutrophil value at baseline (2.50 x 10^9 cells/L) and a potentially clinically low value at Week 4 (1.36 x 10^9 cells/L). The neutrophil level had returned to normal at Week 6 of randomized treatment (2.36 x 10^9/L). The patient's WBC counts were normal at baseline, Week 4, and the end of treatment (6.4 x 10^9 cells/L, 5.8 x 10^9 cells/L, and 7.3 x 10^9 cells/L, respectively). An AE of sinusitis was reported for this patient 4 days after the Week 4 visit. The AE of neutrophil count decreased was of moderate intensity, was not an SAE, did not result in discontinuation of the patient from the study, and was not considered by the investigator to be possibly related to study medication.

There were no cases of agranulocytosis.

MAINTAINENCE THERAPY:

There were no cases of agranulocytosis reported during the open-label phase. The incidence of AEs potentially related to neutropenia or agranulocytosis was low (0.4%). AEs included neutrophil count decreased (0.3%) and neutropenia (0.1%). No patients discontinued due to an AE potentially related to neutropenia during the open-label phase. None of the AEs potentially related to neutropenia and agranulocytosis reported during the open-label phase were considered serious. Most AEs potentially related to neutropenia and agranulocytosis were considered mild or moderate in intensity, and most were considered drug-related.

There were no cases of agranulocytosis reported during the randomized phase phase. The incidence of AEs potentially related to neutropenia was low overall: 0.3% in the placebo group and 0 patients in the quetiapine XR group. During the randomized phase, only 1 patient in the placebo group reported neutrophil count decreased, which occurred during the first week of study treatment; the AE was not serious and it was moderate in intensity. No patients discontinued due to an AE potentially related to neutropenia.

EPS:

MONO
The incidence of AEs potentially associated with EPS was 3.2% in the placebo group and 5.4% in the quetiapine XR groups. Tremor (1.7%), restlessness (1.3%), and akathesia (1.3%) accounted for the majority of reports in the quetiapine XR groups.

All but 2 of the AEs associated with EPS in quetiapine-treated patients were either mild or moderate in intensity. The 2 severe AEs were coded under the preferred term 'restlessness'.

None of the AEs potentially associated with EPS were considered an SAE. Discontinuation due to an AE potentially associated with EPS was reported for 4 patients in the quetiapine XR groups (3 in the 150 mg/day group and 1 in the 300 mg/day group) and no patients in the placebo group. The median day of onset was Day 5 in the quetiapine XR groups and Day 16

in the placebo group.

ADJUCTIVE

The incidence of AEs potentially associated with EPS was 4.2% in the placebo group, 3.8% in the quetiapine XR 150 mg/day group, and 6.4% in the quetiapine XR 300 mg/day group. Akathisia, restlessness, and tremor accounted for most of the reports in the quetiapine XR groups.

All but 2 of the AEs associated with EPS in quetiapine-treated patients were either mild or moderate in severity, and there was no clinically important differences in severity of EPSassociated AEs across treatments.

None of the AEs potentially associated with EPS were considered an SAE. Discontinuation due to an AE potentially associated with EPS was reported for 3 patients in the quetiapine XR groups and zero patients in the placebo group. The median day of onset was Day 8 in the quetiapine XR groups and Day 17 in the placebo group.

Maintenance therapy

The incidence of AEs potentially related to EPS during the open-label phase was 6.7%. The most frequent AEs during the open-label phase were restlessness (2.1%), extrapyramidal disorder and tremor (1.5% for both AEs), and akathisia (1.2%). A small proportion of patients discontinued the study due to AEs potentially related to EPS: extrapyramidal disorder (0.3%), akathisia (0.2%), and restlessness (0.1%). AEs potentially related to EPS during the open label phase occurred within the first 12 weeks of open-label treatment and incidences generally decreased during that time.

None of the AEs potentially related to EPS reported during the open-label phase were considered serious. Most AEs potentially related to EPS were considered mild or moderate in intensity, and most were considered drug-related.

During the randomized phase, the incidence of AEs potentially related to EPS was low in both the quetiapine XR group (2.8%) and the placebo group (1.8%). The most frequent AEs reported for the quetiapine XR group during the randomized phase were extrapyramidal disorder (0.8%), tremor (0.8%), and restlessness (0.5%), all of which had an incidence comparable to placebo (0.5%, 0.3%, and 1.0%, respectively). No patients discontinued the study due to AEs potentially related to EPS during the randomized phase.

None of the AEs potentially related to EPS reported during the randomized phase were considered serious. Most AEs potentially related to EPS were considered mild or moderate in intensity, and most were considered drug-related.

SEXUAL ADVESE EVENTS:

MONO

The incidence of AEs potentially associated with sexual dysfunction was 1.2% in the placebo group and 1.4% in the quetiapine XR group.

In study 2 the results were as follows.

The incidence of AEs potentially related to sexual dysfunction was low in both quetiapine XR groups and comparable to placebo (1.3% in all 3 groups). The incidence was higher in the duloxetine group (8.1%); these events occurred primarily in males. Based on the change from baseline to the end of treatment in the CFSQ total score, sexual functioning improved slightly in all 4 treatment groups, with no apparent difference between the groups.

In study 4 the results were as follows.

The overall incidence of AEs relating to sexual dysfunction was low (<3%) but tended to occur more often in the escitalopram and placebo groups (2.6% and 1.9%, respectively) than in the quetiapine XR group. The number of events was small in this study. See below.

Table 49 Adverse events potentially related to sexual dysfunction (safety analysis set)

MedDRA preferred term[a]	PLA N=155 n (%)	QTP N=157 n (%)	ESC N=156 n (%)
Total	3 (1.9)	1 (0.6)	4 (2.6)
Erectile dysfunction	1 (0.6)	1 (0.6)	0
Libido decreased	1 (0.6)	0	2 (1.3)
Anorgasmia	0	0	1 (0.6)
Ejaculation failure	0	0	1 (0.6)
Loss of libido	1 (0.6)	0	0

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
ESC Escitalopram. MedDRA Medical Dictionary for Regulatory Activities. n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.

ADJUNCTIVE

The incidence of AEs associated with sexual dysfunction was 0.3% in the placebo group, 0.3% in the quetiapine XR 150 mg/day group, and 1.6% in the quetiapine XR 300 mg group.

Maintenance:

The incidence of AEs potentially related to sexual dysfunction during the open-label phase

was low (1.2%). No AEs potentially related to sexual dysfunction resulted in discontinuation from the study. None of the AEs were considered serious, most were considered mild or moderate in intensity, and most were considered drugrelated.

During the randomized phase, the incidence of AEs potentially related to sexual dysfunction was slightly higher for the quetiapine XR group (1.5%) compared with the placebo group (0.5%). None of the AEs resulted in discontinuation from the study, none were considered serious, and most were considered mild or moderate in intensity. Most of the AEs reported for the quetiapine XR group were considered drugrelated, but neither of the 2 AEs reported for the placebo group were considered drug-related.

WEIGHT:

Acute monotherapy

The incidence of patients showing a weight gain from baseline of ≥7% of body weight was 2.4% in the placebo group, 1.1% in the quetiapine XR 50 mg/day group, 3.8% in the quetiapine XR 150 mg/day group, and 5.5% in the quetiapine XR 300 mg/day group.

Acute adjunct therapy

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The incidence of patients showing a weight gain from baseline of ≥7% of body weight was 1.7% in the placebo group, 3.2% in the quetiapine XR 150 mg/day group, and 7.2% in the quetiapine XR 300 mg/day group.

Maintenance therapy

The incidence of patients showing a weight gain of ≥7% of body weight during prolonged exposure (randomization phase) was 2.9% in the placebo group and 5.4% in the quetiapine XR group.

7.1.10 Immunogenicity

n/a

7.1.11 Human Carcinogenicity

n/a

7.1.12 Special Safety Studies

SUICIDALITY

There have been 3 previous Columbia-type analyses of suicidality in quetiapine studies: 1 for the use of quetiapine in the treatment of bipolar depression, 1 for the use of quetiapine XR in the treatment of schizophrenia, and 1 for the use of quetiapine in the treatment of bipolar maintenance. In these previous reports, quetiapine exhibited no tendency to increase suicidal behavior or ideation in adults with bipolar disorder (at doses of 300 mg to 600 mg once daily) or in adults with schizophrenia (at daily doses of 300 mg to 800 mg).

AstraZeneca conducted an in-house review of suicidal behavior and ideation in the 7 studies in the quetiapine XR MDD treatment program, following the process developed by the group at Columbia University under the leadership of Kelly Posner PhD. A group of AstraZeneca medical staff trained in psychiatry, but not associated with the 7 studies in this program, was identified to review the adverse events (AEs) for patients from these studies. These reviewers were trained in the Columbia review process and were apprised of the reconciliation process to be used in the event of discordant categorization of a particular patient with possible suicidal behavior by the 3 reviewers involved; the 3 reviewers were required to come to agreement on all cases. All study data were blinded to the reviewers.

Analysis of suicidality according to the Columbia method revealed relative risk estimates for quetiapine XR 50, 150 and 300 mg that were not statistically separable from placebo. The adjusted risk ratio for all patients in Studies 1, 2, 3, 4, 6 and 7 who were treated with quetiapine XR compared to those treated with placebo was 0.84 (95% CI: 0.36, 1.97) for events classified as suicidal behavior/ideation, and risk ratios for individual quetiapine XR treatment groups in the data pool ranged from 0.40 to 0.88, with confidence intervals that included the value 1.0. The incidence of AEs classified as suicidality was low and similar across treatment groups.

In these studies of patients with MDD, there was no increased risk of suicidal behavior or ideation with the administration of quetiapine XR at doses of 50 mg to 300 mg daily, compared with the administration of placebo, when used in the treatment of MDD as monotherapy or adjunct therapy.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Overall, abrupt treatment discontinuation led to an increase in the incidence and/or intensity of a spectrum of signs and symptoms. The most prominent effects were seen for the symptoms of vomiting, nausea, headache, diarrhea, insomnia, irritability, and dizziness, regardless of the length of previous exposure to quetiapine XR treatment.

7.1.14 Human Reproduction and Pregnancy Data

In order to capture and report all cases of pregnancy that occurred during treatment with quetiapine XR (including those not reported as AEs or SAEs), the Clintrace database was searched covering all 7 studies (1, 2, 3, 4, 5, 6 & 7) for all pregnancy cases reported during these studies in which patients were treated with quetiapine XR.

All of the patients with pregnancies reported during study treatment had negative serum pregnancy tests at enrollment as required by the study inclusion criteria. To qualify for enrollment, female patients of childbearing potential were required to use a reliable method of contraception, such as 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, or tubal ligation. The use of hormonal contraceptives was recorded as concomitant medication.

There was one pregnancy in acute adjunct therapy Study 7. The patient was assigned the 300 mg/day quetiapine XR group. The pregnancy was terminated by elective abortion. There were eight pregnancies in the maintenance study. A majority of the pregnancies lead to timely delivery of healthy babies or elective abortions. One patient delivered a full-term baby with possible congenital bladder abnormality. This event was captured as a post-treatment SAE.

7.1.15 Assessment of Effect on Growth

N/A

7.1.16 Overdose Experience

There were no cases of overdose with quetiapine XR in any of the acute monotherapy studies.

There were no cases of overdose with quetiapine XR in any of the acute adjunct studies.

In the maintenance study (Study 5), a total of 15 patients had a reported overdose during the study that involved, or was suspected to involve, quetiapine XR. There were no reports of completed suicide associated with quetiapine XR overdose during the study. Of the 15 reported overdoses, 5 were considered intentional overdoses and/or suicide attempts, 5 were considered accidental overdoses, and 8 were considered possible overdoses. The maximum single quetiapine XR dose reported was 9300 mg; the patient recovered without sequelae. Five reports of overdose were considered to be SAEs or were associated with SAEs; 10 reports were considered to be, or were associated with, nonserious AEs.

7.1.17 Postmarketing Experience

Patient-years of SEROQUEL use has been calculated from the number of tablets delivered to

wholesalers worldwide during the PSUR period. A daily dose of 300 to 450 mg/patient/day has been assumed based upon a one-year exposure. There have been an estimated 2,035,069 to 1,356,713 patient-years (respectively) of SEROQUEL use during this reporting period, based on those average daily doses.

It has been estimated that about 25.9 million patients worldwide (an estimate of almost 15.9 million patients in the United States (US) and 10 million patients outside the US) have been exposed to SEROQUEL since launch through 31 July 2007 for the US and through second quarter 2007 for countries outside the US.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table S 5 Safety population data sets

Data Pool	Studies Included	Number of Patients treated with Quetiapine XR
Acute monotherapy pool	Studies 1, 2, 3 and 4	1149
Acute fixed-dose monotherapy pool	Studies 1 and 2	840
Acute modified fixed-dose monotherapy pool	Studies 3 and 4	309
Acute adjunct therapy pool	Studies 6 and 7	627
Maintenance study	Study 5	1854

7.2.1.2 Demographics

MONO

The populations of Study 1 and Study 2 were similar with respect to their demographic profiles. Females constituted more than half of the MITT population (51.0% to 64.5% across treatment groups) in the 2 studies. The mean age was closely matched between the studies (range from 40.2 to 42.3 years). Most of the population of both studies was Caucasian (range from 69.1% to 76.4%), and 17.7% to 25.7% were Black. The majority of patients in both studies were in the overweight to obese categories at screening (BMI ε25).

Both study 3 and 4 populations were similar with respect to their demographic profiles. Females were the majority of the MITT population (range from 64.5% to 75.7% across the treatment groups) in the 2 studies. The mean age was closely matched between the studies (range from approximately 39.7 to 43.3 years). The majority of patients in both studies were Caucasian (range from 52.6% to 68.7%), and 13.0% to 27.6% were Black.

ADJUCTIVE

The majority of patients across both studies 6 and 7were diagnosed as having recurrent MDD, but the percentage of patients with recurrent MDD was higher in Study 6 (90.4% to 94.4%) than in Study 7 (80.6% to 82.0%). The mean number of previous depressed episodes over lifetime was higher among patients in Study 6 (13.0 to 14.0) than did patients in Study 7 (11.8 to 17.8). In Study 3, a total of 46.7% to 53.7% of patients had family members with a known diagnosis of MDD, compared with only 34.3% to 42.5% of patients in Study 4. Mean MADRS total scores ranged from 27.2 to 28.6 points across treatment groups in the 2 studies. A minor difference between studies was that the percentage of patients with a HAM D total score ≥28 at randomization was lower in Study 6 than in Study 7 (11.6 to 15.4 points in Study 6 and 18.7 to 21.1 points in Study 7).

MAINTAINANCE

The majority of study 5 patients in the 2 treatment groups were diagnosed as having recurrent MDD, (83.3% and 86.8% for placebo and quetiapine XR, respectively). The mean number of previous depressed episodes over lifetime was similar for the 2 treatment groups (9.0 and 10.2 for placebo and quetiapine XR, respectively). A similar percentage of patients in the 2 treatment groups had family members with a known diagnosis of MDD (51.8% and 48.6% for placebo and quetiapine XR, respectively). Mean MADRS total scores were 5.3 for the placebo group and 5.8 for the quetiapine XR group.

7.2.1.3 Extent of exposure (dose/duration)

This Summary of Clinical Safety provides an integrated view of the safety data from the clinical program for quetiapine XR in MDD. The program comprised 7 studies and included 5933 patients with MDD, of whom 4086 were treated with quetiapine XR. There were 2116 MDD patients assigned to randomized treatment in 4 Phase III acute monotherapy studies (Studies 1, 2, 3, and 4), of whom 1149 received quetiapine XR. There were 939 MDD patients assigned to randomized treatment in 2 Phase III acute adjunct therapy studies (Studies 6 and 7), of whom 627 received quetiapine XR. Moreover, the clinical program included a Phase III maintenance therapy study (Study 5) which exposed 1854 MDD patients to quetiapine XR during the open-label phase.

Table O 6 **Total exposure to quetiapine XR for the combined data of Studies 1, 2, 3 and 4 (safety population)**

	Studies 1 + 2 + 3 + 4				
	PLA N=648	**All QTP XR N=1149**	**QTP XR 50 mg N=181**	**QTP XR 150 mg N=595**	**QTP XR 300 mg N=373**
Duration of exposure (days)[a]					
Mean (SD)	44.4 (16.9)	39.4 (17.4)	35.9 (12.9)	40.5 (19.2)	39.2 (16.1)
Median	49	43	42	44	43
Min	1	1	1	1	1
Max	77	73	49	73	65
Total exposure (patient-years[b])	78.8	123.6	17.7	66.0	40.0
Compliance during randomized phase					
≥80% and ≤120%	631 (97.4)	1107 (96.3)	173 (95.6)	573 (96.3)	361 (96.8)
<80%	10 (1.5)	28 (2.4)	7 (3.9)	15 (2.5)	6 (1.6)
>120%	7 (1.1)	14 (1.2)	1 (0.6)	7 (1.2)	6 (1.6)

[a] Does not include treatment withdrawal period.
[b] Includes treatment withdrawal period.
Refer to Section 1.2 in 2.7.4 Summary of Clinical Safety, Module 2
N Number of patients in dose group. n Number of patients in analysis subgroup. PLA Placebo. QTP XR Quetiapine XR. Study 1 Study D1448C00001. Study 2 Study D1448C00002. Study 3 Study D1448C00003. Study 4 Study D1448C00004.
Note: Patient-years defined as the sum of the duration of exposure across patients in days divided by 365.

Table O 7 Total exposure to quetiapine XR as an adjunct to antidepressants for the combined data of Studies 6 and 7 (safety population)

	Studies 6 + 7		
	PLA N=309	QTP XR 150 mg N=315	QTP XR 300 mg N=312
Duration of exposure (days)[a]			
Mean (SD)	39.2 (9.4)	38.3 (10.6)	35.7 (13.1)
Median	42	42	42
Min	1	1	1
Max	64	58	56
Total exposure (patient-years[b])	33.2	32.8	30.4
Compliance during randomized phase			
≥80% and ≤120%	301 (97.4)	306 (97.1)	303 (97.1)
<80%	4 (1.3)	6 (1.9)	7 (2.2)
>120%	4 (1.3)	3 (1.0)	2 (0.6)

[a] Does not include treatment withdrawal period for Study 6.
[b] Includes treatment withdrawal period for Study 6.
Refer to Section 1.2 in 2.7.4 Summary of Clinical Safety, Module 2.
N Number of patients in dose group. n Number of patients in analysis subgroup. PLA Placebo. QTP XR Quetiapine XR. Study 6 Study D1448C00006. Study 7 Study D1448C00007.
Note: Patient-years defined as the sum of the duration of exposure across patients in days divided by 365.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The sponsor did a literature search and post marketing search.

7.2.2.1 Other studies

n/a

7.2.2.2 Postmarketing experience

There is extensive postmarketing experience. That experience is consistent with this review.

7.2.2.3 Literature

There were literature references presented without methodology as to where the literature was obtained. There were no significant findings in the literature presented that are inconsistent with this review or the existing label.

7.2.3 Adequacy of Overall Clinical Experience

By agreement the studies provide an adequate clinical experience.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

N/A

7.2.5 Adequacy of Routine Clinical Testing

This testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

N/A

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of data is adequate.

7.2.9 Additional Submissions, Including Safety Update

N/A

7.4 General Methodology

The general methodology of these studies are adequate.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The studies in this submission used SEROQUEL XR at doses of 50 mg, 150 mg, and 300 mg once daily. The sponsor recommends dosing as follows in their draft label.

Initial dosing should begin at 50 mg on Days 1 and 2, and be increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if necessary, adjustments can be made upwards or downwards within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

8.2 Drug-Drug Interactions

There was no evidence from the SAE reports that quetiapine XR interacted with other medications during the acute monotherapy, acute adjunct therapy, and maintenance studies. Adjunct therapy with quetiapine XR at doses of 150mg/day or 300mg/day did not appear to have a consistent overall effect on the plasma concentrations of any of the adjunct antidepressants and their metabolites.

8.3 Special Populations

Safety in special groups defined by sex, age and race was explored by tabulating adverse event incidence by those factors. The incidence of common AEs in patients was generally consistent across gender, age from 18 to 65 and race in both monotherapy and adjunct treatment trials, and did not give rise to any new safety issues regarding the use of quetiapine XR in special groups and situations.

8.4 Pediatrics

AstraZeneca is currently working to fulfill the Written Request through the conduct of a pediatric clinical development program. On February 11, 2003, the Division issued a Pediatric Written Request for SEROQUEL Tablets (NDA 20-639) for the treatment of schizophrenia and bipolar mania. The Division agreed (October 11, 2005) that one pharmacokinetic study comparing the XR and immediate-release (IR) formulations of quetiapine will satisfy AstraZeneca's pediatric study obligations for SEROQUEL XR, provided that the IR formulation is demonstrated to be efficacious in pediatric patients in the Pediatric Written Request program.

8.5 Advisory Committee Meeting

I do not feel a meeting is needed.

8.6 Literature Review

There were literature references presented without methodology. There were no new significant findings in the literature.

8.7 Postmarketing Risk Management Plan

No special plan is required beyond the usual procedures.

9 OVERALL ASSESSMENT

I will list selected points derived from the sponsor's analysis that I have verified and am in agreement with.

Acute monotherapy

A higher incidence of adverse events was seen for quetiapine XR-treated patients compared to placebo-treated patients. This incidence was higher in the quetiapine XR 150 mg/day and 300 mg/day groups than in the 50 mg/day group. The most common adverse events associated with quetiapine XR treatment were dry mouth, sedation, somnolence, and dizziness. The incidence of syncope was low and similar in all treatment groups. The incidence of AEs were similar irrespective of age, race, sex, or region and showed no consistent relationship to dose group.

The initial dose of 50 mg daily and the subsequent titration schedule was safe and well-tolerated for quetiapine-treated patients. The incidence of discontinuations due to adverse events was 5.2% for the placebo group, 8.8% for the quetiapine XR 50 mg/day group, 15.8% for the quetiapine XR 150 mg/day group, and 16.4% for the quetiapine XR 300 mg/day group. The predominant symptoms leading to discontinuation were somnolence and sedation. After titration to the assigned dose, rates of discontinuation were low for all treatment groups.

A higher proportion of reports of extrapyramidal symptoms (EPS) was observed for quetiapine XR-treated patients (5.4%) compared to placebo-treated patients (3.2%). The symptoms were mild to moderate in intensity and seldom led to discontinuation.

The incidence of suicidality was low and similar for both quetiapine XR-treated patients and placebo-treated patients.

No clinically important effects on vital signs were observed for quetiapine XRtreated patients compared to placebo-treated patients.

The incidence of patients showing a weight gain from baseline of ≥7% of body weight was 2.4% in the placebo group, 1.1% in the quetiapine XR 50 mg/day

group, 3.8% in the quetiapine XR 150 mg/day group, and 5.5% in the quetiapine XR 300 mg/day group.

An increase in triglyceride values was observed for quetiapine XR-treated patients compared to placebo-treated patients.

The mean change in glucose appeared to be dose dependent and shifts to clinically important glucose values were greatest in the quetiapine XR 300 mg/day dose group for patients defined as being at risk for diabetes.

Treatment emergent diabetes was not observed for quetiapine XR-treated patients compared to placebo-treated patients.

Abrupt discontinuation of treatment resulted in an increased incidence of mild to moderate adverse events in quetiapine XR-treated patients (23.8%) compared to placebo-treated patients (14.8%). These symptoms usually resolved within one week. The incidence of these discontinuation symptoms were mitigated by gradual down-titration from the 300 mg/day dose.

Acute adjunct therapy

A higher incidence of adverse events was seen for quetiapine XR-treated patients compared to placebo-treated patients. The most common adverse events associated with quetiapine XR treatment were dry mouth, sedation, somnolence, and dizziness. The incidence of syncope was low and similar in all treatment groups. Most adverse events were mild to moderate in intensity. The incidence of AEs were similar irrespective of age, race, sex, or region and showed no consistent relationship to dose group.

The initial dose of 50 mg daily and the subsequent titration schedule was safe and well-tolerated for quetiapine-treated patients. The incidence of discontinuations due to adverse events was 1.9% for the placebo group, 8.9% for the quetiapine XR 150 mg/day group, and 15.4% for the quetiapine XR 300 mg/day group. The predominant symptoms leading to discontinuation were somnolence and sedation. After titration to the assigned dose, rates of discontinuation were low for all treatment groups.

A higher incidence of discontinuation due to adverse events was observed for quetiapine XR-treated patients compared to placebo-treated patients. This rate was higher in the quetiapine XR 300 mg/day group compared to the quetiapine XR 150 mg/day group.

The proportion of reports of extrapyramidal symptoms (EPS) was 4.2% for the placebo group, 3.8% for the quetiapine XR 150 mg/day group, and 6.4% for the quetiapine XR 300 mg/day group. The symptoms were mild to moderate in

intensity and seldom led to discontinuation. Increases in EPS, as determined by changes in SAS and BARS scores, were similar in all treatment groups.

The incidence of suicidality was low and similar for both quetiapine XR-treated patients and placebo-treated patients.

No clinically important effects on vital signs were observed for quetiapine XR treated patients compared to placebo-treated patients.

The incidence of patients showing a weight gain from baseline of ≥7% of body weight was 1.7% in the placebo group, 3.2% in the quetiapine XR 150 mg/day group, and 7.2% in the quetiapine XR 300 mg/day group.

An increase in triglycerideand cholesterol values was observed for quetiapine XRtreated patients compared to placebo-treated patients.

The effects of quetiapine XR treatment on glucose regulation parameters appeared to be small in comparison to that of placebo. The mean change in glucose was greater in the quetiapine XR 300 mg/day group than in the quetiapine XR 150 mg/day group. Shifts to clinically important glucose values were greatest in the quetiapine XR 300 mg/day dose group and for patients defined as being at risk for diabetes.

Treatment emergent diabetes was not observed for quetiapine XR-treated patients compared to placebo-treated patients.

Abrupt discontinuation of treatment resulted in an increased incidence of mild to moderate adverse events in quetiapine XR-treated patients compared to placebo treated patients. These symptoms usually resolved within one week.

Maintenance therapy

The proportion of reports of extrapyramidal symptoms (EPS) during prolonged exposure (randomization phase) was 1.8% for the placebo group and 2.8% for the quetiapine XR group. The symptoms were mild to moderate in intensity and seldom led to discontinuation. Increases in EPS, as determined by changes in SAS and BARS scores, were similar in all treatment groups.

The incidence of patients showing a weight gain of ≥7% of body weight during prolonged exposure (randomization phase) was 2.9% in the placebo group and 5.4% in the quetiapine XR group.

During prolonged exposure (randomization phase) triglyceride values decreased in both the quetiapine XR and placebo treatment groups.

9.1 Conclusions

The safety data in this submission are generally consistent with current labeling for Seroquel SR. No new safety issues have been identified.

9.2 Recommendation on Regulatory Action

I recommend the three supplements for MDD be approved.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommendations other than the usual procedures.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

The labeling must be reworded so that no claims are made regarding HAM-A claims.

Also the claim that a significant improvement was observed within the first week is not justified.

The sexual claims should not be celebrated in the label.

9.5 Comments to Applicant

Labeling changes will need to be communicated.

10 APPENDICES

10.1 Line-by-Line Labeling Review

The labeling was updated for the increased exposure in many safety sections. Labeling was added for the new indications. The key sections are presented below. I have indicated suggested changes elsewhere in this review.

AstraZeneca is proposing a table for dosing in the highlights section. Currently, all proposed indications have been included and, if accepted, will be modified as indications are approved.

1.1 Major Depressive Disorder

SEROQUEL XR is indicated for the treatment of major depressive disorder as:

- monotherapy or adjunct therapy to other antidepressants
- maintenance of antidepressant effect

The efficacy of SEROQUEL XR was demonstrated in 6 clinical trials in patients with major depressive disorder. Of these trials, 3 were monotherapy, 2 were adjunct therapy to other antidepressants and 1 was maintenance of antidepressant effect. [*see Clinical Studies* (14.1)].

2.1 Major Depressive Disorder

Antidepressant efficacy was demonstrated with SEROQUEL XR at doses of 50 mg, 150 mg, and 300 mg once daily.

Initial dosing should begin at 50 mg on Days 1 and 2, and be increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if necessary, adjustments can be made upwards or downwards within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient. [*see Clinical Studies* (14.1)].

2.4 Maintenance Treatment

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, a longer-term schizophrenia study with SEROQUEL XR has shown this drug to be effective in delaying time to relapse in patients who were stabilized on SEROQUEL XR at doses of 400 to 800 mg/day for 16 weeks [s*ee Clinical Studies* (14.2)]. In addition, a longer-term major depressive disorder study with SEROQUEL XR has shown this drug to be effective in maintaining antidepressant effect in patients who were stabilized on SEROQUEL XR at doses of 50 to 300 mg/day for 12 weeks [s*ee Clinical Studies* (14.1)]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment. [~~s*ee Clinical Studies* (14.2)~~].

3 DOSAGE FORMS AND STRENGTHS

50 mg extended-release tablets
200 mg extended-release tablets
300 mg extended-release tablets
400 mg extended-release tablets

5.18 Suicide

In six, 6- and 8-week clinical studies in patients with major depressive disorder (n=2733, 1776 on SEROQUEL XR and 957 on placebo) the incidence of treatment emergent suicidal ideation or suicide attempt was 0.7% in SEROQUEL XR treated patients and 0.7% in placebo. In a longer-term 52-week study in patients with major depressive disorder (n=776, 391 for SEROQUEL XR and 385 for placebo) the incidence was 0.3% for SEROQUEL XR and 0.5% for placebo.

6.0

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

There was no difference in the incidence and type of adverse reactions associated with discontinuation (6.4% for SEROQUEL XR vs. 7.5% for placebo) in a pool of schizophrenia controlled trials. In monotherapy clinical trials in patients with major depressive disorder 14.3% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 5.2% on placebo. In adjunct therapy clinical trials in patients with major depressive disorder 8.9% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 1.9% on placebo.

[25]Summary of Clinical Safety 2.7.4.1.2.2.1 and 2.7.4.1.2.2.2

[7]Summary of Clinical Efficacy 2.7.3.3.2.3.1

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during short-term monotherapy of major depressive disorder (up to 8 weeks) in ≥ 5% patients treated with SEROQUEL XR (doses 50mg, 150mg and 300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

[27]Summary of Clinical Safety 2.7.4.2.1.2.2, and SA043d

Table 3. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Monotherapy Clinical Trials for the Treatment of Major Depressive Disorder [1]

Body System/Preferred Term	SEROQUEL XR (n=1149)	PLACEBO (n=648)
Gastrointestinal Disorders		
Dry mouth	35%	8%
Constipation	8%	4%
General Disorders and Administration Site Conditions		
Fatigue	7%	3%
Irritability	5%	4%
Metabolism and Nutrition Disorders		
Increased Appetite	5%	3%
Nervous System Disorders		
Sedation	29%	5%
Somnolence	25%	7%
Dizziness	15%	9%

[1]Reactions for which the SEROQUEL XR incidence was >5% but equal to or less than placebo are not listed in the table, but included the following: diarrhea, headache, insomnia, and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were dry mouth (35%), sedation (29%), somnolence (25%), constipation (8%), and fatigue (7%).

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during short-term adjunct therapy of major depressive disorder (up to 6 weeks) in ≥ 5% patients treated with SEROQUEL XR (doses 150 mg and 300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

Table 4. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunct Therapy Clinical Trials for the Treatment of Major Depressive Disorder[1]

Body System/Preferred	SEROQUEL XR (n=627)	PLACEBO (n=309)

Term		
Gastrointestinal Disorders		
Dry Mouth	33%	8%
Constipation	8%	4%
General Disorders and Administration Site Conditions		
Fatigue	13%	4%
Nervous System Disorders		
Somnolence	24%	4%
Sedation	15%	4%
Dizziness	11%	7%

[1]Reactions for which the SEROQUEL XR incidence was >5% but equal to or less than placebo are not listed in the table, but included the following: headache, insomnia and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were dry mouth (33%), somnolence (24%), sedation 15%, fatigue (13%), and constipation (8%).

In a longer-term placebo-controlled trial, adult patients with major depressive disorder who remained clinically stable on SEROQUEL XR during open label treatment for at least 12 weeks were randomized to placebo (n=385) or to continue on SEROQUEL XR (n=391) for up to 52 weeks of observation for possible relapse. Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during longer-term treatment of major depressive disorder in ≥ 5% patients treated with SEROQUEL XR (doses 50 mg and 300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

Table 5. Treatment-Emergent Adverse Reaction Incidence in a Longer-Term Clinical Trial for the Treatment of Major Depressive Disorder[1]

	SEROQUEL XR (n=391)	Placebo (n=385)
Weight Gain	10%	2%
Dizziness	7%	4%
Arthralgia	5%	2%

[1]Reactions for which the SEROQUEL XR incidence was >5% but equal to or less than placebo are not listed in the table, but included the following: headache, nasopharyngitis, insomnia and diarrhea.

In four short-term placebo-controlled monotherapy clinical trials for the treatment of major depressive disorder utilizing between 50 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 5.4% for SEROQUEL XR and 3.2% in the placebo group. In two placebo-controlled short-term adjunct therapy clinical trials for the treatment of major depressive disorder utilizing between 150 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 5.1% SEROQUEL XR and 4.2% for the placebo group. In one longer-term placebo-controlled clinical trial for the treatment of major depressive disorder utilizing between 50 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 2.8% for SEROQUEL XR and 1.8% in the placebo group.

Sexual Dysfunction

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacological treatment.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Table 6 shows the incidence rates of sexual adverse Effects in patients with major depressive disorder in placebo controlled-trials. In SEROQUEL XR and placebo treated patients, the total incidence of adverse effects related to sexual dysfunction was generally low (≤1.5%) and did not exceed 0.6% in any individual item.

[33]Summary of Clinical Safety 2.7.4.2.1.6.6, 2.7.4.4.2.6.1 and 2.7.4.4.2.6.2

Table 6: Incidence of Sexual Adverse Effects in Placebo-Controlled Major Depressive Disorder Clinical Trials

Short-term Monotherapy Trials		
	SEROQUEL XR (n=1149)	Placebo (n=648)
Total	1.4%	1.2%
Anorgasmia	0.3%	0%
Dyspareunia	0.1%	0%
*Ejaculation delayed	0.1%	0%
*Erectile dysfunction	0.3%	0.5%
Libido decreased	0.5%	0.5%
Loss of Libido	0%	0.2%
Orgasm abnormal	0.1%	0%
Vulvovaginal dryness	0.1%	0.2%

Short-Term Adjunct Therapy Trials		
	SEROQUEL XR (n=627)	Placebo (n=309)
Total	0.9%	0.3%
Libido decreased	0.6%	0%
Libido increased	0 %	0.3%
Loss of Libido	0.1%	0%
Sexual dysfunction	0.1%	0%

*occurred only in males

In one longer-term maintenance study, the incidence of adverse effects potentially associated with sexual dysfunction was 1.5% for SEROQUEL XR and 0.5% for placebo.

There are no adequately designed studies examining sexual dysfunction with quetiapine treatment. While it is difficult to know the precise risk of sexual dysfunction associated with the use of quetiapine, physicians should routinely inquire about such possible side effects.

[37]Summary of Clinical Pharmacology Studies, 2.7.2.3.1.2

Antidepressants:

Coadministration of amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine with quetiapine did not appear to have a consistent overall effect on the plasma concentrations of the coadministered drug.

[42]Summary of Clinical Efficacy 2.7.3.3.1.1.1 and 2.7.3.3.2.1.1

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

[43]Summary of Clinical Efficacy 2.7.3.3.1.4.1 Tables E24 and E 25

The efficacy of SEROQUEL XR in the treatment of major depressive disorder (MDD) was established in 3 placebo-controlled monotherapy clinical trials, 2 adjunct therapy clinical trials, and 1 monotherapy, placebo-controlled maintenance trial. All trials included patients who met DSM-IV criteria for major depressive disorder, single or recurrent episodes, with and without psychotic features.

Monotherapy

[44]Summary of Clinical Efficacy 2.7.3.3.2.1.1 and 2.7.3.3.2.1.3
[45]Summary of Clinical Efficacy 2.7.3.3.2.1.8

The efficacy of SEROQUEL XR as monotherapy in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed dose trials, and one 8-week placebo-controlled, modified fixed dose trial (optional one time dose increase) (n=1445). The primary endpoint in these trials was the change from baseline to week 6 or 8 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) with total scores ranging from 0 (no depressive features) to 60 (maximum score). A Hamilton Rating Scale for Depression (HAM-D-17) total score of >22 was a requirement for study entry; the mean HAM-D total score at entry was 26, and 23% percent of patients scored 28 or greater.

[46]Summary of Clinical Efficacy 2.7.3.3.1.1.2 and 2.7.3.3.2.2.1

SEROQUEL XR at a dose of 50 mg, 150 mg, and 300 mg once daily was superior to placebo in reduction of depressive symptoms as measured by change in MADRS total score, with significant improvement observed within the first week (Days 4 and 8) and continuing throughout the study. Superior improvements were also seen in anxiety symptoms as measured by the Hamilton Rating Scale for Anxiety (HAM-A).

Adjunct Therapy

The efficacy of SEROQUEL XR as adjunct therapy in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed dose trials (n=936). The primary endpoint for these trials was the change from baseline to end of treatment (week 6) in the MADRS total score. A HAM-D-17 total score of ≥20 was a requirement for study entry; the mean HAM-D total score at entry was 24, and 17 percent of patients scored 28 or greater. SEROQUEL XR at a dose of 150 mg/day or 300 mg/day once daily was given as adjunct to existing antidepressant therapy in patients who had previously shown an inadequate response to at least one antidepressant.

[48]Clinical Study Report D1448C00006 section 5.1 and D1448C00007 section 5.1

Inadequate response was defined as having continued depressive symptoms for the current episode (HAM-D total score of ≥20) despite using an antidepressant for 6 weeks at or above the minimally effective labeled dose. Patients were on various antidepressants prior to study entry including SSRI's (paroxetine, fluoxetine, sertraline escitalopram, or citalopram), SNRI's, (duloxetine and venlafaxine,) TCA (amitriptyline) and other (bupropion).

[49]Summary of Clinical Efficacy 2.7.3.3.2.2.1 and [50]Summary of Clinical Efficacy 2.7.3.3.2.2.8

SEROQUEL XR 300 mg once daily as adjunct treatment to other antidepressant therapy was superior to antidepressant alone in reduction of MADRS total score in both trials, with improvement in depressive symptoms seen at week 1 through end of study (6 weeks). SEROQUEL XR 150 mg once daily as adjunct treatment was superior to antidepressant therapy alone in reduction of MADRS total score in one trial, with improvement in depressive symptoms seen at week 1 through end of study (6 weeks). Superior improvements in anxiety symptoms as measured by the HAM-A were also seen.

[51]Summary of Clinical Efficacy 2.7.3.3.1.1.3
[52]Clinical Study Report D1448C00005 section 5.1

Maintenance

A longer-term, maintenance clinical trial consisted of open-label run-in treatment and stabilization phases followed by a double-blind randomized treatment phase. 1854 patients entered the open-label phase and received SEROQUEL XR. Patients who had a HAM D-17 score of 20 or greater received SEROQUEL XR (flexibly dosed at 50 mg, 150 mg, or 300 mg once daily) for 4 to 8 weeks. Patients who were stabilized (CGI-S ≤3 and a MADRS total score ≤12) received SEROQUEL XR for an additional 12 to 18 weeks, within the same dose range. Stability was defined as above with the additional requirement of MADRS total score not to exceed 15 for two consecutive visits and CGI-S not to exceed 5 at any visit.

[53]Summary of Clinical Efficacy 2.7.3.3.1.1.3

[47]Summary of Clinical Efficacy 2.7.3.3.1.4.2 Tables E26

Patients meeting these criteria (n=771) were randomized to placebo or to continue on SEROQUEL XR for up to 52 weeks. Relapse during the double-blind phase was defined as: initiation of other drug treatment by the investigator; additional antidepressant treatment by

the patient for at least 1 week; hospitalization; MADRS total score ≥18 at 2 consecutive assessments one week apart or the final assessment if patient discontinues; CGI-S score ≥5; or suicide attempt or imminent risk of suicide.

[54]Summary of Clinical Efficacy 2.7.3.3.2.3.1

Patients on SEROQUEL XR (mean dose 177 mg/day) experienced a statistically significant longer time to relapse than did patients on placebo.

REFERENCES

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/s/

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11/3/2008 10:02:54 AM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-047 / S-010, S-011, S-012
Drug Name:	Seroquel XR (quetiapine fumarate)
Indication(s):	Major Depressive Disorder (monotherapy, adjunctive therapy, and maintenance)
Applicant:	AstraZeneca
Date(s):	Received: Feb 27, 2008;
	PDUFA Due Date: Dec 27, 2008
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewers:	Phillip Dinh, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatric Products, HFD-130
Clinical Team:	Earl Hearst M.D., Medical Reviewer, HFD-130
	Robert Levin M.D., Medical Team Leader, HFD-130
Project Manager:	Renmeet Grewal, Pharm.D., HFD-130

Keywords: Clinical studies; NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor submitted seven efficacy and safety studies to seek claims for monotherapy, adjunctive therapy, and maintenance treatment for adult patients with major depressive disorder (MDD). Evidence of effectiveness for the monotherapy was demonstrated from three studies: D1448C00001, D1448C00002, and D1448C00003. Evidence of effectiveness for the adjunctive therapy to an antidepressant was demonstrated from two studies: D1448C0006 and D1448C00007. Evidence of effectiveness for maintenance therapy was demonstrated from one study: D1448C00005.

In studies D1448C00001, D1448C00002, D1448C00003, D1448C00006, and D1448C00007, the primary efficacy variable was the change from randomization to end visit (week 6 or week 8) in the Montgomery-Asberg Depression Rating (MADRS) total score. The Hamilton Rating Scale for Anxiety (HAM-A) was not a pre-specified endpoint, thus it can only serve as exploratory findings and do not support labeling claims. Furthermore, the claim that significant improvement was observed within the first week and continuing through the study was not justified because there were not appropriate statistical methods pre-specified.

1.2 Brief Overview of Clinical Studies

Study D1448C00001 was an 8-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The double-blind treatment phase lasted for 6 weeks. Three doses of quetiapine XR were investigated: 50 mg/day, 150 mg/day, and 300 mg/day. The randomized sample consisted of 725 subjects between the age of 18 and 65 years. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Quality of Life Enjoyment Satisfaction Questionnaire (Q-LES-Q) percent maximum total score.

Study D1448C00002 was an 8-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The double-blind treatment phase lasted 6 weeks. Quetiapine XR at 150 mg/day and 300 mg/day were investigated. The study also included duloxetine 60 mg/day as assay sensitivity. The randomized sample consisted of 612 patients between the age of 18 and 65 years. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

Study D1448C00003 was a 10-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, modified fixed-dosed study. The randomized double-blind treatment period lasted 8 weeks. Patients were randomized to either quetiapine XR 150 mg/day or placebo. After 2 weeks of treatment, patients with an inadequate response were up-titrated to 300 mg/day or matching placebo. Three hundreds and ten subjects between the age of 18 and 65 years were randomized. The primary

efficacy variable was the change from randomization to week 8 in the MADRS total score. The key secondary variable was the change from randomization to week 8 in the Q-LES-Q percent maximum total score.

Study D1448C00005 was an international, multi-center, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study. The study consisted of 4 periods: an enrollment period of up to 28 days, an open-label run-in treatment period of 4 to 8 weeks, the open-label stabilization treatment period of 12 to 18 weeks, and a double-blind, randomized treatment period of up to 52 weeks. In this study, quetiapine XR could be adjusted to 50, 150, or 300 mg/day to maximize efficacy and tolerability. The randomized sample consisted of 776 patients between the age of 18 and 65 years. The primary efficacy variable was the time from randomization to a depressed event.

Study D1448C00006 was an 8-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, adjunctive therapy study. The double-blind treatment period lasted 6 weeks. Two doses of quetiapine XR were under investigation: quetiapine XR 150 mg/day and quetiapine XR 300 mg/day (in combination with an antidepressant). The randomized sample consisted of 446 patients between the age of 18 and 65 years who had inadequate responses to an antidepressant. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

Study D1448C00007 was a 6-week, international, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, adjunctive therapy study. The double-blind treatment period lasted 6 weeks. Two doses of quetiapine XR were under investigation: quetiapine XR 150 mg/day and quetiapine XR 300 mg/day (in combination with an antidepressant). The randomized sample consisted of 493 patients between the age of 18 and 65 years who had inadequate responses to an antidepressant. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

In addition to these six studies, the sponsor also submitted study D1448C00004. Study D1448C00004 was an international, multi-center, double-blind, randomized, parallel-group, placebo-controlled, modified fixed-dosed study. The study investigated quetiapine XR 150/300 mg against placebo. The study also included escitalopram for assay sensitivity. This study was considered a failed study because both quetiapine XR and escitalopram did not separate from placebo. This study is not included in this review.

1.3 Statistical Issues and Findings

All six studies were positive on the primary efficacy variable on at least one dose under investigation. Among five studies that had the key secondary endpoint (Q-LES-Q percent maximum score), none of the studies was positive on the key secondary endpoint. The HAM-A was not a pre-specified endpoint, thus it cannot be used to support labeling claims.

Although the numerical evidence suggested that patients who took quetiapine XR benefited from the treatment early in the course of the trials, no appropriate statistical methods were pre-specified to assess this claim formally. Thus the claim that a significant improvement was observed within the first week and continuing throughout the study was not justified and could only be used descriptively.

2. INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of quetiapine XR as a monotherapy, adjunctive therapy, and maintenance therapy for major depressive disorder (MDD).

According to the sponsor, quetiapine is a dibenzothiazepine derivative. The immediate-release (IR) formulation was approved by the Food and Drug Administration (FDA) in September 1997 for the treatment of schizophrenia, in January 2004 for the treatment of bipolar mania, and in October 2006 for the treatment of depressive episodes associated with bipolar disorder. Quetiapine XR is an extended-release formulation of quetiapine. The formulation was approved in May 2007 for the treatment of schizophrenia.

MDD is a psychiatric disorder characterized by the presence of one or more depressive episodes without a history of manic, mixed, or hypo-manic episodes. The lifetime prevalence of MDD varies from 6.7% to as much as 13.2%. MDD affects about 120 million people worldwide and is among the leading causes of disability. The burden of the illness is high on the patients and on the society. It is estimated that up to 15% of patients with severe major depressive episodes commit suicide. Patients with MDD often have decreased social, occupational, and educational functioning. There are currently more than 25 agents approved for the treatment of MDD; however, it is estimated that 10% to 20% of depressed patients are unable to tolerate the treatment. Furthermore, 25% to 35% of those who complete a generally prescribed course of an approved antidepressant do not show an acceptable response.

In an attempt to expand the treatment options to MDD patients, AstraZeneca has been investigating the efficacy and safety of quetiapine XR in an extensive clinical program. The program included 7 phase III, safety and efficacy studies: four studies where quetiapine XR was investigated as a monotherapy (studies D1448C00001, D1448C00002, D1448C00003, D1448C00004), two studies where quetiapine XR was investigated as an adjunctive therapy to an antidepressant (studies D1448C00006, D1448C00007), and one study as a maintenance therapy (study D1448C00005).

In study D1448C00004, both quetiapine XR and the active control (escitalopram) did not separate from placebo. This study will be not evaluated in this review.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\evsprod\NDA022047\0007.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study D1448C00001

3.1.1.1 Objectives

Primary: The primary objective of this study was to evaluate the efficacy of 3 doses of quetiapine XR versus placebo in the change from randomization to Week 6 in the Montgomery-Asberg Depression Rating (MADRS) total score.

Key Secondary: The key secondary objective was to evaluate if quetiapine XR improved the health-related quality of life in patients with major depressive disorder (MDD) by evaluating the change from randomization to Week 6 in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score.

3.1.1.2 Study Design

This was an 8-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study enrolled subjects from 38 centers in the United States. The study consisted of three periods. The washout period lasted from 7 days up to 28 days. The double-blind period lasted for six-week in which eligible patients were randomly assigned to 1 of 4 treatment groups: quetiapine XR 50 mg/day, quetiapine XR 150mg/day, quetiapine XR 300 mg/day, or placebo. Patients in the quetiapine XR 150mg/day and quetiapine XR 300 mg/day were titrated to their assigned doses. Following the double-blind period was a two-week post-treatment period where discontinuation symptoms were assessed.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to May 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 22 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment and at randomization. Assessments of the primary endpoint, MADRS, were done on Days 1, 4, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on Days 1, 29, and 43.

It was determined that 166 patients/arm were needed to detect a 3.5 unit difference (standard deviation of 9) for the change in the MADRS total score from baseline to Week 6 at a 0.05 level of significance and an 80% power.

3.1.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the Last Observation Carried Forward (LOCF) method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q totals core} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

To control for multiple testing, a tree-structured gatekeeping procedure was employed. The hypotheses tree is presented in Figure 1. In a tree-structured gatekeeping procedure, hypotheses are tested in a hierarchical way. A hypothesis is not tested unless its parental hypotheses are rejected. For example, a 300 mg dose on the Q-LES-Q is not tested unless a 300 mg dose on the MADRS is significant. Likewise, a 50 mg dose on the MADRS is not tested unless either a 300 mg dose or a 150 mg dose is significant on the MADRS. Uniform weights were assumed for all hypotheses in each family.

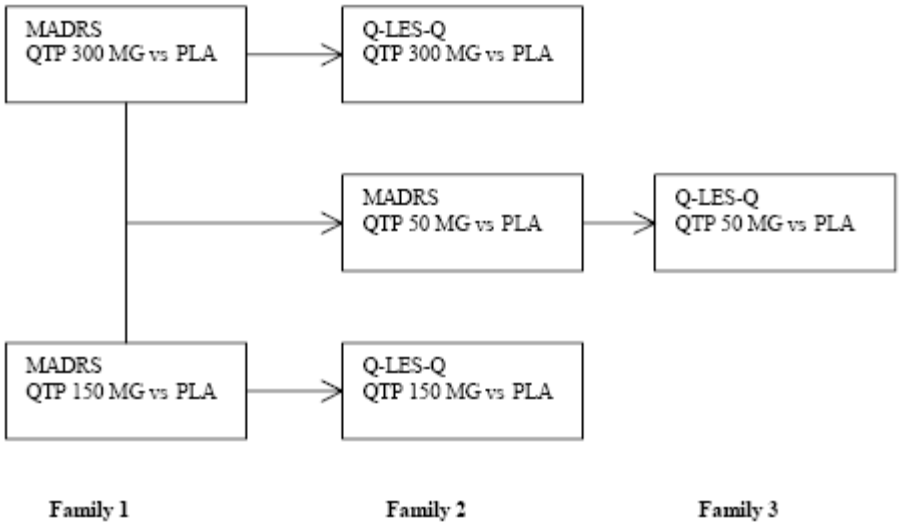


Figure 1. Study D1448C00001: Tree gatekeeping structure
(Source: d1448c0001-SAP; Figure 1, page 34)

3.1.1.4 Efficacy Results

3.1.1.4.1 Study Population

Subjects were enrolled from 40 centers in the United States. A total of 1075 subjects were screened and 725 subjects were randomized to 1 of the four treatment groups: placebo, quetiapine XR 50 mg, quetiapine XR 150 mg, and quetiapine XR 300 mg. The disposition of the subjects is summarized in Table 1. Approximately 71% of the subjects completed the 6-week randomized treatment period. Among the reasons for discontinuations, adverse events, lost to follow-up, and patients not willing to continue were main reasons. There were more adverse events in the quetiapine XR arms than in the placebo. There were slightly more dropouts in the middle and high dose of quetiapine XR than in the placebo and the low dose.

Table 1. Study D1448C00001: Disposition of patients

	Placebo (N = 184)	QTP 50mg (N = 182)	QTP 150mg (N = 178)	QTP 300mg (N =179)	Total (N = 723)
Randomized (not treated)	3	1	2	0	6
Randomized (treated)	181	181	176	179	717
Discontinued study	**50 (27.2)**	**48 (26.4)**	**55 (30.9)**	**59 (33.0)**	**212 (29.3)**
Lost to follow-up	18 (9.8)	14 (7.7)	10 (5.6)	12 (6.7)	54 (7.5)
Adverse event	11 (6.0)	15 (8.2)	25 (14.0)	34 (19.0)	85 (11.8)
Development of study specific discontinuation criteria	1 (0.5)	3 (1.6)		1 (0.6)	5 (0.7)
Patients not willing to continue	10 (5.4)	9 (4.9)	9 (5.1)	8 (4.5)	36 (5.0)
Condition under investigation worsened			1 (0.6)		5 (0.7)
Severe non-compliance to study protocol	2 (1.1)	6 (3.3)	8 (4.5)	3 (1.7)	19 (2.6)
Eligibility criteria not fulfilled	1 (0.5)		2 (1.1)		3 (0.4)
Other	3 (1.6)	1 (0.5)		1 (0.6)	5 (0.7)
Completed 6-week randomized treatment period	**134 (72.8)**	**134 (73.6)**	**123 (69.1)**	**120 (67.0)**	**511 (70.7)**

(Source: d1448c00001 Study Report; Figure 3, pages 80-81)

The demographics and baseline disease characteristics of the modified intent-to-treat (MITT) sample are presented in Table 2. Patients in this study were between 18 and 65 years of age. The average age was 41 years old. There were more females than males. The majority of the subjects was Caucasian (73%) and black (23%). The distribution of the baseline MADRS total score appeared balanced across the four treatment arms.

Table 2. Study D1448C00001: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 178	QTP 50 mg N = 178	QTP 150 mg N = 168	QTP 300 mg N = 176	Total N = 700
Age (yr) n					
Mean (SD)	40.3 (11.8)	40.6 (11.1)	41.5 (11.7)	40.7 (12.2)	40.7 (11.7)
Median	40.5	42.0	43.0	41.0	42.0
Min – Max	18 – 65	18 – 63	19 – 65	18 – 64	18 – 65
Sex – n (%)					
Male	65 (36.5)	83 (46.6)	64 (38.1)	73 (41.5)	285 (40.7)
Female	113 (63.5)	95 (53.4)	104 (61.9)	103 (58.5)	415 (59.3)
Race – n (%)					
Black	35 (19.7)	39 (21.9)	40 (23.8)	44 (25.0)	158 (22.6)
Caucasian	136 (76.4)	131 (73.6)	124 (73.8)	123 (69.9)	514 (73.4)
Oriental	2 (1.1)	2 (1.1)	1 (0.6)	0 (0.0)	5 (0.7)
Others	5 (2.8)	6 (3.4)	3 (1.8)	9 (5.1)	23 (3.3)
Baseline MADRS-total score					
Mean (SD)	30.5 (5.2)	30.9 (4.5)	30.9 (5.0)	30.6 (4.8)	30.7 (4.9)
Median	31.0	31.0	31.0	30.0	31.0
Min – Max	19 – 46	19 – 45	17 – 47	18 – 42	17 – 47

(Source: d1448c00001 Study Report; Tables 14-15, pages 84-85)

3.1.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested using the tree-structured gatekeeping procedure described above. The primary analysis is summarized in Table 3. All three doses of quetiapine XR were statistically significantly different from placebo.

Table 3. Study D1448C00001: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Sample size	178	178	168	176
LS Means	-11.07	-13.56	-14.50	-14.18
Difference from placebo		-2.50	-3.44	-3.11
(95% confidence interval)		(-4.48, -0.51)	(-5.45, -1.42)	(-5.10, -1.12)
Unadjusted p-values		0.014	0.001	0.002
Adjusted p-values		0.042	0.002	0.004

(Source: d1448c00001 Study Report; Table 17, pages 90-91)

3.1.1.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Table 4 summarizes the key secondary results. None of the doses was statistically significantly different from placebo.

Table 4. Study D1448C00001: Sponsor's key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Sample size	158	161	160	156
LS Means	12.59	12.50	12.30	11.56
Difference from placebo		-0.08	-0.29	-1.02
(95% confidence interval)		(-3.44, 3.28)	(-3.66, 3.08)	(-4.40, 2.35)
Unadjusted p-values		0.962	0.867	0.552
Adjusted p-values		1.000	1.000	1.000

(Source: d1448c00001 Study Report; Table 17, pages 90-91)

3.1.1.4.4 Sponsor's Other Efficacy Results

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 5. The model included visit, treatment, and treatment-by-visit interaction as fixed factors, center as a random factor, and randomization MADRS total score as a covariate. Robust variance estimates of the fixed effects were used. Within subject variability was modeled using an unstructured covariance pattern. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

Table 5. Study D1448C00001: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Sample size	178	178	168	176
LS Means	-12.14	-14.76	-15.99	-16.05
Difference from placebo		-2.62	-3.84	-3.91
(95% confidence interval)		(-4.35, -0.89)	(-5.42, -2.27)	(-5.91, -1.91)
Unadjusted p-values		0.003	<0.001	<0.001

(Source: d1448c00001 Study Report; Table 11.2.1.4, page 325)

An analysis on the primary endpoint over time (LOCF): Table 6 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The responses appeared consistent over time.

Table 6. Study D1448C00001: Sponsor's efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample

	Pbo	QTP 50mg	QTP 150mg	QTP 300mg	QTP 50mg – Pbo Diff	QTP 50mg – Pbo p-value*	QTP 150mg – Pbo Diff	QTP 150mg – Pbo p-value*	QTP 300mg – Pbo Diff	QTP 300mg – Pbo p-value*
Day 4	-3.27	-4.91	-5.43	-5.35	-1.64	0.006	-2.16	<0.001	-2.08	0.001
Week 1	-6.47	-8.68	-8.35	-8.79	-2.22	0.001	-1.89	0.006	-2.32	0.001
Week 2	-9.15	-11.76	-11.68	-12.06	-2.61	0.001	-2.53	0.002	-2.91	<0.001
Week 4	-10.62	-12.53	-13.37	-12.89	-1.91	0.035	-2.75	0.003	-2.27	0.012
Week 6	-11.07	-13.56	-14.50	-14.18	-2.50	0.014	-3.44	0.001	-3.11	0.002

(Source: d1448c00001 Study Report; Table 11.2.1.3.1, pages 319-322)
*p-values are not adjusted for multiplicity

3.1.1.4.5 Reviewer's Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 3 and Table 4. All three doses of quetiapine XR were superior to placebo on the change from randomization to week 6 in the MADRS total score, but not on the Q-LES-Q percent maximum score.

3.1.2 Study D1448C00002

3.1.2.1 Objectives

Primary: The primary objective of this study was to evaluate the efficacy quetiapine XR versus placebo in patients with MDD by evaluation of the change from randomization to Week 6 in the MADRS total score.

Key Secondary: The key secondary objective of this study was to evaluate if quetiapine XR improved the health-related quality of life of patients with MDD, compared to placebo by assessing the change from randomization to Week 6 in the Q-LES-Q percent maximum total score (Items 1-14).

3.1.2.2 Study Design

This was an 8-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study consisted of three phases. The first phase was a washout period of at least 7 days and up to 28 days. The second phase was a six-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to receive quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine 60 mg/day, or placebo. The third phase was a two-week post-treatment follow-up period. Patients were asked to call in for discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to May 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 22 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment and at randomization. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 43.

The sample size calculation was based on an 80% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

3.1.2.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a

mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q totals core} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons across the primary and secondary hypotheses. First, both primary hypotheses were tested. The Hommel procedure was used control the type I error rate among the two primary hypotheses. If both doses of quetiapine XR were statistically significantly superior to placebo, then the two secondary hypotheses would be tested. The Hommel procedure would also be used to control the type I error rate among the two secondary hypotheses.

3.1.2.4 Efficacy Results

3.1.2.4.1 Study Population

Subjects were enrolled from 38 centers in the United States. A total of 912 subjects were screened and 612 subjects were randomized to 1 of the four treatment groups: placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and duloxetine 60 mg/day. The disposition of the subjects is summarized in Table 7. Approximately 28% of the subjects discontinued the study prematurely. Main reasons for discontinuations were adverse events, lost to follow-up, and subjects not willing to continue. There were more adverse events in the active arms than in the placebo arm. There were also more discontinuations in the active arms than in the placebo arm.

Table 7. Study D1448C00002: Disposition of Patients

	Placebo (N = 157)	QTP 150mg (N = 152)	QTP 300mg (N = 152)	DUL (N = 151)	Total (N = 612)
Randomized – no treatment	0	0	0	2	2
Randomized – received treatment	157	152	152	149	610
Discontinued study	**33 (21.0)**	**52 (34.2)**	**39 (25.7)**	**46 (30.5)**	**170 (27.8)**
Adverse event	7 (4.5)	30 (19.7)	23 (15.1)	20 (13.1)	80 (13.1)
Condition worsened	3 (1.9)		0	2 (1.3)	5 (0.8)
Death	0	1 (0.7)	0	0	1 (0.2)
Development of study specific discontinuation criteria	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.7)	4 (0.7)
Eligibility criteria not fulfilled	0	1 (0.7)	0	2 (1.3)	3 (0.5)
Other	1 (0.6)	0	1 (0.7)	2 (1.3)	4 (0.7)
Severe noncompliance	3 (1.9)	2 (1.3)	1 (0.7)	0	6 (1.0)
Subject lost to follow-up	9 (5.7)	10 (6.6)	6 (3.9)	7 (4.6)	32 (5.2)
Subject not willing to continue	9 (5.7)	7 (4.6)	7 (4.6)	12 (7.9)	35 (5.7)
Completed 6-week randomized treatment phase	**124 (79.0)**	**100 (65.8)**	**113 (74.3)**	**105 (69.5)**	**442 (72.2)**

(Source: d1448c00002 Study Report; Figure 3, pages 86)

The modified intent-to-treat (MITT) sample had 587 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 8. Patients in this study were between 18 and 65 years of age. The average age was 41 years old. There were more females than males. The majority of the subjects was Caucasian (74%) and black (21%). The distribution of the baseline MADRS total score appeared balanced across the four treatment arms.

Table 8. Study D1448C00002: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 152	QTP 150 mg N = 147	QTP 300 mg N = 147	DUL N = 141	Total N = 587
Age (yr) n					
Mean (SD)	42.3 (11.5)	40.9 (12.3)	41.6 (12.0)	40.2 (12.5)	41.3 (12.1)
Median	43.5	40.0	42.0	40.0	42.0
Min – Max	19 – 63	18 – 64	19 – 65	19 – 65	18 – 65
Sex – n (%)					
Male	54 (35.5)	54 (36.7)	72 (49.0)	53 (37.6)	233 (39.7)
Female	98 (64.5)	93 (63.3)	75 (51.0)	88 (62.4)	354 (60.3)
Race – n (%)					
Black	39 (25.7)	30 (20.4)	31 (21.1)	25 (17.7)	125 (21.3)
Caucasian	105 (69.1)	111 (75.5)	110 (74.8)	107 (75.9)	433 (73.8)
Oriental	2 (1.3)	1 (0.7)	1 (0.7)	1 (0.7)	5 (0.9)
Others	6 (4.0)	5 (3.4)	5 (3.4)	8 (5.7)	24 (4.1)
Baseline MADRS-total score					
Mean (SD)	30.3 (5.0)	29.8 (5.3)	30.1 (5.2)	30.4 (4.5)	30.1 (5.0)
Median	30.0	30.0	30.0	30.0	30.0
Min – Max	17 – 43	14 – 43	16 – 42	18 – 40	14 – 43

(Source: d1448c00002 Study Report; Tables 14 & 16, pages 90 & 92)

3.1.2.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested sequentially. First the two primary hypotheses were tested using the Hommel procedure. If both primary hypotheses were significant, then the two secondary hypotheses were tested using the Hommel procedure. The primary analysis is summarized in Table 9. Both doses of quetiapine XR were statistically significantly different from placebo.

Table 9. Study D1448C00002: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg	DUL
Sample size	152	147	147	141
LS Means	-11.18	-14.81	-15.29	-14.64
Difference from placebo		-3.63	-4.11	-3.46
(95% confidence interval)		(-5.73, -1.53)	(-6.21, -2.01)	(-5.59, -1.34)
Unadjusted p-values		0.001	<0.001	0.002
Adjusted p-values		0.001	<0.001	Not done

(Source: d1448c00001 Study Report; Table 18, pages 98)

3.1.2.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Table 10 summarizes the key secondary results. None of the doses was statistically significantly different from placebo.

Table 10. Study D1448C00002: Sponsor's key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg	DUL
Sample size	144	136	141	129
LS Means	11.26	13.68	13.59	16.69
Difference from placebo		2.42	2.33	5.43
(95% confidence interval)		(-1.41, 6.26)	(-1.46, 6.12)	(1.54, 9.31)
Unadjusted p-values		0.215	0.227	0.006
Adjusted p-values		0.227	0.227	Not done

(Source: d1448c00002 Study Report; Table 32, pages 114)

3.1.1.4.4 Sponsor's Other Efficacy Results

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 11. The model included treatment, visit, and treatment-by-visit interaction as fixed effects, center as random effect, and baseline MADRS total score as a covariate. Robust variance estimates for the fixed effects were

used to test the treatment differences. The within subject variance was unstructured. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

Table 11. Study D1448C00002: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg	DUL
Sample size	152	147	147	141
LS Means	-11.69	-15.87	-16.29	-16.23
Difference from placebo		-4.18	-4.60	-4.54
(95% confidence interval)		(-5.91, -2.45)	(-6.64, -2.26)	(-6.68, -2.41)
Unadjusted p-values		<0.001	<0.001	<0.001

(Source: d1448c00002 Study Report; Table 11.2.1.4, page 335)

An analysis on the primary endpoint over time (LOCF): Table 12 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The responses appeared consistent over time.

Table 12. Study D1448C00002: Sponsor's efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample

	Pbo	QTP 150mg	QTP 300mg	DUL	QTP 150mg – Pbo		QTP 300mg – Pbo		DUL - Pbo	
					Diff	p-value*	Diff	p-value*	Diff	p-value*
Week 1	-6.01	-8.36	-8.19	-6.81	-2.35	0.002	-2.17	0.004	-0.79	0.301
Week 2	-9.03	-12.43	-11.34	-10.95	-3.40	<0.001	-2.31	0.009	-1.92	0.031
Week 4	-10.39	-14.22	-13.65	-13.17	-3.84	<0.001	-3.26	0.001	-2.79	0.005
Week 6	-11.18	-14.81	-15.29	-14.64	-3.63	0.001	-4.11	<0.001	-3.46	0.002

(Source: d1448c00002 Study Report; Table 11.2.1.3.1, pages 327-330)
*p-values are not adjusted for multiplicity

3.1.2.4.5 Reviewer's Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 9 and Table 10. Both doses of quetiapine XR were superior to placebo on the change from randomization to week 6 in the MADRS total score, but not on the Q-LES-Q percent maximum score.

3.1.3 Study D1448C00003

3.1.3.1 Objectives

Primary: The primary objective of this study was to evaluate the efficacy quetiapine XR versus placebo in patients with MDD by evaluation of the change from randomization to Week 8 in the MADRS total score.

Key Secondary: The key secondary objective of this study was to evaluate if quetiapine XR improved the health-related quality of life in patients with MDD, compared to placebo by assessing the change from randomization to Week 8 in the Q-LES-Q percent maximum total score (Items 1-14).

3.1.3.2 Study Design

This was a 10-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, modified fixed-dosed study. The study consisted of three phases. The first phase was an enrollment period of at least 7 days and up to 28 days. The second phase was an eight-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to either quetiapine XR 150 mg/day or placebo. After 2 weeks of treatment, patients with an inadequate response (defined as failure to achieve at least 20% improvement from randomization in MADRS total score) were up-titrated to 300 mg/day or matching placebo. The third phase was a two-week post-treatment follow-up period. Patients were asked to complete the TDSS assessment for drug discontinuation signs and symptoms.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to May 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 22 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment and at randomization. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, 43, and 57. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 57.

The sample size calculation was based on a 90% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

3.1.3.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 8 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 8. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q totals core} - 14}{56} \times 100.$$

Missing values are imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons between the primary and secondary hypotheses. First, the primary outcome variable was tested. If it was statistically significant, then the secondary outcome variable was tested.

3.1.3.4 Efficacy Results

3.1.3.4.1 Study Population

Subjects were enrolled from 36 centers in the United States. A total of 513 subjects were screened and 310 subjects were randomized to quetiapine XR 150/300 mg/day, or placebo. Initially, subjects receiving quetiapine XR were titrated to 150 mg/day. If the treatment yielded inadequate responses, then patients were up-titrated to 300 mg/day. The disposition of the subjects is summarized in Table 13. Approximately 29% of the subjects discontinued prematurely. Main reasons for discontinuation were adverse events, lack of therapeutic response, lost to follow-up, and not willing to continue. There were more adverse events in the quetiapine XR arm than in the placebo arm.

Table 13. Study D1448C00003: Disposition of patients

	Placebo (N = 156)	QTP 150/300 mg (N = 154)	Total (N = 310)
Randomized, not treated	1	2	3
Randomized, treated	155	152	307
Discontinued the study: N (%)	**45 (28.8)**	**46 (29.9)**	**91 (29.4)**
Adverse event	4 (2.6)	13 (8.4)	17 (5.5)
Eligibility criteria not fulfilled	1 (0.6)	2 (1.3)	3 (1.0)
Lack of therapeutic response	7 (4.5)	7 (4.5)	14 (4.5)
Other	3 (1.9)		3 (1.0)
Severe noncompliance to protocol	3 (1.9)	1 (0.6)	4 (1.3)
Did not complete ≥50 days of treatment	1 (0.6)		1 (0.3)
Lost to follow-up	12 (7.7)	11 (7.1)	23 (7.4)
Not willing to continue the study	14 (9.0)	12 (7.8)	26 (8.4)
Completed 8-week randomized treatment period	**111 (71.2)**	**108 (70.1)**	**219 (70.6)**

(Source: d1448c00003 Study Report; Figure 2, page 81)

The modified intent-to-treat (MITT) sample had 299 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 14. Patients in this study were between 18 and 65 years of age. The average age was 43 years old. There were more females than males. The majority of the subjects was Caucasian (67%) and black (27%). The distribution of the baseline MADRS total score appeared similar between the two treatment arms.

Table 14. Study D1448C00003: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 152	QTP 150/300 mg N = 147	Total N = 299
Age (yr) n			
Mean (SD)	42.6 (11.7)	43.3 (10.5)	42.9 (11.1)
Median	44.0	45.0	45.0
Min – Max	18 – 64	19 – 61	18 – 64
Sex – n (%)			
Male	54 (35.5)	52 (35.4)	106 (35.5)
Female	98 (64.5)	95 (64.6)	193 (64.5)
Race – n (%)			
Black	42 (27.6)	40 (27.2)	82 (27.4)
Caucasian	100 (65.8)	101 (68.7)	201 (67.2)
Oriental	3 (2.0)	0 (0.0)	3 (1.0)
Others	7 (4.6)	6 (4.1)	13 (4.4)
Baseline MADRS-total score			
Mean (SD)	29.3 (5.3)	29.7 (6.2)	29.5 (5.8)
Median	30.0	30.0	30.0
Min – Max	15 – 44	13 – 48	13 – 48

(Source: d1448c00003 Study Report; Tables 14 & 16, pages 84-85 & 87)

Patients who failed to achieve adequate response (defined as at least 20% reduction in the MADRS total score from randomization after two weeks of treatment) had their doses up-titrated to 300 mg/day. The sponsor reported 35 subjects (23.0%) in the placebo arm and 22 subjects (15.0%) in the quetiapine arm did not achieve adequate response after two weeks of treatment. However, when examining the change from baseline in the MADRS total score at week 2, this reviewer found that there were 39 subjects (25.7%) in the placebo arm and 28 subjects (19.0%) in the quetiapine arm who failed to achieve at least 20% reduction in the MADRS total score from randomization.

3.1.3.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 8 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. The primary analysis is summarized in Table 15. Quetiapine XR was statistically significantly superior to placebo in the change from randomization to week 8 in the MADRS total score.

Table 15. Study D1448C00003: Sponsor's primary efficacy results: change from randomization to week 8 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150/300 mg
Sample size	152	147
LS Means	-13.10	-16.49
Difference from placebo		-3.39
(95% confidence interval)		(-5.48, -1.30)
Unadjusted p-values		0.002
Adjusted p-values		0.002

(Source: d1448c00003 Study Report; Table 18, pages 92)

3.1.3.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The key secondary efficacy variable was the change from randomization to Week 8 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Table 16 summarizes the key secondary results. Quetiapine XR was not statistically significantly superior to placebo.

Table 16. Study D1448C00003: Sponsor's key secondary efficacy results: change from randomization to week 8 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample

	Placebo	QTP 150/300 mg
Sample size	137	138
LS Means	11.93	13.80
Difference from placebo		1.87
(95% confidence interval)		(-1.76, 5.50)
Unadjusted p-values		0.311

(Source: d1448c00003 Study Report; Table 29, pages 105)

3.1.3.4.4 Sponsor's Other Efficacy Results

A primary sensitivity analysis: An analysis on the change from randomization to week 8 in the MADRS total score using a mixed model for repeated measures is summarized in Table 17. The model included visit, treatment, and treatment-by-visit interaction as fixed factors, center as a random factor, and randomization MADRS total score as a covariate. Robust variance estimates of the fixed effects were used for testing treatment differences. The model used an unstructured covariance pattern. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

Table 17. Study D1448C00003: Sponsor's primary sensitivity analysis: change from randomization to week 8 in the MADRS total score (OC) in the MITT sample

	Placebo	QTP 150/300 mg
Sample size	152	147
LS Means	-14.26	-18.12
Difference from placebo		-3.87
(95% confidence interval)		(-6.02, -1.71)
Unadjusted p-values		<0.001

(Source: d1448c00003 Study Report; Table 11.2.1.1.3, page 266)

An analysis on the primary endpoint over time (LOCF): Table 18 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. Quetiapine XR showed numerically consistently better responses than placebo over time.

Table 18. Study D1448C00003: Sponsor's efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample

	Pbo	QTP 150/300mg	QTP - Pbo Diff	QTP - Pbo p-value*
Week 1	-7.29	-9.22	-1.93	0.010
Week 2	-9.96	-12.64	-2.68	0.004
Week 4	-11.62	-14.07	-2.45	0.011
Week 6	-13.22	-15.57	-2.36	0.021
Week 8	-13.10	-16.49	-3.39	0.002

(Source: d1448c00003 Study Report; Table 11.2.1.1.1, pages 258-261)
*p-values are not adjusted for multiplicity

3.1.3.4.5 Reviewer's Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 15 and Table 16. Quetiapine XR was superior to placebo on the change from randomization to week 8 in the MADRS total score, but not on the Q-LES-Q percent maximum score.

3.1.4 Study D1448C00005

3.1.4.1 Objectives

Primary: The primary objective of the study was to evaluate the efficacy of quetiapine XR compared with placebo in the time from randomization to a depressed event in patients with MDD.

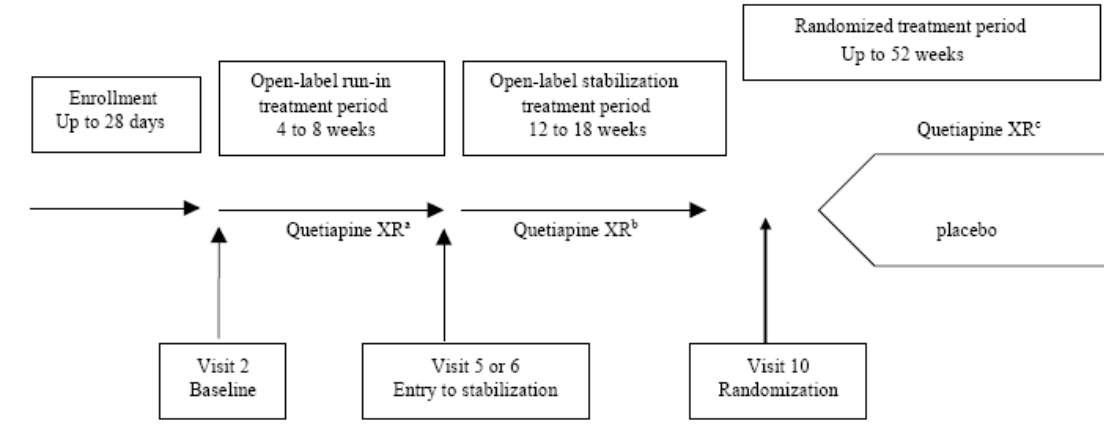
A depressed event is defined as fulfilling at least one of the following:

a. Initiation of pharmacological treatment by the investigator, other than the allowed hypnotics, to treat depressive symptoms.
b. Initiation of pharmacological treatment by the patient for at least 1 week, other than the allowed hypnotics, to treat depressive symptoms.
c. Hospitalization for depressive symptoms.

d. MADRS > 18 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinues.
e. Clinical Global Impressive-Severity of Illness (CGI-S) of at least 5.
f. Suicide attempt or discontinuation from study due to imminent risk of suicide.

3.1.4.2 Study Design

This was a multi-center, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study. The study consisted of 4 periods: enrollment (up to 28 days), an open-label run-in treatment period (4 to 8 weeks), an open-label stabilization treatment period (12 to 18 weeks), and a double-blind, randomized treatment period (up to 52 weeks). During the open-label stabilization period, patients were treated with open-label quetiapine XR for at least 12 weeks. The dosage could be adjusted to 50, 150, or 300 mg/day to maximize efficacy and tolerability. Patients must have responded to acute treatment during the open-label treatment phase in order to be eligible to continue maintenance treatment during the randomized treatment phase. Eligible patients would be randomized to continue quetiapine XR or switch to placebo for up to 52 weeks. The dosage could be adjusted to 50, 150, or 300 mg/day as clinically indicated during the study. The study flow chart is summarized in Figure 2.



[a] The dose of quetiapine XR was titrated as 50 mg on Day 1 to Day 2 and then 150 mg on Day 3 to Day 4. On Day 5 and thereafter, the dose could have been adjusted to 50 mg, 150 mg, or 300 mg/day based on the clinical judgment of the Investigator.
[b] The dose of quetiapine XR could have been adjusted to 50 mg, 150 mg, or 300 mg/day based on the clinical judgment of the Investigator.
[c] Patients were randomized to quetiapine XR or matching placebo at the same dose as taken at the last study visit in the open-label stabilization treatment period. During the randomized treatment period, quetiapine XR could have been adjusted to 50 mg, 150 mg, or 300 mg/day based on the clinical judgment of the Investigator.
XR Extended release.

Figure 2. Study D1448C00005: Flow chart

(Source: d1448c00005 Study Report; Figure 1, page 41)

Male and female patients between the age of 18 and 65 years old were enrolled from December 2005 to August 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 20 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment. Key entry criteria are summarized in Table 19.

Table 19. Study D1448C00005: Key entry criteria

Entry criteria[a]	Enrollment entry	Entry to OLST (Week 4 or 8 of OLT)	During OLST	Entry to randomization (Day of randomization)
HAM-D total score	≥20			
HAM-D Item 1	≥2			
MADRS		≤12	≤14	≤12
CGI-S		≤3	≤4	≤3

[a] See additional entry and exclusion criteria, Sections 5.3.1 and 5.3.2.

CGI-S Clinical Global Impression-Severity of Illness. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Åsberg Depression Rating Scale. OLT Open-label run-in treatment. OLST Open-label stabilization treatment.

(Source: d1448c00005 Study Report; Table 2, page 42)

The sample size for this study was calculated based on an 85% power assuming a hazard ratio of 0.55. It was estimated that 101 depressed events were required in the quetiapine XR and placebo groups.

3.1.4.3 Efficacy Endpoints and Analyses

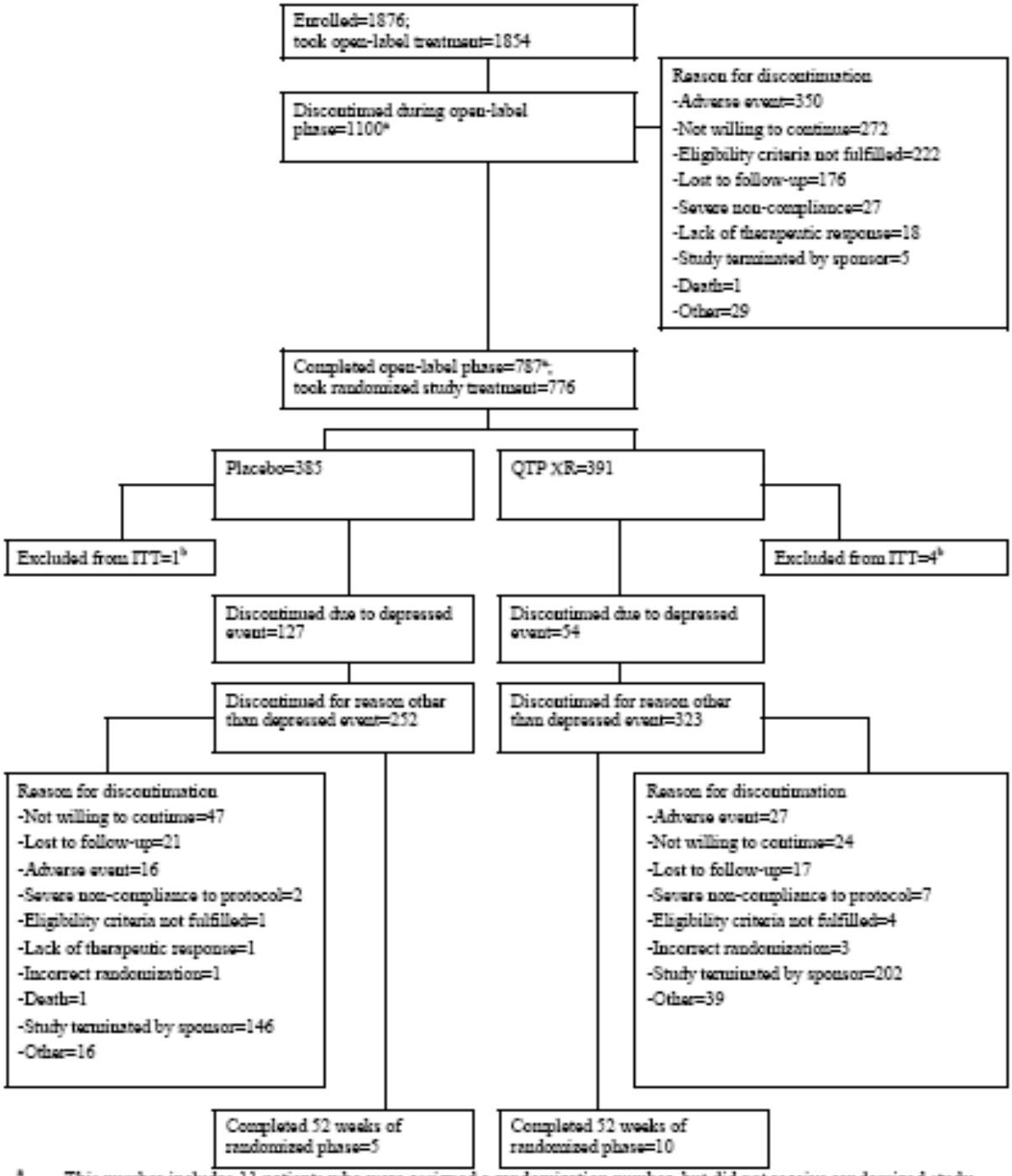
Primary endpoint and analysis: The primary efficacy variable was the time from randomization to an occurrence of a depressed event. A depressed event was defined in section 3.1.4.1. The time to a depressed event was analyzed by a Cox proportional hazards model. The null hypothesis of equality between the two arms was tested by a 2-sided Wald test. Region (U.S. versus non-U.S.) was included as a stratification variable in the analysis.

3.1.4.4 Efficacy Results

3.1.4.4.1 Study Population

Subjects were enrolled from Bulgaria (6 sites), Canada (10 sites), Finland (5 sites), France (10 sites), Germany (9 sites), Romania (5 sites), Russia (7 sites), Slovakia (8 sites), South Africa (4 sites), U.K. (9 sites), and U.S.A (164 sites). A total of 2883 subjects were screened and 1876 subjects enrolled. The randomized sample consisted of 787 subjects and 776 subjects received treatment.

The disposition of the patients is summarized in Figure 3. In the randomized treatment period, excluding subjects who discontinued due to depressed events, the main reasons for discontinuation were not willing to continue, adverse events, and lost to follow-up. Only 15 patients completed the 52 weeks randomized phase.



[a] This number includes 11 patients who were assigned a randomization number, but did not receive randomized study treatment.

[b] All 5 patients from Site 1047 (1 patient in the placebo group and 4 patients in the quetiapine XR group) were excluded from the ITT population because the site was not compliant with GCP and the integrity of the data pertaining to these patients could not be verified.

Figure 3. Study D1448C00005: Disposition of patients

The intent-to-treat (ITT) sample consisted of 771 subjects. The demographics and baseline disease characteristics of the ITT sample are presented in Table 20. Patients in this study were between 19 and 65 years of age. The average age was

45 years old. The ratio of female to male was approximately 2 to 1. The majority of the subjects was Caucasian (88%) and black (9%).

Table 20. Study D1448C00005: Demographic and baseline disease characteristics (ITT sample)

	Placebo N = 384	QTP XR N = 387	Total N = 771
Age (yr) n			
Mean (SD)	43.8 (11.5)	45.4 (11.2)	44.6 (11.4)
Median	46.0	47.0	46.0
Min – Max	19 – 65	19 – 65	19 – 65
Sex – n (%)			
Male	130 (33.9)	132 (34.1)	262 (34.0)
Female	254 (66.1)	255 (65.9)	509 (66.0)
Race – n (%)			
Black	37 (9.6)	33 (8.5)	70 (9.1)
Caucasian	339 (88.3)	336 (86.8)	675 (87.6)
Oriental	3 (0.8)	2 (0.5)	5 (0.7)
Others	5 (1.3)	16 (4.1)	21 (2.7)
Enrollment MADRS-total score			
Mean (SD)	27.7 (5.8)	28.6 (5.9)	28.2 (5.9)
Median	28.0	29.0	28.0
Min – Max	4 – 44	9 – 45	4 – 45
Randomization MADRS-total score			
Mean (SD)	5.3 (3.7)	5.8 (3.6)	5.5 (3.7)
Median	5.0	6.0	6.0
Min – Max	4 – 12	0 – 12	0 – 12

(Source: d1448c00005 Study Report; Tables 18 & 19, pages 113 & 115)

3.1.4.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to a depressed event. The primary efficacy variable was analyzed by a Cox proportional hazard model with U.S. as a stratification factor. The Wald's test was used to test the difference between quetiapine XR and placebo. The results are presented in Table 21. Quetiapine XR flexible dose (50 mg/day, 150 mg/day, or 300 mg/day) significantly increased the time to a depressed event compared with placebo.

Table 21. Study D1448C00005: Sponsor's primary efficacy analysis: Time to depressed event (ITT sample). Wald's test, comparison of QTP XR versus Placebo with Cox Regression

	Placebo (N=384)	QTP XR (N=387)
Numbers of relapses (%)	132 (34.4)	55 (14.2)
Comparison between treatment groups		
Hazard ratio		0.34
95% confidence interval		(0.25, 0.46)
p-value		< 0.001

(Source: Clinical Study Report: Study d1448C00005; Table 22, page 122)

3.1.4.4.3 Sponsor's Other Efficacy Results

Primary sensitivity analysis (primary analysis on per-protocol sample): The primary efficacy variable was analyzed using the per-protocol (PP) sample. The same Cox model as in the primary analysis was used. The results are summarized in Table 22. This analysis corroborates with the primary analysis.

Table 22. Study D1448C00005: Sponsor's primary sensitivity analysis: Time to depressed event (PP sample). Wald's test, comparison of QTP XR versus Placebo with Cox Regression

	Placebo (N=290)	QTP XR (N=303)
Numbers of relapses (%)	92 (31.7)	39 (12.9)
Comparison between treatment groups		
Hazard ratio		0.33
95% confidence interval		(0.23, 0.49)
p-value		<0.001

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.1.5, page 588)

Primary sensitivity analysis (excluding events occurred up to 30 days after randomization): To ensure the depressed events were not due to the immediate effects of treatment discontinuation, the primary efficacy variable was reanalyzed excluding all events occurred up to 30 days after randomization. For this analysis, all events that occurred in the first 29 days after randomization were censored. Table 23 summarizes the results. This analysis also corroborates with the primary analysis.

Table 23. Study D1448C00005: Sponsor's primary sensitivity analysis: Time to depressed event (ITT sample), excluding events occurred up to first 30 days after randomization. Wald's test, comparison of QTP XR versus Placebo with Cox Regression

	Placebo (N=384)	QTP XR (N=387)
Numbers of relapses (%)	59 (15.4)	39 (10.1)
Comparison between treatment groups		
Hazard ratio		0.49
95% confidence interval		(0.33, 0.73)
p-value		0.001

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.1.1, page 584)

Kaplan-Meier curves for time to a depressed event: The Kaplan-Meier curves for time to a depressed event are presented in Figure 4 showing a separation between quetiapine XR and placebo.

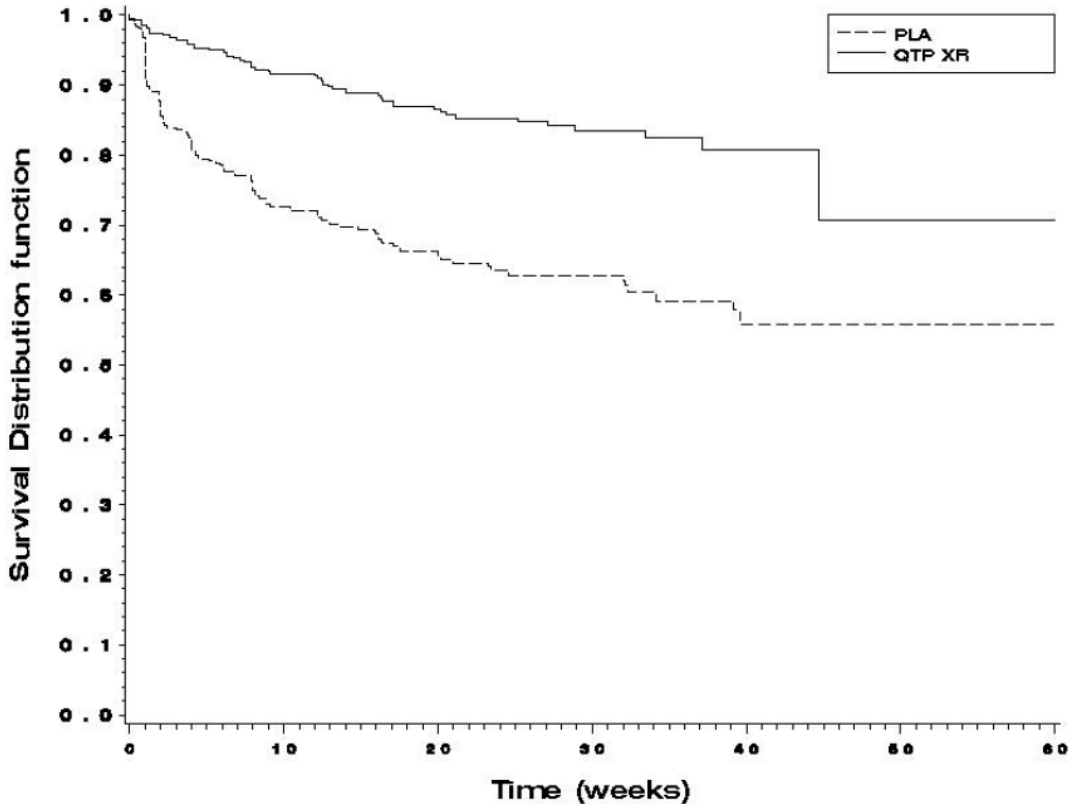


Figure 4. Study D1448C00005: Time to a depressed event, Kaplan-Meier Curves (ITT sample)
(Source: Clinical Study Report: Study d1448C00005; Figure 4, page 123)

3.1.4.4.4 Reviewer's Results and Comments

This reviewer confirms the sponsor's finding on the primary efficacy endpoint presented in Table 21. Quetiapine XR statistically significantly increased the time to a depressed event.

The Cox model relies on the proportional hazard assumption. To examine this assumption, a log(-log (survival)) curve was produced. Figure 5 plots the log(-log(survival (week))) versus log(week). The proportional hazard assumption is reasonable when the two curves are parallel. Figure 5 suggests that the proportional hazard assumption is reasonable for this study.

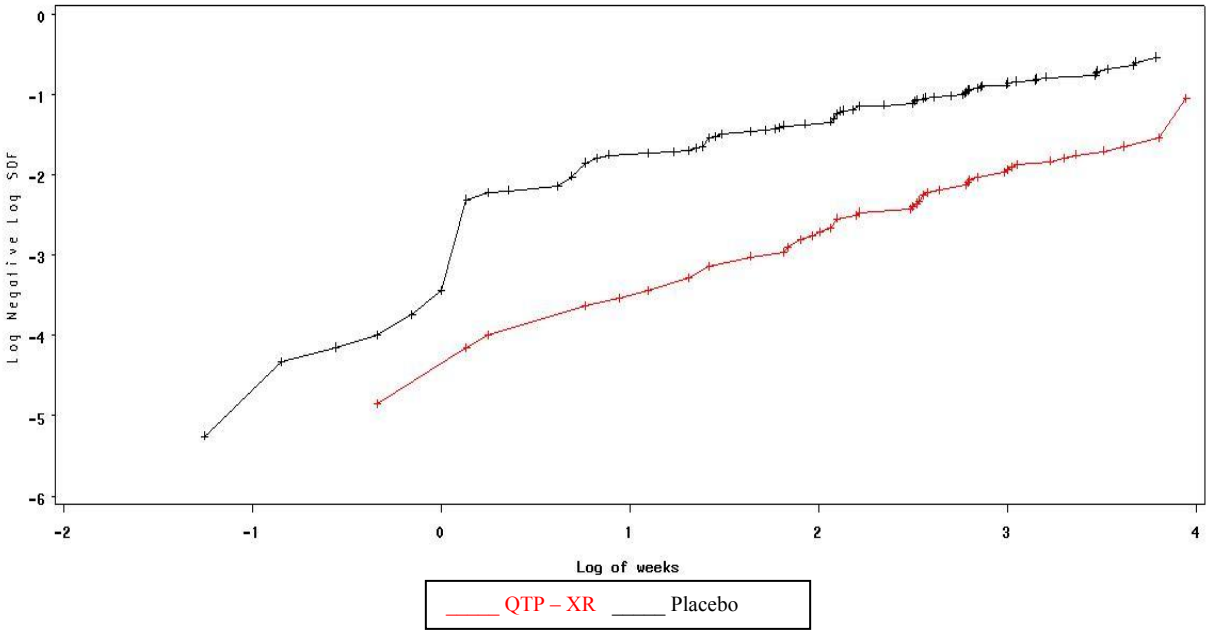


Figure 5. Study D1448C00005: Log(-Log(Survival)) Curve (ITT sample)
(Source: Reviewer's result)

Figure 6 plots the time to censoring for the quetiapine and placebo groups. The quetiapine group has a slightly longer time to censoring than the placebo group.

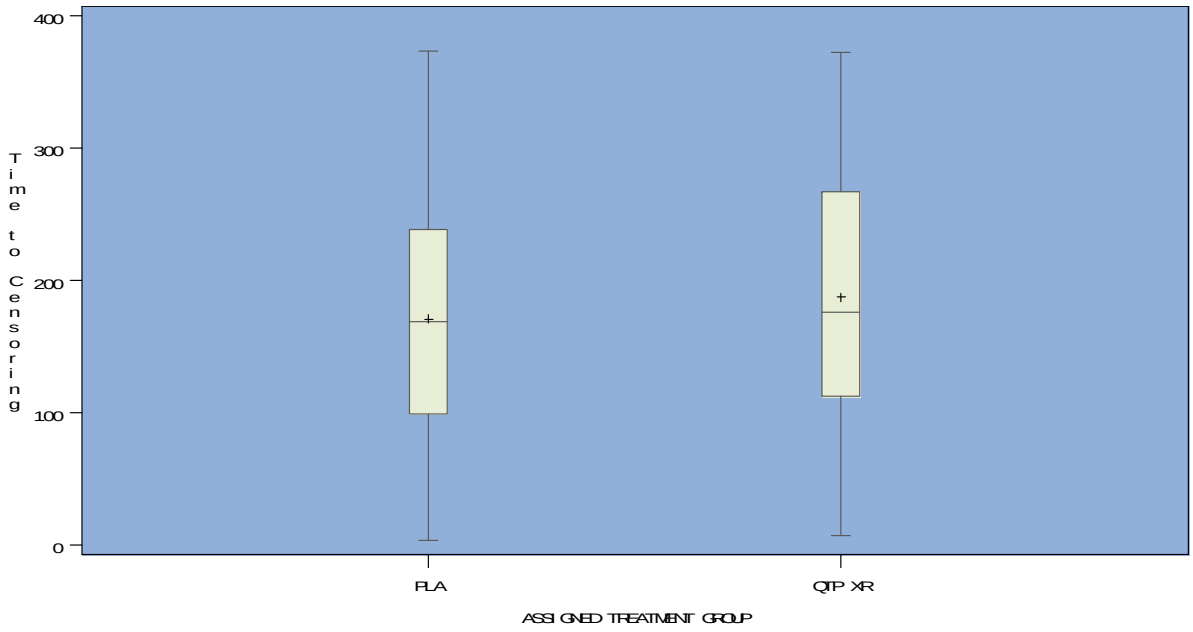


Figure 6. Study D1448C00005: Time to Censoring
(Source: Reviewer's result)

In the intent-to-treat (ITT) sample, the sponsor excluded 5 subjects from site # 1047 due to non-compliance. Four subjects came from the quetiapine XR group and 1 from the placebo. As a sensitivity analysis, this reviewer classified the four

subjects from the quetiapine XR group as events and kept the subject from the placebo arm as censor. A Cox regression model similar to the primary analysis was performed. The results are presented in Table 24 and are supportive of the primary analysis.

Table 24. Study D1448C00005: Reviewer's sensitivity efficacy analysis: Time to depressed event (ITT sample). Wald's test, comparison of QTP XR versus Placebo with Cox Regression

	Placebo (N=385)	QTP XR (N=391)
Numbers of relapses (%)	132 (34.3)	59 (15.1)
Comparison between treatment groups		
Hazard ratio		0.36
95% confidence interval		(0.27, 0.49)
p-value		< 0.001

(Source: Reviewer's results)

3.1.5 Study D1448C00006

3.1.5.1 Objectives

Primary: The primary objective of the study was to evaluate the efficacy of quetiapine XR in combination with an antidepressant versus an antidepressant in combination with placebo in patients with Major Depressive Disorder (MDD) who have had an inadequate response to antidepressant monotherapy.

Key Secondary: The key secondary objective of this study was to evaluate if quetiapine XR in combination with an antidepressant improved the health-related quality of life in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo by assessing the change from randomization to Week 6 in the Q-LES-Q percent maximum total score (Items 1-14).

3.1.5.2 Study Design

This was an 8-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study consisted of three periods. The first period was an enrollment period of up to 14 days. The second period was a six-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to receive quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo in combination with the ongoing antidepressant treatment. The third period was a two-week post-treatment follow-up period. Patients were asked to call in for discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to July 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 20 and HAM-D Item 1 (depressed mood) score of

at least 2 both at enrollment and at randomization. Patients should have been on treatment with antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to the prescribing information), with at least 1 dose increase when permitted according to the prescribing information. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 43.

The sample size calculation was based on a 90% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

3.1.5.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q total score} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons across the primary and secondary hypotheses. First, both primary hypotheses were tested. The Hommel procedure was used control the type I error rate between the two primary hypotheses. If both doses of quetiapine XR were statistically significantly superior to placebo, then the two secondary hypotheses would be tested. The Hommel procedure would also be used to control the type I error rate between the two secondary hypotheses.

3.1.5.4 Efficacy Results

3.1.5.4.1 Study Population

Subjects were enrolled from 53 centers in the United States. A total of 659 subjects were screened and 446 subjects were randomized to 1 of the three treatment groups: placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant. The disposition of the subjects is summarized in Table 25. In Table 25 and all subsequent tables of this study, placebo, QTP 150 mg, QTP 300 mg are used to denote placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant. Both quetiapine XR groups had more patients who discontinued the study prematurely than the placebo group. Main reasons for patients to discontinue were adverse events, lost to follow-up, and patients not willing to continue. There were more adverse events in the two quetiapine XR groups than in the placebo group.

Table 25. Study D1448C00006: Disposition of patients

	Placebo (N = 148)	QTP 150mg (N = 148)	QTP 300mg (N =150)	Total (N = 446)
Randomized (not treated)	0	0	1	1
Randomized (treated)	148	148	149	445
Discontinued study: n (%)	**23 (15.5)**	**34 (23.0)**	**45 (30.0)**	**102 (22.9)**
Adverse event	1 (0.7)	16 (10.8)	27 (18.0)	44 (9.9)
Eligibility criteria not fulfilled		1 (0.7)	1 (0.7)	2 (0.4)
Lack of therapeutic response	4 (2.7)	2 (1.4)		6 (1.3)
Severe non-compliance with the study protocol		2 (1.4)		2 (0.4)
Did not complete ≥ 36 days of study treatment		1 (0.7)	1 (0.7)	2 (0.4)
Lost to follow-up	10 (6.8)	8 (5.4)	7 (4.7)	25 (5.6)
Patients not willing to continue	8 (5.4)	4 (2.7)	6 (4.0)	18 (4.0)
Other			3 (2.0)	3 (0.7)
Completed 6-week randomized treatment period: n (%)	**125 (84.5)**	**114 (77.0)**	**105 (70.0)**	**344 (77.1)**

(Source: d1448c00006 Study Report; Figure 3, page 92)

The modified intent-to-treat (MITT) sample had 432 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 26. Patients in this study were between 19 and 65 years of age. The average age was 45 years old. The ratio of female to male was more than 2 to 1. The majority of the subjects was Caucasian (90%). The distribution of the baseline MADRS total score appeared balanced across the three treatment arms.

Table 26. Study D1448C00006: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 143	QTP 150 mg N = 143	QTP 300 mg N = 146	Total N = 432
Age (yr) n				
Mean (SD)	46.2 (10.9)	45.9 (11.0)	44.3 (11.3)	45.4 (11.1)
Median	48.0	47.0	46.0	47.0
Min – Max	20 – 65	20 – 64	19 – 64	19 – 65
Sex – n (%)				
Male	45 (31.5)	34 (23.8)	40 (27.4)	119 (27.5)
Female	98 (68.5)	109 (76.2)	106 (72.6)	313 (72.5)
Race – n (%)				
Black	14 (9.8)	10 (7.0)	11 (7.5)	35 (8.1)
Caucasian	128 (89.5)	128 (89.5)	133 (91.1)	389 (90.1)
Oriental	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Others	1 (0.7)	4 (2.8)	2 (1.4)	7 (1.6)
Baseline MADRS-total score				
Mean (SD)	27.6 (5.5)	27.2 (5.2)	27.6 (5.0)	27.5 (5.2)
Median	28.0	27.0	27.0	27.0
Min – Max	12 – 43	12 – 45	13 – 43	12 – 45

(Source: d1448c00006 Study Report; Tables 16 & 18, pages 97 & 99)

3.1.5.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested sequentially. First the two primary hypotheses were tested using the Hommel procedure. If both primary hypotheses were significant, then the two secondary hypotheses were tested using the Hommel procedure. The primary analysis is summarized in Table 27. Quetiapine XR at 300 mg/day in combination with an antidepressant was statistically significantly superior to placebo in combination with an antidepressant. Quetiapine XR at 150 mg/day in combination with an antidepressant was not statistically significantly superior to placebo in combination with an antidepressant.

Table 27. Study D1448C00006: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Sample size	143	143	146
LS Means	-11.70	-13.60	-14.70
Difference from placebo		-1.90	-2.99
(95% confidence interval)		(-3.93, 0.14)	(-5.02, -0.97)
Unadjusted p-values		0.067	0.004
Adjusted p-values		0.067	0.008

(Source: d1448c00006 Study Report; Table 21, page 106)

3.1.5.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Because only one dose of the primary hypotheses was rejected, the key secondary hypotheses were not tested. The results of the key secondary results presented in Table 28 are for descriptive purposes only.

Table 28. Study D1448C00006: Sponsor's key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Sample size	136	135	136
LS Means	11.32	10.37	11.82
Difference from placebo		-0.96	0.50
(95% confidence interval)		(-4.59, 2.68)	(-3.15, 4.15)
Unadjusted p-values		0.606	0.789

(Source: d1448c00006 Study Report; Table 35, pages 121)

3.1.5.4.4 Sponsor's Other Efficacy Results

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 29. The model included treatment, visit, and treatment-by-visit interaction as fixed effects, center as random effect, and baseline MADRS total score as a covariate. Robust variance estimates for the fixed effects were used to test the treatment differences. The within subject variance was unstructured. Based on this sensitivity analysis, both doses of quetiapine were superior to placebo on the change from randomization to week 6 in the MADRS total score.

Table 29. Study D1448C00006: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Sample size	143	143	146
LS Means	-11.72	-14.28	-15.95
Difference from placebo		-2.56	-4.24
(95% confidence interval)		(-4.33, -0.80)	(-6.07, -2.40)
Unadjusted p-values		0.005	<0.001

(Source: d1448c00006 Study Report; Table 11.2.1.4, page 329)

An analysis on the primary endpoint over time (LOCF): Table 30 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The response appeared consistent over time for the quetiapine XR 300 mg/day arm. In the 150 mg/day arm, greater responses appeared in Weeks 1 and 2 than in Weeks 4 and 6.

Table 30. Study D1448C00006: Sponsor's efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample

	Pbo	QTP 150mg	QTP 300mg	QTP 150mg – Pbo Diff	QTP 150mg – Pbo p-value*	QTP 300mg – Pbo Diff	QTP 300mg – Pbo p-value*
Week 1	-5.95	-9.06	-8.20	-3.10	<0.001	-2.25	0.002
Week 2	-9.05	-11.62	-11.46	-2.57	0.003	-2.40	0.005
Week 4	-11.51	-13.06	-13.72	-1.55	0.100	-2.21	0.019
Week 6	-11.70	-13.60	-14.70	-1.90	0.067	-2.99	0.004

(Source: d1448c00006 Study Report; Table 11.2.1.3.1, pages 322-324)
*p-values are not adjusted for multiplicity

3.1.5.4.5 Reviewer's Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 27 and Table 28. Quetiapine XR at a 300 mg/day in combination with an antidepressant was superior to placebo in combination with an antidepressant on the change from randomization to week 6 in the MADRS total score.

Quetiapine XR at a 150 mg/day in combination with an antidepressant was not superior to placebo in combination with an antidepressant. Quetiapine XR was also not superior to placebo on the Q-LES-Q percent maximum score change from randomization to week 6.

3.1.6 Study D1448C00007

3.1.6.1 Objectives

Primary: The primary objective of this study was to evaluate the efficacy of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant versus antidepressant in combination with placebo in patients with MDD, as assessed by the change from randomization to week 6 in the MADRS total score.

Key Secondary: The key secondary objective was to evaluate if quetiapine XR in combination with an antidepressant improves the health-related quality of life of patients with MDD, compared to an antidepressant in combination with placebo by assessing the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

3.1.6.2 Study Design

This was a 6-week, multicenter, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study consisted of two periods. The first period was an enrollment period of up to 14 days. The second period was a six-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to receive quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo in combination with the ongoing antidepressant treatment.

Male and female patients between the age of 18 and 65 years old were enrolled from May 2006 to April 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D total score of at least 20 and HAM-D Item 1 score of at least 2 both at enrollment and at randomization; had a history during the current depressive episode of an inadequate response to 1 of the following antidepressants: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 43.

The sample size calculation was based on a 90% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

3.1.6.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q totals core} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons across the primary and secondary hypotheses. First, both primary hypotheses were tested. The Hommel procedure was used control the type I error rate between the two primary hypotheses. If both doses of quetiapine XR were statistically significantly superior to placebo, then the two secondary hypotheses would be tested. The Hommel procedure would also be used to control the type I error rate between the two secondary hypotheses.

3.1.6.4 Efficacy Results

3.1.6.4.1 Study Population

Subjects were enrolled from 87 centers in Australia, Belgium, Canada, Czech, Finland, France, Germany, Norway, Poland, Romania, South Africa, and Sweden. A total of 572 subjects were screened and 493 subjects were randomized to 1 of the three treatment groups: placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant. The disposition of the subjects is summarized in Table 31. In Table 31 and all subsequent tables of this study, placebo, QTP 150 mg, QTP 300 mg are used to denote placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant.

Fourteen percent of the randomized subjects discontinued the study prematurely. The main reasons for the discontinuation were adverse events and patients not willing to continue. There were more adverse events in the quetiapine XR arms than in placebo. The discontinuation rate was highest for quetiapine XR 300 mg/day (18.4%), followed by the quetiapine XR 150 mg/day (12.6%), and then the placebo (11.0%).

Table 31. Study D1448C00007: Disposition of patients

	Placebo (N = 163)	QTP 150mg (N = 167)	QTP 300mg (N =163)	Total (N = 493)
Randomized (not treated)	2	0	0	2
Randomized (treated)	161	167	163	491
Discontinued study: n (%)	**18 (11.0)**	**21 (12.6)**	**30 (18.4)**	**69 (14.0)**
-Lost to follow-up		3 (1.8)		3 (0.6)
-Adverse event	5 (3.1)	11 (6.6)	19 (11.7)	35 (7.1)
-Development of study specific discontinuation criteria			2 (1.2)	2 (0.4)
-Patients not willing to continue	5 (3.1)	7 (4.2)	3 (1.8)	15 (3.0)
-Lack of therapeutic response	5 (3.1)		1 (0.6)	6 (1.2)
-Eligibility criteria not fulfilled	1 (0.6)		2 (1.2)	3 (0.6)
-Severe non-compliance to protocol	1 (0.6)		3 (1.8)	4 (0.8)
-Other	1 (0.6)			1 (0.2)
Completed 6-week randomized treatment period: n (%)	**145 (89.0)**	**146 (87.4)**	**133 (81.6)**	**424 (86.0)**

(Source: d1448c00007 Study Report; Table 11.1.3.1, page 198)

The modified intent-to-treat (MITT) sample had 487 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 32. Patients in this study were between 18 and 65 years of age. The average age was 45 years old. The ratio of females to males was about than 2 to 1. The majority of the subjects was Caucasian (98%). The distribution of the baseline MADRS total score appeared balanced across the three treatment arms.

Table 32. Study D1448C00007: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 160	QTP 150 mg N = 166	QTP 300 mg N = 161	Total N = 487
Age (yr) n				
Mean (SD)	44.8 (10.4)	46.0 (10.1)	45.5 (11.1)	45.4 (10.5)
Median	46.0	47.0	47.0	47.0
Min – Max	20 – 64	21 – 65	18 – 65	18 - 65
Sex – n (%)				
Male	56 (35.0)	51 (30.7)	51 (31.7)	158 (32.4)
Female	104 (65.0)	115 (69.3)	110 (68.3)	329 (67.6)
Race – n (%)				
Black	2 (1.3)	0 (0.0)	2 (1.2)	4 (0.8)
Caucasian	157 (98.1)	165 (99.4)	156 (96.9)	478 (98.2)
Oriental	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Others	0 (0.0)	1 (0.6)	2 (1.2)	3 (0.6)
Baseline MADRS-total score				
Mean (SD)	28.2 (5.6)	28.6 (5.4)	28.4 (5.5)	28.4 (5.5)
Median	28.0	29.0	29.0	28.0
Min – Max	7 – 42	14 – 44	14 – 44	7 – 44

(Source: d1448c00007 Study Report; Tables 16 & 17, pages 90 & 91)

3.1.6.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested sequentially. First the two primary hypotheses were tested using the Hommel procedure. If both primary hypotheses were significant, then the two secondary hypotheses were tested using the Hommel procedure. The primary analysis is summarized in Table 33. Quetiapine XR at 150 mg/day and 300 mg/day in combination with an antidepressant were statistically significantly superior to placebo in combination with an antidepressant.

Table 33. Study D1448C00007: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Sample size	160	166	161
LS Means	-12.21	-15.26	-14.94
Difference from placebo		-3.05	-2.73
(95% confidence interval)		(-4.92, -1.17)	-4.62, -0.84)
Unadjusted p-values		0.002	0.005
Adjusted p-values		0.003	0.005

(Source: d1448c00007 Study Report; Table 20, pages 98-99)

3.1.6.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. The key secondary analysis results are presented in Table 34. Both quetiapine XR in combination with an antidepressant groups did not separate from placebo in combination with an antidepressant.

Table 34. Study D1448C00007: Sponsor's key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Sample size	160	160	157
LS Means	12.58	14.70	12.81
Difference from placebo		2.12	0.24
(95% confidence interval)		(-1.09, 5.33)	(-2.98, 3.46)
Unadjusted p-values		0.194	0.884
Adjusted p-values		0.389	0.884

(Source: d1448c00007 Study Report; Table 33, pages 113)

3.1.6.4.4 Sponsor's Other Efficacy Results

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 29. The model included treatment, visit, and treatment-by-visit interaction as fixed effects, center as random effect, and baseline MADRS total score as a covariate. Robust variance estimates for the fixed effects were used to test the treatment differences. The within subject variance was unstructured. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

Table 35. Study D1448C00007: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Sample size	160	166	161
LS Means	-12.51	-15.98	-16.16
Difference from placebo		-3.47	-3.65
(95% confidence interval)		(-5.55, -1.39)	(-5.69, -1.62)
Unadjusted p-values		0.001	<0.001

(Source: d1448c00007 Study Report; Table 11.2.1.4, page 300)

An analysis on the primary endpoint over time (LOCF): Table 40 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The effects appeared consistent over time for both dose groups.

Table 36. Study D1448C00007: Sponsor's efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample

	Pbo	QTP 150mg	QTP 300mg	QTP 150mg – Pbo Diff	QTP 150mg – Pbo p-value*	QTP 300mg – Pbo Diff	QTP 300mg – Pbo p-value*
Week 1	-4.16	-6.52	-6.38	-2.36	<0.001	-2.22	<0.001
Week 2	-7.71	-10.03	-10.44	-2.32	0.002	-2.73	<0.001
Week 4	-10.77	-12.93	-12.97	-2.16	0.011	-2.20	0.010
Week 6	-12.21	-15.26	-14.94	-3.05	0.002	-2.73	0.005

(Source: d1448c00007 Study Report; Table 11.2.1.3.1, pages 293-295)
*p-values are not adjusted for multiplicity

3.1.6.4.5 Reviewer's Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 33 and Table 34. Quetiapine XR at 150 mg/day and 300 mg/day in combination with an antidepressant were superior to placebo in combination with an antidepressant based on the primary endpoint, change from randomization to week 6 in the MADRS total score, but not on the key secondary endpoint, the Q-LES-Q percent of maximum score.

3.2 Evaluation of Safety

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study D1448C00001

4.1.1.1 Gender

The primary analysis stratified by gender is presented in Table 37. All three doses showed numerical improvements over placebo across males and females.

Table 37. Study D1448C00001: Sponsor's primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Females				
Sample size	113	95	104	103
LS Means	-11.45	-13.90	-13.74	-15.21
Difference from placebo		-2.45	-2.29	-3.76
(95% confidence interval)		(-5.22, 0,31)	(-5.00, 0.41)	(-6.46, -1.06)
Males				
Sample size	65	83	64	73
LS Means	-9.85	-12.50	-14.90	-11.87
Difference from placebo		-2.65	-5.04	-2.02
(95% confidence interval)		(-5.75, 0.46)	(-8.35, -1.74)	(-5.22, 1.18)

(Source: d1448c00001 Study Report; Table 11.2.1.5.2, pages 333, 335)

4.1.1.2 Race

Approximately 73% of the subjects were Caucasians and approximately 23% were black. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 38. The efficacy appeared consistent across the two race categories.

Table 38. Study D1448C00001: Sponsor's primary efficacy results by race: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Caucasians				
Sample size	136	131	124	123
LS Means	-10.53	-12.94	-13.70	-13.64
Difference from placebo		-2.41	-3.18	-3.11
(95% confidence interval)		(-4.82, -0.01)	-5.62, -0.74)	(-5.55, -0.67)
Others				
Sample size	43	47	44	53
LS Means	-11.78	-14.14	-15.61	-14.30
Difference from placebo		-2.35	-3.83	-2.51
(95% confidence interval)		(-6.42, 1.71)	(-7.95, 0.29)	(-6.46, 1.43)

(Source: d1448c00001 Study Report; Table 11.2.1.5.4, page 343 and reviewer's results)

4.1.1.3 Age

All subjects in this study were between 18 and 65 at entry. An analysis stratified by age is omitted from this review.

4.1.2 Study D1448C00002

4.1.2.1 Gender

The primary analysis stratified by gender is presented in Table 39. For quetiapine XR, the treatment effect appeared higher for females than males.

Table 39. Study D1448C00002: Sponsor's primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg	DUL
Females				
Sample size	98	93	75	88
LS Means	-10.87	-15.04	-16.06	-13.99
Difference from placebo		-4.17	-5.18	-3.12
(95% confidence interval)		(-6.90, -1.43)	(-8.08, -2.29)	(-5.89, -0.34)
Males				
Sample size	54	54	72	53
LS Means	-11.33	-13.49	-14.00	-14.90
Difference from placebo		-2.16	-2.66	-3.57
(95% confidence interval)		(-5.77, 1,46)	(-6.04, 0.71)	(-7.21, 0.07)

(Source: d1448c00002 Study Report; Table 11.2.1.5.2, pages 342, 345)

4.1.2.2 Race

Approximately 74% of the subjects were Caucasians and approximately 21% were black. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 40. Caucasians patients appeared to have a larger treatment effect than non-Caucasians. This could be due to the larger placebo effect seen among non-Caucasian patients.

Table 40. Study D1448C00002: Sponsor's primary efficacy results by race: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg	DUL
Caucasians				
Sample size	105	111	110	107
LS Means	-9.53	-14.83	-14.80	-14.82
Difference from placebo		-5.30	-5.27	-5.29
(95% confidence interval)		(-7.84, -2.76)	(-7.82, -2.73)	(-7.86, -2.73)
Others				
Sample size	47	36	37	34
LS Means	-14.27	-13.27	-15.81	-13.05
Difference from placebo		1.00	-1.54	1.22
(95% confidence interval)		(-3.23, 5.22)	(-5.73, 2.65)	(-3.07, 5.51)

(Source: d1448c00002 Study Report; Table 11.2.1.5.4, page 352 and reviewer's results)

4.1.2.3 Age

All subjects in this study were between 18 and 65 at entry. An analysis stratified by age is omitted from this review.

4.1.3 Study D1448C00003

4.1.3.1 Gender

The primary analysis stratified by gender is presented in Table 41. Consistent responses were seen both in males and females.

Table 41. Study D1448C00003: Sponsor's primary efficacy results by gender: change from randomization to week 8 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150/300 mg
Females		
Sample size	98	95
LS Means	-13.34	-16.80
Difference from placebo		-3.46
(95% confidence interval)		(-6.18, -0.74)
Males		
Sample size	54	52
LS Means	-12.55	-16.06
Difference from placebo		-3.51
(95% confidence interval)		(-6.71, -0.30)

(Source: d1448c00003 Study Report; Table 11.2.1.1.9, pages 289, 291)

4.1.3.2 Race

Approximately 67% of the subjects were Caucasians and approximately 27% were black. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 42. The effect appeared smaller for Caucasian patients than for other patients.

Table 42. Study D1448C00003: Sponsor's primary efficacy results by race: change from randomization to week 8 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150/300 mg
Caucasians		
Sample size	100	101
LS Means	-12.75	-15.51
Difference from placebo		-2.76
(95% confidence interval)		(-5.37, -0.14)
Others		
Sample size	52	46
LS Means	-13.85	-18.59
Difference from placebo		-4.74
(95% confidence interval)		(-8.14, -1.34)

(Source: d1448c00003 Study Report; Table 11.2.1.1.10, page 294 and reviewer's results)

4.1.3.3 Age

All subjects in this study were between 18 and 64 at entry. An analysis stratified by age is omitted from this review.

4.1.4 Study D1448C00005

4.1.4.1 Gender

The primary analysis stratified by gender is summarized below. The treatment effect appeared greater for males than for females.

Table 43. Study D1448C00005: Sponsor's primary efficacy analysis by gender: Time to depressed event (ITT sample). Wald's test, comparison of QTP XR versus Placebo with Cox Regression

	Placebo	QTP XR
Females		
Sample size	254	255
Numbers of relapses (%)	81 (31.9)	42 (16.5)
Comparison between treatment groups		
Hazard ratio		0.41
95% confidence interval		(0.29, 0.60)
Males		
Sample size	130	132
Numbers of relapses (%)	51 (39.2)	13 (9.8)
Comparison between treatment groups		
Hazard ratio		0.21
95% confidence interval		(0.11, 0.39)

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.3, pages 591-592)

4.1.4.2 Race

The majority of the subjects was Caucasians (88%) and black (9%). To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is summarized below. Caucasians appeared to have a greater treatment effect than other patients.

Table 44. Study D1448C00005: Sponsor's primary efficacy analysis by race: Time to depressed event (ITT sample). Wald's test, comparison of QTP XR versus Placebo with Cox Regression

	Placebo	QTP XR
Caucasians		
Sample size	339	336
Numbers of relapses (%)	121 (35.7)	48 (14.3)
Comparison between treatment groups		
Hazard ratio		0.32
95% confidence interval		(0.23, 0.45)
Others		
Sample size	45	51
Numbers of relapses (%)	11 (24.4)	7 (13.7)
Comparison between treatment groups		
Hazard ratio		0.51
95% confidence interval		(0.20, 1.32)

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.3, page 592 and reviewer's results)

4.1.4.3 Age

All subjects in this study were between 19 and 65 at entry. An analysis stratified by age is omitted from this review.

4.1.5 Study D1448C00006

4.1.5.1 Gender

The primary analysis stratified by gender is presented in Table 45. The effects appeared larger for male patients than for female patients.

Table 45. Study D1448C00006: Sponsor's primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Females			
Sample size	98	109	106
LS Means	-12.18	-13.28	-14.72
Difference from placebo		-1.10	-2.55
(95% confidence interval)		(-3.58, 1.37)	(-5.03, -0.06)
Males			
Sample size	45	34	40
LS Means	-11.67	-15.52	-15.51
Difference from placebo		-3.86	-3.84
(95% confidence interval)		(-7.79, 0.08)	(-7.61, -0.07)

(Source: d1448c00006 Study Report; Table 11.2.1.5.2, pages 336-339)

4.1.5.2 Race

Approximately 90% of the subjects were Caucasians. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 46. Due to small sample sizes, it is difficult to assess the treatment effect for other races. For Caucasians, the treatment effects appeared consistent with the overall results.

Table 46. Study D1448C00006: Sponsor's primary efficacy results by race: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Caucasians			
Sample size	128	128	133
LS Means	-12.14	-13.56	-14.85
Difference from placebo		-1.42	-2.71
(95% confidence interval)		(-3.63, 0.79)	(-4.90, -0.53)
Others			
Sample size	15	15	13
LS Means	-10.58	-16.24	-16.05
Difference from placebo		-5.66	-5.46
(95% confidence interval)		(-11.90, 0.58)	(-11.94, 1.01)

(Source: d1448c00006 Study Report; Table 11.2.1.5.4, page 346 and reviewer's results)

4.1.5.3 Age

All subjects in this study were between 19 and 65 at entry. An analysis stratified by age is omitted from this review.

4.1.6 Study D1448C00007

4.1.6.1 Gender

The primary analysis stratified by gender is presented in Table 47. The effects appeared consistent for both females and males.

Table 47. Study D1448C00007: Sponsor's primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample

	Placebo	QTP 150mg	QTP 300mg
Females			
Sample size	104	115	110
LS Means	-12.67	-15.83	-15.40
Difference from placebo		-3.16	-2.73
(95% confidence interval)		(-5.48, -0.84)	(-5.07, -0.38)
Males			
Sample size	56	51	51
LS Means	-11.38	-13.81	-13.96
Difference from placebo		-2.43	-2.58
(95% confidence interval)		(-5.89, 1.04)	(-6.03, 0.88)

(Source: d1448c00007 Study Report; Table 11.2.1.5.2, pages 307 & 309)

4.1.6.2 Race

Approximately 98% of the subjects were Caucasians. An analysis stratified by race is omitted from this review.

4.1.6.3 Age

All subjects in this study were between 18 and 65 at entry. An analysis stratified by age is omitted from this review.

4.2 Other Subgroups

4.2.1 Study D1448C00005

4.2.1.1 U.S.A. versus non-U.S.A.

The primary analysis stratified by U.S. versus non-U.S. is summarized below. The treatment effect appeared consistent in both strata.

Table 48. Study D1448C00005: Sponsor's primary efficacy analysis by region: Time to depressed event (ITT sample). Wald's test, comparison of QTP XR versus Placebo with Cox Regression

	Placebo	QTP XR
U.S.A.		
Sample size	250	252
Numbers of relapses (%)	94 (37.6)	38 (15.1)
Comparison between treatment groups		
Hazard ratio		0.32
95% confidence interval		(0.22, 0.47)
Non-U.S.A.		
Sample size	134	135
Numbers of relapses (%)	38 (28.4)	17 (12.6)
Comparison between treatment groups		
Hazard ratio		0.37
95% confidence interval		(0.21, 0.66)

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.3, pages 593-594)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

All six studies were positive on the primary efficacy variable on at least one dose under investigation. Among five studies that had the key secondary endpoint (Q-LES-Q percent maximum score), none of the studies was positive on the key secondary endpoint. The HAM-A was not a pre-specified endpoint, thus it cannot be used to support labeling claims.

Although the numerical evidence suggested that patients who took quetiapine XR benefited from the treatment early in the course of the trials, no appropriate statistical methods were pre-specified to assess this claim formally. Thus the claim that a significant improvement was observed within the first week and continuing throughout the study was not justified and could only be used descriptively.

5.2 Conclusions and Recommendations

The sponsor submitted seven efficacy and safety studies to seek claims for monotherapy, adjunctive therapy, and maintenance treatment for adult patients with major depressive disorder (MDD). Evidence of effectiveness for the monotherapy was demonstrated from three studies: D1448C00001, D1448C00002, and D1448C00003. Evidence of effectiveness for the adjunctive therapy to an antidepressant was demonstrated from two studies: D1448C0006 and D1448C00007. Evidence of effectiveness for maintenance therapy was demonstrated from one study: D1448C00005.

In studies D1448C00001, D1448C00002, D1448C00003, D1448C00006, and D1448C00007, the primary efficacy variable was the change from randomization to end visit (week 6 or week 8) in the Montgomery-Asberg Depression Rating (MADRS) total score. The Hamilton Rating Scale for Anxiety (HAM-A) was not a pre-specified endpoint, thus it can only serve as exploratory findings and do not support labeling claims. Furthermore, the claim that significant improvement was observed within the first week and continuing through the study was not justified because there were not appropriate statistical methods pre-specified.

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M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 22, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Complete Response action for Seroquel (quetiapine) XR tablets for acute monotherapy and maintenance monotherapy of generalized anxiety disorder (GAD)

TO: File NDA 22-047/S-014/015
[Note: This overview should be filed with the 5-6-08 and 5-7-08 original submissions of these supplements.]

1.0 BACKGROUND

Seroquel (quetiapine immediate release) is an atypical antipsychotic that is approved (1) as monotherapy for the acute treatment of schizophrenia, (2) as monotherapy and as adjunctive therapy to lithium or valproate for the acute treatment of manic episodes associated with bipolar disorder, (3) as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder, and (4) as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar disorder. The extended release formulation of quetiapine (i.e., Seroquel XR) is approved (1) as monotherapy for the acute and maintenance treatment of schizophrenia, (2) as monotherapy for the acute treatment of bipolar depression and mania, and (3) as adjunctive therapy for the acute treatment of bipolar mania.

This supplement provides data in support of claims for Seroquel XR for acute monotherapy and maintenance monotherapy of generalized anxiety disorder (GAD). These studies were conducted under IND 73,851. There are currently no atypical antipsychotics approved for the treatment of GAD.

The sponsor's proposed dose range of Seroquel XR for GAD is 50 to 300 mg/day.

The primary review of the efficacy and safety data was done by Kavneet Kohli-Chhabra, M.D., from the clinical group. John Lawrence, Ph.D., from the biometrics group, also reviewed the efficacy data.

We will be taking these applications to the Psychopharmacological Drugs Advisory Committee (PDAC) in the near future.

2.0 CHEMISTRY

Seroquel XR is an approved product, and there were no CMC issues that required review as part of this supplement, except for an environmental assessment for which a request for categorical exclusion was made and accepted.

3.0 PHARMACOLOGY

Seroquel XR is an approved product. There were no pharm/tox issues that required review as part of these supplements.

4.0 BIOPHARMACEUTICS

Seroquel XR is an approved product, and there were no biopharmaceutics issues that required review as part of this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The sponsor submitted 4 studies in support of its new claims in GAD, including 3 short-term monotherapy studies in support of an acute monotherapy claim (studies 9, 10, and 11) and a randomized withdrawal study (study 12) in support of a maintenance monotherapy claim. For all short-term studies, change from baseline to endpoint on the HAMA total score was the primary endpoint. All of the short-term studies were randomized, double-blind, parallel group, placebo-controlled, fixed-dose, 8-week trials in adult outpatients meeting DSM-IV criteria for GAD. Studies 10 and 11 included an active control arm.

Acute Monotherapy Studies

-Study 9 was a US study including fixed Seroquel XR doses of 50, 150, and 300 mg/day. Only the 2 lower doses in Study 1 were superior to placebo, with only a slight numerical advantage for the 150 mg/day dose vs the 50 mg/day dose, and both numerically superior to the 300 mg/day dose (Pbo: -11.1; 50 mg: -13.3; 150 mg: -13.5; $p<0.001$ vs pbo for both). The 300 mg/day dose was only slightly numerically superior to placebo (Pbo: -11.1; 300 mg: -11.9; NS).

-Study 10 was a US study including fixed Seroquel XR doses of 150 and 300 mg/day, and escitalopram 10 mg/day as the active control. Both Seroquel XR doses were superior to placebo, with the lower dose actually showing a numerical advantage over the 300 mg/day dose (Pbo: -11.0; 150 mg: -14.0; 300 mg: -12.6; p<0.001 vs pbo for 150 mg/day and p=0.025 vs pbo for 300 mg/day). Escitalopram was also superior to placebo (Pbo: -11.0; escitalopram 10 mg/day: -12.2; p=0.03).
-Study 11 was a non-US study including fixed Seroquel XR doses of 50 and 150 mg/day, and paroxetine 20 mg/day as the active control. Both Seroquel XR doses were superior to placebo, with the 150 mg/day dose showing a numerical advantage over the 50 mg/day dose (Pbo: -12.5; 50 mg: -14.1; 150 mg: -16.0; p<0.001 vs pbo for 150 mg/day and p=0.027 vs pbo for 50 mg/day). Paroxetine was also superior to placebo (Pbo: -12.5; paroxetine 20 mg/day: -14.7; p=0.004).

Maintenance Study (Study 12)

This was a randomized withdrawal study involving an open stabilization period of 12 to 26 weeks of acute treatment with Seroquel XR (dose range of 50 to 300 mg/day; mean dose was 140 mg/day) in patients with GAD. The mean stabilization period for patients was 15.3 weeks. Responders during the open label phase were randomized to either continue on Seroquel XR or receive placebo, and they were observed for relapse for up to 52 weeks. The mean Seroquel XR dose during the double-blind phase was 163 mg/day. Time to relapse was statistically significantly increased in patients randomized to continued treatment with Seroquel XR (Hazard Ratio = 0.19; p < 0.001). The relapse rates were 10% for Seroquel XR vs 39% for placebo. Since there was some concern about the possibility that the relapse events might have represented withdrawal events (no tapering in patients assigned to placebo), we did an exploratory analysis involving only events occurring after 13 days. This analysis still very significantly favored Seroquel XR over placebo.

5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

For the acute monotherapy studies, all 3 doses studied were superior to placebo in at least one study. There was a numerical advantage for the 150 mg/day dose compared to the 50 mg/day dose, but the 300 mg/day dose was numerically inferior to both other doses, possibly due to higher early dropouts due to intolerability.

	50 mg/day	150 mg/day	300 mg/day
Study 9	P<0.001	P<0.001	NS
Study 10	---	P<0.001	P=0.025
Study 11	P=0.027	P<0.001	---

The sponsor has proposed a dose range of 50 to 300 mg/day for GAD. However, given the weak evidence for efficacy at 300 mg/day, and the poor tolerability of this dose, I will recommend a dose range of 50 to 150 mg/day. Although the advantage of the 150 mg/day over the 50 mg/day dose was slight in study 9, it was more substantial in study 11. Thus, I think we should remain silent on whether or not there is any advantage for the 150 mg/day dose, but we can note that side effects were more prominent at this dose.

Key Secondary Endpoints

The Q-LES-Q was designated as key secondary in all 3 short-term trials. However, the results favored Seroquel XR only inconsistently (2 of 3 instances for 150 mg/day, and not at all for either 50 or 300 mg/day). So the sponsor will not be permitted to mention these findings in labeling.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of age, gender, and race. There was no indication of any difference in effectiveness based on these analyses.

Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline on the HAMA were similar to effect sizes seen in other positive trials.

Duration of Treatment

The randomized withdrawal study did demonstrate maintenance efficacy for Seroquel XR as monotherapy in GAD.

PREA Requirements

The sponsor will get a waiver for ages less than 7, and a deferral for ages 7-17 for the treatment of MDD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support claims for acute monotherapy and maintenance monotherapy for Seroquel XR in GAD.

5.2 Safety Data

The safety review for these supplements was based on data from the 3 acute studies in this program, data from 2 recently completed trials in elderly patients with GAD, and the maintenance study. Overall, the safety findings for these supplements were consistent with the

known adverse event profile for quetiapine and no important new adverse events that could be considered causally related to quetiapine were discovered as a result of the safety review. We are currently reviewing a comprehensive submission from the sponsor regarding metabolic effects of quetiapine. Both Drs. Khin and Kohli-Chhabra feel that the safety profile of Seroquel XR in GAD can be adequately characterized in labeling. I agree that the safety profile we are seeing in the GAD population is not different from the profile we have already observed in other populations. The troublesome adverse events such as somnolence are clearly dose-related, and I think this argues for cautious prescribing in this population to find the lowest effective dose.

The sponsor has made an argument that they should be able to include language in labeling suggesting that quetiapine is no different than placebo with regard to sexual dysfunction. In fact, we agreed with the sponsor at a preNDA meeting to consider a pooled noninferiority analysis of sexual dysfunction data (collected using the CSFQ) across the MDD and GAD studies, with a non-inferiority margin set at -0.75 units on the CSFQ. The sponsor provided data for a meta-analysis involving 7 short-term studies, including 4 that had an SSRI as an active control. Neither quetiapine nor either of the active control drugs was different from placebo, suggesting to us that the assessments had insufficient assay sensitivity, given that SSRIs are generally easily distinguishable from placebo on these measures. Thus, we have not accepted the proposed language.

Another concern, however, is that approving these claims will likely greatly expand the use of this product. Thus, we need to think carefully about the risks and benefits of such expanded use, particularly with regard to longer-term risks that are not yet fully established. Tardive dyskinesia is an accepted risk in schizophrenic and bipolar patients, and in fact, thought to be somewhat reduced in association with atypical antipsychotic drugs, such as quetiapine. However, the sponsor has not addressed this concern. Furthermore, there is accumulating evidence that quetiapine may have substantial metabolic risks (weight gain, hyperlipidemia, and hyperglycemia) with all the attendant longer-term cardiovascular and other risks. Thus, if these new claims are to be approved, it will be important to ensure that labeling, and perhaps other educational materials, fully inform prescribers and patients about these known and potential risks. In addition, a recent paper by Wayne Ray (NEJM, 2009) raises a concern that atypical antipsychotics may be associated with an increased risk of sudden cardiac death. Thus, we have decided to bring these supplements to the PDAC for a public discussion of the risks and benefits in this expanded population before taking a final action.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling and asked them to make a number of additional modifications.

6.0 WORLD LITERATURE

The sponsor apparently provided literature references but without any comment on methodology or any assessment of what they provided. We will ask the sponsor for some review and discussion of these papers in our CR letter.

7.0 FOREIGN REGULATORY ACTIONS

The reviewer does not comment on whether or not Seroquel XR is approved in any other countries for the treatment of GAD. We can ask the sponsor in the CR letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We are planning on taking these applications to the PDAC in the near future.

9.0 DSI INSPECTIONS

Inspections were conducted at four sites that enrolled patients from pivotal studies. The data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

Our proposal for labeling will be included in the CR letter.

11.0 CONCLUSIONS AND RECOMMENDATIONS

The sponsor has submitted sufficient data to support the conclusion that Seroquel XR is effective as acute monotherapy and as maintenance monotherapy in the treatment of GAD. The safety profile, to the extent that it can be characterized, appears to be similar to that observed with this drug in other conditions. However, there remains a concern about longer-term risks with this drug, in particular risks related to metabolic changes with this drug and the possibility of tardive dyskinesia. There is also some concern about a possible risk of sudden cardiac death with atypical antipsychotic drugs, including quetiapine (see recent paper in NEJM by Wayne Ray). These issues become even more important as the distribution of this drug to a much broader patient population is considered. Thus, we will ask the sponsor to strengthen labeling, particularly with regard to the metabolic concerns, and gather whatever additional evidence might be available to address the concern about tardive dyskinesia. In addition, as noted, we will

have these issues discussed at an upcoming PDAC meeting. Thus, I will issue a Complete Response letter for these supplements.

cc:
Orig NDA 22-047S-014/015
HFD-130
HFD-130/TLaughren/MMathis/NKhin/KKohli-Chhabra/JCliatt

DOC: Laughren_NDA22047_S-14-15_Seroquel XR_CR Memo.doc

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/s/

Thomas Laughren
2/22/2009 04:22:18 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 30, 2009

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 22-047/SE1-014 and 015
(This overview should be filed with the 05-07-2008 original submission)

SUBJECT: Quetiapine Fumarate Extended Release (Seroquel® XR) in Acute and Maintenance Treatment of Generalized Anxiety Disorder (GAD)

1. BACKGROUND

Quetiapine fumarate (Seroquel®) is an atypical antipsychotic agent. In the U.S., the immediate release (IR) oral formulation of quetiapine (NDA 20-639) was first approved in September 1997 for the treatment of schizophrenia. It is also approved for the treatment of Bipolar I disorder, both in mania and depression. Quetiapine's efficacy in schizophrenia and bipolar disorder is thought to be mediated through a combination of dopamine D_2 and serotonin 5-HT_2 antagonism.

The extended release tablets (Seroquel XR) was approved on May 17, 2007 (NDA 22-047). The dose range of Seroquel XR in the treatment of schizophrenia is 400-800 mg/day, administered once daily. The Seroquel XR oral tablet formulation is available as 50, 150, 200, 300, and 400 mg strength. In October 2008, the Division also approved the use of Seroquel XR in acute treatment of bipolar depression, acute treatment of bipolar mania (mono and adjunctive therapy), and maintenance treatment of bipolar I disorder as adjunctive therapy.

The sponsor, AstraZeneca, conducted three short-term placebo-controlled studies [D1448C00009, D1448C00010, and D1448C00011 (hereafter referred to study 09, 10 and 11)] for Seroquel XR in acute treatment of GAD under IND 73,851. The sponsor also conducted one maintenance study of randomized withdrawal design (study 12). On May 7, 2008, the sponsor has submitted results from these studies in supplemental new drug applications to get marketing approval of Seroquel XR for acute and maintenance treatment of GAD.

Several classes of drugs (Benzodiazepines, SSRIs, SNRIs,) have been approved in the treatment of anxiety disorders, including GAD. The approved drugs in GAD include alprazolam, venlafaxine XR, duloxetine, paroxetine, and escitalopram for acute treatment; and buspirone, venlafaxine XR, duloxetine, and paroxetine for maintenance therapy. Currently, no atypical antipsychotic has been approved for the treatment of GAD in the U.S.

This set of supplemental NDA (S-014 and 015) has been reviewed by Julia Pinto, Ph.D, CMC reviewer, ONDQA (review dated 10/29/08), John Lawrence, Ph.D., Statistical Reviewer, the Office of Biostatistics (review dated 1/6/09), and Kavneet Kohli-Chhabra, M.D., Medical Officer, DPP (review dated 01/14/09).

2.0 CHEMISTRY

There was no new CMC information required for review in this submission, except for environmental assessment (EA) issues. In the Chemistry review, Dr. Pinto noted that an environmental assessment was conducted by Raanan Bloom, Ph.D., from the Office of New Drug Quality Assessment. The EA was found acceptable and categorical exclusion was granted. From a CMC perspective, she recommended approval of this set of NDA supplements.

3.0 PHARMACOLOGY/TOXICOLOGY

There is no new pharmacology/toxicology data presented in this submission.

4.0 CLINICAL PHARMACOLOGY

No new PK/PD data in this submission which would require an OCP review.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was mainly based on the results of three short-term, placebo-controlled studies (Study 9, 10 and 11) and one maintenance study of randomized withdrawal design (Study 12) in adult patients with GAD.

All three short-term double-blind trials were of 10 weeks duration (8 weeks of double-blind treatment period and 2 weeks of post-treatment follow up period), and used fixed doses of quetiapine extended release (QTP XR) as compared to placebo:
Study 09 - QTP XR 50, 150 and 300 mg;
Study 10 - QTP XR 150 and 300 mg, and Escitalopram 10 mg as active control;
Study 11 - QTP XR 50 and 150 mg, and Paroxetine 20 mg as active control.

The sponsor indicated that results of all three studies demonstrated that QTP XR was superior to placebo on the primary efficacy variable as measured by change from baseline to final visit in HAM-A total score.

The maintenance study (Study 12) employed QTP XR flexible doses of 50 to 300 mg (mean daily dose of 163 mg). The sponsor indicated that this trial supports the efficacy of QTP XR for the maintenance treatment of GAD as evidenced by a longer time to relapse for an anxiety event during the double-blind phase in the QTP-XR group compared to placebo in patients who had

been stable in an open-label QTP XR treatment phase. The mean stabilization period was of approximately 15.3 weeks.

I would briefly describe the results of each of these studies in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

5.1.2.1 Study D1444CC00009 (Study 9)

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, fixed-dose, outpatient study comparing the effect of QTP XR and placebo in adults (aged 18 to 65 yrs) who met a DSM-IV diagnosis of GAD and confirmed by the Mini-International Neuropsychiatric Interview (MINI). After screening, eligible patients who entered into a 8 week double-blind treatment period were randomized to receive either QTP XR 50, 150, 300 mg or placebo, oral dose given once daily in the evening. No titration was done for the QTP-XR 50 mg group. For the 150 mg group, the QTP XR was titrated from 50 mg on Days 1-2 and then to a fixed dose of 150 mg on Days 3-56. The QTP XR dose was titrated to 300 mg/day within 4 days: 50 mg on Day 1-2, 150 mg on Days 3-4 and beginning on Day 5 through the remainder of the study, a fixed dose of 300 mg.

The study was conducted at 63 centers in the U.S. Out of a total of 1364 patients screened for the study, 951 subjects randomized to the double-blind treatment but 9 did not take the study medication after randomization. The ITT population (942) consisted of 232 patients receiving QTP XR 50 mg, 238 patients receiving QTP XR 150 mg, 238 patients receiving QTP XR 300 mg and 234 patients receiving placebo. A total of 895 patients were included in the MITT analysis after 47 patients were excluded because they did not have valid baseline or post-baseline HAM-A scores.

Approximately 65% of randomized patients completed the 8 Week randomized period of the study, with the rates of completion in the QTP XR 50, 150, 300 mg and the placebo groups were 69%, 64%, 58%, and 70%, respectively. The adverse event dropout rates included in the QTP XR 50, 150, 300 mg and the placebo groups were 15%, 17%, 24%, and 24%, respectively. Other significant reason for dropout (7-9%) included patients lost to follow up and patients not willing to continue the study. The sponsor did not further identify if dropouts were due to lack of efficacy.

The subjects enrolled were mostly White (80%), mean age was 40 yrs, and had approximately 60% female subjects. Treatment groups had no major differences with respect to mean baseline HAM-A total scores.

The efficacy assessment included the Hamilton Anxiety Rating Scale (HAM-A), the CGI rating scales and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q % maximum total score). The primary outcome variable was the change from baseline in the HAM-A total score at final visit (Week 8). The MITT analysis set included all randomized patients who received at least 1 dose of study treatment and who had a randomization (baseline) value and at least one post-randomized HAM-A assessment. The ANCOVA was the statistical model employed, with baseline HAM-A total score as a covariate using the LOCF method. OC was

also done as sensitivity analysis. Dr. Lawrence confirmed the sponsor's efficacy results. The primary efficacy results can be seen in Table 1 below:

Table 1: Efficacy Results on Change from baseline in HAM-A Total Scores at endpoint (LOCF)

Treatment Groups (Number of subjects)	Mean Baseline total HAM-A (SD)	Mean Endpoint total HAM-A (SD)	LS mean Change from Baseline Mean at endpoint	Placebo adjusted LS-mean difference; p-values (drug vs. placebo)
QTP XR 50 mg (N=219)	24.6(3.8)	11.3(7.0)	-13.31	-2.21 (p<0.001)
QTP XR 150 mg (N=226)	24.5(3.4)	11.1(6.5)	-13.54	-2.44 (p<0.001)
QTP XR 300 mg (N=224)	24.5(3.4)	12.7(7.5)	-11.87	-0.77 (ns)
Placebo (N=225)	24.9(4.0)	13.7(8.1)	-11.10	-

ns= not significant (p=0.24)

Comment: Both Drs. Kohli-Chhabra and Lawrence considered this a positive study for Seroquel XR 50 mg and 150 mg (not at 300 mg), and I agree with them.

5.1.2.2 Study D1444CC00010 (Study 10)

This was a multicenter, randomized, double-blind, placebo- and active-controlled (escitalopram 10 mg/day), fixed-dose, outpatient study comparing the effect of QTP XR and placebo in adults (aged 18 to 65 yrs) who met a DSM-IV diagnosis of GAD and confirmed by the Mini-International Neuropsychiatric Interview (MINI). After screening, eligible patients who entered into a 8 week double-blind treatment period were randomized to receive either QTP XR 150, QTP XR 300 mg, escitalopram 10 mg or placebo, oral dose given once daily in the evening. For the 150 mg group, the QTP XR was titrated from 50 mg on Days 1-2 and then to a fixed dose of 150 mg on Days 3-56. The QTP XR dose was titrated to 300 mg/day within 4 days: 50 mg on Day 1-2, 150 mg on Days 3-4 and beginning on Day 5 through the remainder of the study, a fixed dose of 300 mg.

The study was conducted at 64 centers in the U.S. Out of a total of 1334 patients screened for the study, 854 subjects randomized to the double-blind treatment but 8 did not take the study medication after randomization. The ITT population (846) consisted of 217 patients receiving QTP XR 150 mg, 206 patients receiving QTP XR 300 mg, 209 patients receiving escitalopram 10 mg and 214 patients receiving placebo. A total of 828 patients were included in the MITT analysis after 18 patients were excluded because they did not have valid baseline or post-baseline HAM-A scores.

Approximately 71% of randomized patients completed the 8 Week randomized period of the study, with the rates of completion in the QTP XR 150, 300 mg, escitalopram 10 mg, and the placebo groups were 71%, 60%, 72%, and 79%, respectively. The adverse event dropout rates included in the QTP XR 50, 150, 300 mg and the placebo groups were 17%, 25%, 9% and 6%, respectively. Other significant reason for dropout included patients lost to follow up and patients not willing to continue the study with similar rates among the treatment groups (4-8%). The sponsor did not further identify if dropouts were due to lack of efficacy.

The subjects enrolled were mostly White (80%), mean age was 40 yrs, and had approximately 65% female subjects. Treatment groups had no major differences with respect to mean baseline HAM-A total scores.

The efficacy assessment included the Hamilton Anxiety Rating Scale (HAM-A), the CGI rating scales and QLES-Q. The primary outcome variable was the change from baseline in the HAM-A total score at final visit (Week 8). The MITT analysis set included all randomized patients who received at least 1 dose of study treatment and who had a randomization (baseline) value and at least one post-randomized HAM-A assessment. The ANCOVA was the statistical model employed, with baseline HAM-A total score as a covariate using the LOCF method. OC was also done as sensitivity analysis. Dr. Lawrence confirmed the sponsor's efficacy results. The primary efficacy results can be seen in Table 2 below:

Table 2: Efficacy Results on Change from baseline in HAM-A Total Scores at endpoint (LOCF)

Treatment Groups (Number of subjects)	Mean Baseline total HAM-A (SD)	Mean Endpoint total HAM-A (SD)	LS mean Change from Baseline Mean at endpoint	Placebo adjusted LS-mean difference; p-values (drug vs. placebo)
QTP XR 150 mg (N=212)	25.0 (4.3)	11.0 (7.5)	-14.0	-3.20 (p=<0.001)
QTP XR 300 mg (N=212)	25.2 (3.9)	12.6 (7.2)	-12.6	-1.60 (p=0.025)
Escitalopram 10 mg (N=201)	24.6 (4.0)	12.4 (7.7)	-12.2	-1.55 (p=0.03)
Placebo (N=203)	25.3 (4.3)	14.2 (8.3)	-11.0	-

Comment: Both Drs. Kohli-Chhabra and Lawrence considered this a positive study for Seroquel XR 150 mg and 300 mg, and I agree with them.

5.1.2.3 Study D1444CC00011 (Study 11)

This was a multicenter, randomized, double-blind, placebo- and active-controlled (paroxetine 20 mg/day), fixed-dose, outpatient study comparing the effect of QTP XR and placebo in adults (aged 18 to 65 yrs) who met a DSM-IV diagnosis of GAD and confirmed by the Mini-International Neuropsychiatric Interview (MINI). After screening, eligible patients who entered into a 8 week double-blind treatment period were randomized to receive either QTP XR 50, QTP XR 150 mg, paroxetine 20 mg or placebo, oral dose given once daily in the evening. For the 150 mg group, the QTP XR was titrated from 50 mg on Days 1-2 and then to a fixed dose of 150 mg on Days 3-56.

The study was conducted at 113 centers outside the U.S: Czech Republic (10), Denmark (4), Finland (6), France (11), Germany (8), Mexico (4), Norway (4), Romania (5), Bulgaria (9), and South Africa (7), Spain (4), Sweden (6), Slovakia (6), Argentina (11), and Canada (17). Out of a total of 1054 patients screened for the study, 873 subjects randomized to the double-blind treatment but 3 did not take the study medication after randomization. The ITT population (870) consisted of 220 patients receiving QTP XR 50 mg, 218 patients receiving QTP XR 150 mg, 215 patients receiving paroxetine 20 mg and 217 patients receiving placebo. A total of 866 patients

were included in the MITT analysis after 4 patients were excluded because they did not have valid baseline or post-baseline HAM-A scores.

Approximately 77% of randomized patients completed the 8 Week randomized period of the study, with the rates of completion in the QTP XR 50, 150 mg, paroxeine 20 mg, and the placebo groups were 74%, 75%, 80%, and 81%, respectively. The adverse event dropout rates included in the QTP XR 50, 150, paroxetine and the placebo groups were 11%, 15%, 7% and 3%, respectively. Other significant reason for dropout included patients not willing to continue the study among the treatment groups (3-7%). The sponsor did not further identify if dropouts were due to lack of efficacy.

The subjects enrolled were mostly White (>90%), mean age was 40 yrs, and had approximately 65% female subjects. Treatment groups had no major differences with respect to mean baseline HAM-A total scores.

The efficacy assessment included the Hamilton Anxiety Rating Scale (HAM-A), the CGI rating scales and QLES-Q. The primary outcome variable was the change from baseline in the HAM-A total score at final visit (Week 8). The MITT analysis set included all randomized patients who received at least 1 dose of study treatment and who had a randomization (baseline) value and at least one post-randomized HAM-A assessment. The ANCOVA was the statistical model employed, with baseline HAM-A total score as a covariate using the LOCF method. OC was also done as sensitivity analysis. Dr. Lawrence confirmed the sponsor's efficacy results. The primary efficacy result can be seen in Table 3 below:

Table 3: Efficacy Results on Change from baseline in HAM-A Total Scores at endpoint (LOCF)

Treatment Groups (Number of subjects)	Mean Baseline total HAM-A (SD)	Mean Endpoint total HAM-A (SD)	LS mean Change from Baseline Mean at endpoint	Placebo adjusted LS-mean difference; p-values (drug vs. placebo)
QTP XR 50 mg (N=219)	26.9 (4.2)	12.8 (8.6)	-14.1	-1.65 (p=0.027)
QTP XR 150 mg (N=206)	26.6 (4.2)	10.6 (7.8)	-16.0	-3.66 (p<0.001)
Paroxetine 20 mg (N=214)	27.1 (4.0)	12.4 (9.3)	-14.7	-2.15 (p=0.004)
Placebo (N=217)	27.3 (4.4)	14.8 (9.5)	-12.5	-

Comment: Both Drs. Kohli-Chhabra and Lawrence considered this a positive study for Seroquel XR 50 mg and 150 mg, and I agree with them.

5.1.2.4 Study D1444CC00011 (Study 12)

The primary objective of this study was to evaluate the efficacy of QTP XR compared to placebo in time from randomization to an anxiety event in adult patients with GAD.

Study 12 was a multicenter, randomized-withdrawal, parallel-group, double-blind, placebo-controlled, flexible-dose (QTP XR 50-300 mg) study preceded by an Open-Label Run-In

Treatment (OLRT) and Open-Label Stabilization Treatment (OLST) phases of 16 to 26 weeks. The double-blind randomized withdrawal treatment period was designed for up to 52 weeks.

During the open-label randomization treatment, patients received QTP XR 50 mg/Day on Days 1 and 2, and then the dose increased to 150 mg/Day on Days 3 and 4. The dose of QTP XR could be increased to 300 mg/Day on Day 5 or thereafter, based on the clinical judgment of the investigator. Patients who met the criteria of HAM-A ≤ 12 and CGI-S score ≤ 3 by 4 weeks would enter into OLST phase. If they did not meet criteria they would be treated for up to 4 more weeks. Patients in the OLRT phase who did not meet the OLST criteria by Week 8 were discontinued from the study.

During the open-label stabilization period, the prescribed QTP XR dosage could be adjusted subsequently to 50 mg/Day, 150 mg/Day, or 300 mg/Day once daily to maximize efficacy and tolerability. Patients in this phase who met the stabilization criteria of *a HAM-A ≤ 12, CGI-S score ≤ 3 and MADRS score < 16* could enter into the double-blind randomized treatment phase. The HAM-A total score could not be more than > 15 at two sequential visits or a score of CGI > 5 at any one visit. If these criteria were not met at the 12-week visit, the patient could stay for up to 6 more weeks to meet the criteria. Patients who did not meet the eligibility criteria for the double-blind randomization by Week 18 were discontinued from the study.

Stable patients (i.e., patients who remained stable and tolerated QTP XR doses of 50 mg/Day, 150 mg/Day or 300 mg/Day for at least 12 weeks) were randomized to a double-blind treatment to continue with blinded QTP XR or switch to matching placebo of the same dose as taken at the last visit of the OLST. There was no tapering of the QTP XR treatment before patient is randomized on placebo. As per the investigators clinical judgment the dose can be adjusted. Patients could continue in the double-blind randomized treatment period for up to 52 weeks. Patients experiencing an anxiety event (relapse) were required to discontinue the study, and when the total number of required relapses (44 anxiety events) 14 or more days after Randomization occurred, the sponsor terminated the study.

The primary efficacy variable was time from randomization to an anxiety event. An anxiety event was described as more than one of the following:

- Initiation of medical treatment by the investigator to treat anxiety symptoms.
- Initiation of medical treatment by the patient for at least 1 week to treat anxiety symptoms.
- HAM-A total score ≥ 15 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinued.
- A suicide attempt or discontinuation from study due to imminent risk of suicide.
- Hospitalization for anxiety symptoms.
- A CGI-S score ≥ 5.

The intention-to-treat (ITT) analysis set included all randomized patients who received study treatment during the RTP, classified according to their randomized treatment. The ITT analysis set was used for Primary variable analysis. The primary variable is the time to relapse performed with Cox proportional hazards Model comparing QTP XR to placebo with a hazard ratio (HR) and associated 95% CI. Time to anxiety event is presented graphically using Kaplan-Meier curves representing the QTP XR and placebo group.

The study was conducted at 127 sites throughout the world: Australia (6), Canada (9), Finland (6), Germany (10), Hungary (7), Indonesia (3), Korea (4), Philippines (4), Russia (8), UK (13), and the US (57).

A total of 1811 patients were screened. The number of patients enrolled in the open-label phase was 1248. Patients randomized to QTP XR and placebo treatments for the open label phase (both OLRT and OLST) were 1224. By the end of open label phase (both OLRT and OLST), 615 patients had discontinued. When the total number of required relapses (46 anxiety events) 14 or more days after Randomization occurred, the sponsor terminated the Study, leaving 200 patients continuing to participate in the study without ever being randomized. 432 patients were randomized to the double-blind randomized withdrawal treatment phase and received either QTP XR or placebo treatment (216 patients in each group). During the double-blind randomized withdrawal treatment, 58 patients experienced an anxiety event at 14 or more days after randomization, and the study was stopped according to the analysis plan.

The baseline demographics of the maintenance study do not show any significant differences between the groups with respect to these variables except age (the subjects in the placebo group tend to be younger). The mean age was about 40; the majorities enrolled were Caucasian and female. At the end of the OLST (mean duration of 15.3 weeks) distributions of QTP-XR doses were: 26% received 50 mg/Day, 49% received 150 mg/Day and 25% received 300 mg/day. Mean daily dosing during the OLST was 140.4 ($\pm$75.9) mg. Mean duration of stabilization was 15.3 weeks. The mean dose of QTP XR during the double-blind randomized withdrawal treatment phase was 163.2 mg/day.

Dr. Lawrence confirmed the sponsor's efficacy results. Analysis of all events following randomization, and analysis of censoring all anxiety events occurring < 14 days after randomization (to ensure that the anxiety events analyzed were not due to the immediate effects of QTP XR treatment discontinuation in the placebo group), were performed. The Kaplan-Meier estimates of the event-free survival curves extracted from the sponsor's submission could be seen in both clinical and statistical reviews.

Results showed QTP XR treatment of patients with GAD significantly increased the time to occurrence of an anxiety event when compared with the placebo group (Table 4).

Analysis of time to recurrence of an anxiety event (all events) results showed the estimated HR (QTP XR versus placebo) of 0.19 (95% CI=0.12 to 0.31; $p<0.0001$). The numbers of patients with anxiety events was 84/216 (38.9%) and 22/216 (10.2%) in the placebo and QTP XR treatment groups, respectively.

Analysis with censoring events in first 13 days showed the estimated HR (QTP XR versus placebo) of 0.27 (95% CI=0.15 to 0.47; $p<0.0001$). The number of anxiety events was 41/166 (24.7%) in placebo and 17/210 (8.1%) in the QTP XR treatment groups.

Table 4: Analysis of Time to Occurrence of an Anxiety Event - ITT Analysis Set

	Hazard Ratio (95% CI)	p- value
Analysis of all events	0.19 (0.12 to 0.31)	< 0.0001
Analysis of events in first 13 days censored	0.27 (0.15 to 0.47)	< 0.0001

Comment: Both Drs. Lawrence and Kohli-Chhabra considered this positive maintenance study for QTP XR as compared to placebo. I concur with their conclusion.

5.1.3 Comments on Other Important Clinical Issues

5.1.3.1 Predictors of Treatment Response

Exploratory subgroup analyses were done to detect subgroup interactions on the basis of age (18-39; 40-65), ethnicity (Caucasian, African American and others) and gender (M, F). In the statistical review, he displayed the numerical differences between the subgroups for each study (see statistical review by Dr. Lawrence for detail). He did not indicate any statistically significant difference in treatment effect in these subgroups.

5.1.3.2 Duration of Treatment

Study 12 addressing the longer-term maintenance efficacy of QTP XR in GAD has been completed. See results in section 5.1.2.4 above.

5.1.3.3 Size of Treatment Effect

Treatment effect size was examined in terms of HAM-A total score change from baseline to endpoint at Day 57. Results are summarized in Table xx below for studies 09, 10, and 11. There is no additional treatment benefit seen at QTP XR 300 mg dose group in study 10. The treatment effect was similar for QTP XR as compared to the effect size seen with the active controls.

Table 5: Treatment Effect Size as expressed by LS Mean Change from Baseline to endpoint in HAM-A Total Score in Three Short Term Studies (09, 10 and 11) - LOCF, MITT Population

Study	QTP XR 50 mg/Day	QTP XR 150 mg/Day	QTP XR 300 mg/Day	ESC 10 mg/Day	PAR 20 mg/Day	Placebo
09	-13.31[a]	-13.54[a]	-11.87[ns]	NA	NA	-11.10
10	NA	-13.92[a]	-12.32[c]	-12.27[c]	NA	-10.72
11	-13.95[c]	-15.96[a]	NA	NA	-14.45[b]	-12.30

a = p<0.001 compared with placebo
b = p<0.01 compared with placebo
c = p<0.05 compared with placebo
ns=p-value not significant (drug vs. placebo)
NA=not available

5.1.3.4 Key secondary and other secondary efficacy variables

Change in the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q % maximum total score) from baseline to endpoint was the key secondary variable in all three short term

studies. As can be seen in the table below, only the 150 mg/day dose showed significant effect as compared to placebo in two out of three studies (studies 10 and 11).

The sponsor used the following formula to derive the percentages of total maximum in Q-LES-Q: 100*(Q-LES-Q Total Score - 14) / 42. The results are shown in the table 6 below.

Table 6: LS Mean Change from Baseline to endpoint Q-LES-Q % maximum total score

Study	QTP XR 50 mg/Day	QTP XR 150 mg/Day	QTP XR 300 mg/Day	ESC 10 mg/Day	PAR 20 mg/Day	Placebo
09	10.36	11.11	9.27	NA	NA	10.96
10	NA	12.25[a]	7.11	11.35[a]	NA	9.14
11	9.08	13.58[b]	NA	NA	11.35[a]	6.48

a = p<0.025 compared with placebo
b = p<0.001 compared with placebo
NA=not available

In addition to Q-LES-Q, other secondary variables that the sponsor proposed to claim in the labeling are listed below. None of these are pre-specified key secondary variables.

- Clinical Global Impression-Global Improvement (CGI-I)
- Clinical Global Impression-Severity of Illness (CGI-S)
- Sleep quality measured by Pittsburgh Sleep Quality Index (PSQI)
- Early efficacy of QTP XR on day 8 (Time of Onset)
- Montgomery-Åsberg Depression Rating Scale (MADRS)

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analysis supported the efficacy claim of Seroquel XR for both acute and maintenance treatment of GAD.

5.2 Safety Data

5.2.1 Safety Database

Dr. Kohli-Chhabra's safety review of this set of NDA supplements was based on the sponsor's safety data from above three short-term studies: study 9, 10 and 11 and one longer-term maintenance study: study 12. As part of the 4-month safety update, the sponsor also submitted safety data from two short-term randomized, double-blind, placebo-controlled studies in elderly subjects with GAD: study 15 and 16. Her safety review entailed an examination of the occurrence of deaths, non-fatal serious adverse events, and premature discontinuations due to adverse events across these trials. Additionally, analyses of common adverse events, vital signs, laboratory test data, and ECG results were conducted on the pool of the three short-term studies (studies 9, 10 and 11).

Total exposure to QTP XR (N=1569) was 197.6 patient years. Mean exposure (as determined by days on randomized treatment) in all QTP XR group was 44 days which was slightly lower (40.3 days) in the QTP XR 300 mg group. Median exposure times were the same across all treatment groups.

There were three deaths reported: Patient E1010712 (study 09) died 60 days post last QTP XR dose, Patient E4510701 (study 11) died before randomization and Patient E6605501 (study 15) in the placebo group died secondary to cardiomyopathy.

Serious adverse events (non-fatal) included worsening of anxiety, syncope, cholelithiasis, CHF, diabetes mellitus, and suicide attempt/suicidal ideation. Most of these adverse events were consistent with the underlying disorder and also occurred in the placebo groups. I will briefly describe a SAE case of diabetes in the metabolic effects subsection below.

The most common adverse events associated with subject discontinuation were sedation (6% QTP-XR vs 1% placebo) and somnolence (5% QTP-XR vs. 0% placebo).

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is approximately twice or more the placebo risk). The following most common adverse events were noted in the quetiapine XR group: somnolence/sedation (50%), dry mouth (31%), dizziness (15%) and constipation (7%). The frequencies of somnolence/sedation and dry mouth seemed higher in these GAD pivotal trials compared to the acute schizophrenia trials.

The incidence of the following AE appeared to be dose related: somnolence, dry mouth, nausea and constipation. I refer to the numbers cited in the table in section 7.1.5.6.1 of Dr. Kohli-Chhabra's clinical review.

5.2.2.2 Metabolic Effects

Hyperglycemia and Diabetes Mellitus

There were 2 cases of diabetes mellitus reported in study 9 (Patient E1045714 and Patient E1026751). One of these events experienced by Patient E1026751 who received quetiapine XR 300 mg/day was considered by the investigator as serious and related to the study drug. The patient withdrew from the study due to the SAE event, diabetes mellitus. This 53-year-old Black male with past medical history of hypertension and chronic pancreatitis, but no family history of diabetes and no history of alcohol and tobacco use, experienced dizziness, numbness in right hand, hot and cold flashes, blurred vision, a loss of appetite, increased urination, nausea, and vomiting on Day 37. At study entry, patient's body weight was 75.9 kg (BMI 20.5 kg/m^2), fasting blood glucose was 120 mg/dL, and HbA1c was 6.5%. Concomitant medications included atenolol, clonidine, valsartan hydrochlorothiazide, and acetylsalicylic acid. On Day 31 of randomized treatment, fasting blood glucose was 147 mg/dL. The patient was hospitalized on Day 45 due to high blood sugar (>900 mg/dL). Blood urea nitrogen and creatinine were elevated at 39 and 2.8, respectively. BP was 180/110. He was diagnosed with new onset diabetes mellitus and acute renal failure. With IV fluid and insulin treatment, patient's condition improved and was discharged from hospital on Day 50. Patient discontinued from study. At the

discontinuation visit, Day 52, no fasting blood glucose was reported; however, HbA1c was noted 10.6% with ongoing insulin treatment.

Table 7 showed mean change from baseline to endpoint in fasting glucose, HbA1c and insulin. The QTP XR 150 mg and 300 mg treatment group had a slight mean increase in fasting glucose data as compared to placebo.

Table 7: Mean Change from Baseline to Endpoint for Glucose, HbA1c and insulin in 3 placebo-controlled studies

	PLA		ALL QTP XR		QTP XR 50		QTP XR 150		QTP XR 300	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Glucose (mg/dL)	572	1.67 (13.8)	1348	1.71 (15.7)	380	-0.52 (14.8)	578	2.27 (14.5)	300	3.06 (18)
HbA1c (%)	560	-0.018 (0.22)	1282	0.003 (0.28)	365	0.0 (0.3)	547	-.015 (0.25)	370	0.031 (0.31)
Insulin (pmol/L)	575	2.5 (18.5)	1337	3.3 (19.7)	386	1.99 (11.65)	569	3.08 (21.44)	382	4.97 (23.2)

The proportion of patients with treatment emergent clinically important glucose and glycated Hb shift is summarized below (Table 8). The highest incidence of patients with clinically important elevated glucose levels occurred in the QTP XR 300 mg group (approximately 5%). Few cases of HbA1c values shifting to clinically important levels were noted: 1 case in the QTP XR 50 mg group and 3 cases in the QTP XR 300 mg group. The sponsor did not elaborate on the magnitude of these shifts.

Table 8: The proportion of patients with treatment emergent clinically important values of glucose and HbA1c

	Placebo N=665			All QTP XR N=1569			QTP XR 50 mg/Day N=452			QTP XR 150 mg/Day N=673			QTP XR 300 mg/Day N=444		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	%
Fasting Glucose															
≤45 mg/dL	572	0	(0.0)	1348	2	(0.1)	380	1	(0.3)	578	0	(0.0)	390	1	(0.3)
≥126 mg/dL	562	19	(3.4)	1331	47	(3.5)	375	11	(2.9)	569	17	(3.0)	387	19	(4.9)
HbA1c															
>7.5%	559	0	(0.0)	1277	4	(0.3)	363	1	(0.3)	545	0	(0.0)	369	3	(0.8)

Lipid Profile

Data presented in Table 9 showed mean change from baseline to endpoint in fasting lipid values. A decrease in mean HDL cholesterol values was noted in all treatment groups, with a dose-dependent larger change in the QTP XR groups. Triglycerides exhibited higher increases from baseline for QTP XR treated patients than for placebo treated patients in a dose-related fashion, with the highest increase in the QTP XR 300 mg group. There were no notable differences between treatment groups in changes in LDL or total cholesterol values.

Table 9: Mean Changes from Baseline to Endpoint on Lipid Data

Treatment Groups	PLA		ALL QTP XR		QTP XR 50 mg		QTP XR 150 mg		QTP XR 300 mg	
Lipid (mg/dL)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Cholesterol	561	-2.7 (26.3)	1289	-0.9 (26.3)	370	-1.1 (27.2)	549	-1.2 (27.5)	370	-0.5 (23.5)
HDL	561	-0.5 (8.0)	1289	-2.1 (9.4)	370	-1.5 (9.3)	549	-2.0 (10)	370	-2.9 (8.3)

LDL	558	-1.6 (23.4)	1289	-1.3 (23.7)	370	-1 (24.1)	549	-1.9 (24.6)	370	-0.7 (22.1)
Triglyceride	561	-4.9 (67)	1289	11.3 (79.8)	370	5.6 (74.2)	549	11.3 (85.3)	370	17.2 (76.4)

The proportion of patients with lipid value shifts to clinically important values can be seen in the table below with a slightly larger percentage of outliers in the QTP XR groups as compared to placebo.

Table 10: Lipid lab values shifts to clinically important values

	PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Cholesterol ≥240 mg/dL	495	19	(3.8)	1125	65	(5.8)	312	20	(6.4)	475	28	(5.9)	338	17	(5.0)
HDL ≤40 mg/dL	470	42	(8.9)	1086	108	(9.9)	315	26	(8.3)	468	43	(9.2)	303	39	(12.9)
LDL ≥160 mg/dL	511	18	(3.5)	1175	47	(4.0)	330	16	(4.8)	496	23	(4.6)	349	8	(2.3)
Triglycerides ≥200 mg/dL	479	34	(7.1)	1107	131	(11.8)	319	28	(8.8)	476	59	(12.4)	312	44	(14.1)

Comment: The Division has requested that the sponsor conduct an analysis of all clinical trial data to study the metabolic effects of QTP IR and XR. The sponsor has recently submitted these requested data and the submitted data are currently under review by the Division. Further modifications to product labeling should be made upon completion of our review of these submitted data.

5.2.2.3 Weight changes

The mean change from baseline for weight was greater in the QTP XR groups than placebo: 0.58 kg, 0.82 kg and 0.93 kg for the 50 mg, 150 mg and 300 mg QTP XR groups, respectively, compared to 0.16 kg in the placebo group.

The percentage of patients with a clinically important weight gain from randomization to end of treatment (≥7% increase from baseline to last visit) was higher for QTP XR-treated patients (4.3% in the QTP XR 50 mg group, 6.0% in the QTP XR 150 mg group, and 4.7% in the QTP XR 300 mg group) compared with placebo-treated patients (2.4%).

5.2.2.4 Hyperprolactinemia

Changes from randomization to end of treatment in mean prolactin laboratory data were 0.21 ng/mL, 0.37 ng/mL and 0.80 ng/mL for the quetiapine XR 50 mg, 150 mg and 300 mg groups, respectively, compared to 0.24 ng/mL for the placebo group.

Table 11: The proportion of patients with Prolactin level shifts to clinically important values

	PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Prolactin															
Male >20 ng/mL	194	0	(0.0)	451	5	(1.1)	141	0	(0.0)	184	3	(1.6)	126	2	(1.6)
Female >30 ng/mL	356	8	(2.2)	820	9	(1.1)	221	2	(0.9)	357	4	(1.1)	242	3	(1.2)

5.2.2.5 Neutropenia and Agranulocytosis

There were no clinically meaningful differences between treatment groups in mean change from baseline to endpoint for the majority of hematology assessments. There was a total of 2 subjects (one each in the 50 mg QTP XR groups and in the placebo) had shifts from normal baseline ANC to values < 1.5 x 10^9L). It should be noted that the Division has recently revised Seroquel labeling language under Warnings/Precautions, a subsection entitled "Leukopenia, Neutropenia and Agranulocytosis."

5.2.2.6 Vital Signs and ECG Changes

Data showed there were no clinically significant differences between treatment groups in mean change from randomization in vital sign data in QTP XR group compared with placebo. A small increase in mean pulse rate was observed in the quetiapine XR 150 mg (1.1 bpm) and 300 mg (2.2 bpm) groups compared to the quetiapine 50 mg (-0.6 bpm) and placebo (-0.2 bpm) groups.

The proportion of patients with vital sign values shifts to clinically values found to be similar between the QTP XR and placebo except for the category of pulse≥15 bpm in that the percentage was greater in the QTP XR group than the placebo, 26.3% and 19.1%, respectively.

Mean decreases in QTcF interval were similar across treatment groups: -1.9 msec, -0.6 msec and -2.1 msec for the QTP-XR 50, 150 and 300 mg doses, respectively, compared to -1.7 msec in the placebo group.

5.2.2.7 Extrapyrimidal Symptoms (EPS)

The sponsor presented data from an integrated search for EPS is based on both AE reports and the results of the Simpson Angus Scale (SAS) and Barnes Akathisia Scale Global Assessment (BARS).

None of the EPS related AEs were reported as SAE. The incidence of adverse events consistent with EPS was higher in the quetiapine XR groups compared to placebo.

Table 12: Incidence of AEs potentially associated with EPS in studies 9, 10, and 11

	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
EPS-related event [a] (%)	77 (4.9 %)	17 (3.8 %)	34 (5.1 %)	26 (5.9 %)	21 (3.2%)
Akathisia	23 (1.5%)	4 (0.9 %)	11 (1.6 %)	8 (1.8 %)	3 (0.5 %)

However, mean scores for all groups from baseline to end of study as measured by SAS and BARS did not show any significant difference; the majority of the patients were in the no change category.

5.2.2.8 Tardive Dyskinesia (TD)

There were no systematic assessments done to evaluate the longer term risk of TD in this GAD subject population. For study 12 (maintenance study), the sponsor stated that there were no AE

reports of TD were observed at any time during the study. It was reported that there was minimal to no change in mean AIMS total score for the QTP XR and the placebo group. Because of the study design as there is some bias in that only subjects who were able to tolerate QTP XR in the open-label phase are then randomized, the data would be difficult to interpret.

The sponsor acknowledged that we have asked the sponsor in the 2005 meeting that the benefit/risk assessment must include TD for this patient population, I am not aware of any additional assessment (e.g. other database searches, literature) by the sponsor was identified in this submission.

5.2.2.9 Sexual Dysfunction Assessment

At the pre-NDA meeting, the sponsor has discussed with the Division regarding their intention to seek a labeling description that sexual dysfunction associated with QTP XR use as measured by change in sexual functioning questionnaire (CSFQ) from baseline to the final visit would show non inferiority of QTP XR compared with placebo. We agreed with the sponsor's plan to submit the pooled analysis of the acute monotherapy studies for MDD and GAD in the NDA submission for GAD indication. The agreed upon non-inferiority margin was set at −0.75.

In this NDA submission, the sponsor's analysis of sexual dysfunction is based on their integrated search in AE reports and changes in Sexual Functioning Questionnaire total score (14 items) evaluating the change from randomization to end of treatment. A pooled meta-analysis of CSFQ Data from 4031 patients in 7 placebo-controlled studies (i.e., 3 in GAD: study 9, 10, 11 and 4 MDD: study 1, 2, 3, 4) was analyzed using an ANCOVA model. As can be seen in the table below, 4 of these 7 studies have an active-control arm. Higher scores in CSFQ indicate higher sexual functioning or lower impairment.

The sponsor claims that QTP-XR's non-inferiority to placebo is demonstrated based on the analysis of CSFQ data. However, based on Dr. Lawrence's FDA analysis, studies that had an active treatment arm such as studies 10 and 11 (GAD), studies 02 and 04 (MDD) and when studies 04 and 10 (ESC groups) are combined, the results of the active treatment group's CSFQ was not significantly different from placebo [i.e. not statistically significant at two-sided alpha level 0.05]. This suggests that either both active controls are similar to placebo for this endpoint or that there was no assay sensitivity to compare arms within any study. It should be noted that sexual side effects is very common in patients treated with SSRI/SNRI drugs such as paroxetine and duloxetine. Considering this fact, it is doubtful that results from this pooled analysis could be reliably used as part of the labeling claim.

Table 13: Analysis of CSFQ data (extracted from Dr. Lawrence's statistical review)

Study or Studies #	Treatment group	N (Trt)	N (Pla)	LS Mean†	SE	95% CI LS Mean ± SE
02	QTP XR 150	152	157	-0.58	0.79	(-2.13, 0.97)
02	QTP XR 300	152	157	-0.18	0.79	(-1.37, 1.73)
02	DUL 60	149	157	-0.18	0.80	(-1.39, 1.75)
04	QTP XR	157	155	-0.9	0.99	(-0.98, 2.90)
04	ESC	156	155	-0.16	0.98	(-1.76, 2.08)
10	QTP XR 150	217	214	-0.24	0.67	(-1.07, 1.55)
10	QTP XR 300	206	214	-0.0	0.68	(-1.36, 1.30)
10	ESC 10	209	214	-0.62	0.67	(-1.93, 0.69)
11	QTP XR 50	220	217	-0.21	0.64	(-1.04, 1.46)
11	QTP XR 150	218	217	-0.84	0.64	(-0.41, 2.09)

11	PAR 20	215	217	-0.36	0.64	(-1.61, 0.89)
04+10	ALL QTP XR	580	369	0.63	0.51	(-0.37, 1.63)
04+10	ESC	365	369	-0.3	0.56	(-1.40, 0.80)
09+10+11	ALL QTP XR	1462	633	0.07	0.31	(-0.54, 0.68)
01+02+03+04 +09+10+11	ALL QTP XR	2482	1208	0.12	0.24	(-0.35, 0.59)

5.2.3 Conclusion Regarding Safety Data

Although this submission revealed no new safety signals which were attributable to Seroquel XR treatment and no safety findings inconsistent with the previously observed safety profile of quetiapine IR and XR, I agree with the position taken by the Division for Seroquel XR in MDD (S-012) that we should ask the sponsor to provide any data to support the use of this atypical antipsychotic drug in the non-psychotic population in addressing the longer term safety risks (metabolic effects and tardive dyskinesia).

6.0 WORLD LITERATURE

The Sponsor included a literature reference including a copy of relevant publications in this submission. However, the Sponsor did not provide any discussion of how the articles were identified or if, upon review, any new safety signal was identified for QTP XR.

7.0 FOREIGN REGULATORY ACTION

Based on the information provided by the sponsor, QTP XR is approved in 24 countries for schizophrenia, 5 countries for bipolar mania and 1 country for bipolar depression. I am not aware of the approved use of this drug for GAD anywhere in the world.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

The Division has decided to take this set of NDA supplements for GAD along with data submitted in the supplemental NDA for MDD to the PDAC. Further discussion of safety risks (metabolic changes, TD, and sudden cardiac death[1]) associated with the use of atypical antipsychotic agent, QTP XR, in non-psychotic patient population will be taken place at the PDAC meeting (including additional members with expertise in Cardiology and Endocrinology) scheduled on April 8, 2009.

9.0 DSI INSPECTIONS

DSI inspection of 4 study sites was requested: center 1026 in Memphis, TN (Dr. McGill) and center 1054 in Miami, FL (Dr. Cuervo) for study 9; center 1021 in Birmingham, AL (Dr. Logue) for study 10; and center 2002 in Quebec, Canada (Dr. Bergeron). These sites were chosen to be inspected due to the high numbers of subject enrollment. Based on our preliminary communication with DSI, the inspectional findings did not indicate any data integrity issues. DSI clinical inspection summary report is still pending. If my conclusion changes upon review of DSI's clinical inspection summary, addendum to this memo will be generated.

[1] Ray, WA et.al., Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death, N Engl J Med (2009) vol. 360:3, pp. 226-235

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling

The sponsor's proposed language has been modified. We should attach this in our complete response letter to the Sponsor.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that Seroquel XR is effective in the acute and maintenance treatment of GAD. Although the sponsor's data from the GAD trials support that use of Seroquel XR seems reasonably safe, I agree with the Division's position that, prior to our approval of expended use of QTP XR in non psychotic patient population such as MDD and GAD, we should ask the sponsor to provide any data in elucidating the longer term safety risks (metabolic effects and tardive dyskinesia) associated with the use of atypical antipsychotic agents like QTP-XR. We will be discussing these safety findings and concerns in a public forum at the PDAC meeting scheduled on April 8, 2009.

Therefore, I recommend the Division should consider issuance of a complete response (CR) letter for this set of NDA supplements (S014 and 015) at the end of current review cycle.

As stated in the CR letter for the set of NDA supplements for MDD indication, we should ask the sponsor to provide data from observational databases, post-marketing data, and literature data elucidating these longer-term metabolic effects and any risk of Tardive Dyskinesia. We should also ask for an update on QTP XR's safety regardless of indication, dosage form or dose level. Draft labeling that incorporates our FDA's revisions in the sponsor's proposed labeling should be attached with the CR letter.

Cc: HFD-130/Laughren/Mathis/Kohli-Chhabra/Cliatt/Grewal

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/s/

Ni Aye Khin

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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-047
Submission Code	SE1
Supplement Number	014 and 015
Letter Date	May 6, 2008
Review Completion Date	January 28, 2009
PDUFA Goal Date	March 7, 2009
Reviewer	Kavneet Kohli-Chhabra, M.D.
Established Name	Quetiapine Fumarate Extended-Release Tablets
Trade Name	Seroquel XR
Therapeutic Class	Antipsychotic
Applicant	AstraZeneca
Priority Designation	S
Formulation	50, 150, 200, 300 mg Tablets
Proposed Dosing Regimen	50-300 mg/day
Intended Population	Adults
Indication	Acute and Maintenance Treatment of Generalized Anxiety Disorder

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

On May 7th 2008, the Sponsor (AstraZeneca) submitted supplemental NDAs SE1-14 and SE1-15 for oral quetiapine fumarate extended-release tablets (hereafter referred to as QTP XR) to support the indication of acute and maintenance treatment of generalized anxiety disorder (hereafter referred to as GAD) in adults. I recommend that the Division issue a complete response letter for both of these efficacy supplements. A final decision to approve QTP XR for acute and maintenance treatment of GAD will be contingent on further discussion of safety risks (metabolic changes and TD) associated with longer-term use of QTP XR in GAD, a satisfactory site inspection report from the Division of Scientific Investigations, and negotiation of labeling.

The Sponsor submitted three short term placebo controlled trials (studies 09, 10 and 11) for GAD. The following pivotal trials support the efficacy of QTP XR for the acute treatment indication.

Study 09	QTP XR 50, 150 and 300 mg compared to Placebo
Study 10	QTP XR 150 and 300 mg compared to Placebo with Escitalopram (ESC) 10 mg as active control
Study 11	QTP XR 50 and 150 mg compared to Placebo with Paroxetine (PAR) 20 mg as active control

The QTP XR 150 mg dose had positive efficacy results in all three short term placebo controlled trials (studies 09, 10 and 11). The QTP XR 50 mg dose had positive efficacy results in both (studies 09 and 11) the trials it was utilized in. However, the QTP XR dose of 300 mg had positive efficacy results in only one (study 10) of the two trials it was utilized in. There were no additional efficacy benefits seen with higher dosing.

The Sponsor also submitted results from one maintenance trial of randomized withdrawal design (Study 12). This trial employed QTP XR flexible doses of 50 to 300 mg (mean daily dose of 163 mg). The mean stabilization period was of approximately 15.3 weeks. This trial supports the efficacy of QTP XR for the maintenance treatment of GAD.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no recommendations for specific risk management activities at this time.

1.2.2 Required Phase 4 Commitments

No Phase 4 Commitments are recommended from a clinical standpoint

1.2.3 Other Phase 4 Requests

Pediatric waivers, deferrals and plans were under review at the time this review was completed. The Written Request from FDA to the sponsor, dated 11 February 2003, specifically asked that AstraZeneca conduct randomized, double-blind, parallel-group, placebo-controlled efficacy and safety studies in pediatric patients who have schizophrenia, mania in the setting of bipolar disorder. In addition, the Written Request stipulated that pharmacokinetic data in the relevant pediatric age group would also be required.

On 4/3/2008 the Sponsor submitted an overview of their plans of the phase IV pediatric obligations for QTP and QTP XR tablets.

The Sponsor plans to conduct at least one eight week, double-blind, randomized, parallel-group, placebo-controlled, monotherapy study to evaluate the efficacy and safety of QTP XR in about 204 pediatric subjects (12 to 18 year old) with GAD. The study plans on utilizing flexible dosing of 50 to 300 mg with adjustments made as per clinical response. The stated primary efficacy variable will be the change from baseline to end of study as measured by the Pediatric Anxiety Rating Scale (PARS) total score.

On 9/5/2008, the division relayed three comments to the Sponsor regarding their GAD pediatric studies development program. The comments are as follows:

1. As pediatric GAD can be reliably diagnosed in patients as young as 7 years of age, the age range as currently proposed for this study (12-18 years) is too narrow.
2. Given the uncertainty in extrapolating from adult studies in GAD to pediatric patients, it will likely be necessary to conduct short term study for pediatric subjects.
3. When utilizing QTP XR formulation, the sponsor should use population pharmacokinetic methods (sparse sampling) to evaluate the pharmacokinetic of quetiapine and its metabolites in pediatric patients.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The efficacy and safety of oral QTP XR for the acute treatment of patients with GAD is supported by three short-term placebo-controlled studies (Studies 09, 10, and 11). These short term studies were of 8 week duration. These studies were submitted to IND 73851. See results in section 6.1 (efficacy) and 7 (safety).

The efficacy and safety of QTP XR for the maintenance treatment of patients with GAD is supported by one randomized withdrawal maintenance study (Study 12). The open label run in treatment and stabilization period was up to 26 Weeks (mean stabilization period of approximately 15.3 weeks). The double-blind randomized treatment phase was for up to 52

Weeks. This study was submitted to IND 73851. See results in section 6.2 (efficacy) and 7 (safety).

1.3.2 Efficacy

The sponsor has provided evidence that supports the claim of short-term efficacy for the use of QTP XR in GAD at doses of 50 mg/Day (statistically superior over placebo in Studies 09 and 11) and 150 mg/Day (statistically superior over placebo in all three studies). The QTP XR 300 mg/Day dose was statistically superior over placebo in Study 10, but not in Study 09. The primary outcome measure in the three studies was Hamilton Anxiety Measurement (HAM-A) score change from baseline to the end of treatment (day 57). There was no additional efficacy benefit evidenced at higher dosing (300 mg).

The sponsor has also provided evidence that supports the claim of QTP XR for the maintenance treatment of GAD. Part I of the study entailed open-label treatment of the patients with QTP XR using flexible dosing in the range of 50 to 300 mg/day. Part II of the study randomized responders from Part I to double-blind treatment with either continued QTP XR or placebo and followed them for relapse for up to 52 additional weeks. Study 12 demonstrates QTP XR (mean daily dose of 163 mg/day) is superior to the placebo in longer time to relapse for an anxiety event in patients who had been stable in an open-label QTP XR treatment phase (mean stabilization period of approximately 15.3 weeks).

Details of the study design, conduct, and results are provided in section 6.

1.3.3 Safety

Per the sponsor's submission, 1569 patients were treated with QTP XR. The clinical review of the pooled safety data from three short term Studies (studies 09, 10, and 11) for the QTP XR (GAD) development program revealed no new signal which were attributable to QTP XR treatment and inconsistent with the previously observed safety profile for quetiapine. See Section 7 for safety findings.

The safety data review of the maintenance Study (12) was focused on identifying serious adverse events, deaths and dropouts due to adverse events. A more comprehensive safety review for the maintenance study 12 was not attempted because the study design did not produce the controlled safety data needed for most standard safety analyses. This is not considered a major obstacle to the approval of this application since there are extensive clinical trial and post marketing spontaneous report safety data with QTP XR that have been previously reviewed. See Section 7 for safety.

1.3.4 Dosing Regimen and Administration

The sponsor proposed titration schedule of acute therapy of GAD with QTP XR begins with 50 mg on Days 1 and 2, and increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if

necessary, adjustments can be made upwards or downwards within the dose range of 50 mg to 300 mg depending upon clinical response and tolerability.

For maintenance therapy, the sponsor proposes to continue on the effective dose of initial treatment during the stabilization period. The dose was adjusted within the dose range of 50 mg to 300 mg per day depending upon a clinician's judgment.

Based on my review of efficacy data provided in this submission, I would recommend the recommended dosing range to be 50 mg-150 mg/day of QTP XR treatment in GAD. I also recommend adding a statement that although the 300 mg dose found to be efficacious in one study, no additional benefits seen at the higher dosing. See section 6.

1.3.5 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. Also, no special drug-drug interaction studies were conducted in support of this application.

1.3.6 Special Populations

In this submission, the Sponsor has indicated their interest to market a 50 mg extended-release dose (which was approved with the original NDA but never marketed). The Sponsor in the proposed label has changed dosing recommendations for the elderly and patients with hepatic impairment. The proposed changes include the patients to be started on QTP XR 50 mg/day dose; it can then be increased in increments of 50 mg/day depending on the clinical response and tolerability. When indicated, dose escalation should be performed with caution in these patients. Recently, these proposed labeling changes were reviewed and included as part of the approved label dated October 8, 2008, for the bipolar efficacy supplements (S-006, 007 and 008).

On 9/4/08, the sponsor submitted a 4-Month Safety Update (hereafter referred to as 4MSU) to this supplement. This was a completed 11-week study D1448C00015 (hereafter referred to study 15) entitled "A Multicenter, Double-blind, Randomized, Parallel Group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate XR as Mono-therapy in the Treatment of Elderly Patients with Generalized Anxiety Disorder". The findings from this study were submitted as part of a separate NDA supplement and both efficacy and safety data will be reviewed in detail for efficacy supplement submitted under S-020. However, a safety review consisting of identifying serious adverse events, deaths and dropouts due to adverse events was conducted and discussed in section 7 for safety. The safety review of study 15, revealed no new findings which were attributable to QTP XR treatment and inconsistent with the previously observed safety profile for QTP XR.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

QTP IR is currently approved for schizophrenia, bipolar mania and bipolar depression and is registered worldwide in more than 89 countries, 82 countries and 20 countries, respectively.

QTP XR has been approved for the acute treatment of schizophrenia since May 17, 2007 and for the maintenance treatment of schizophrenia since November 16, 2007. It is registered in more than 24 countries for schizophrenia at dose strengths of 50 mg, 200 mg, 300 mg, and 400 mg. There are 5 countries that have approved QTP XR for bipolar mania and one country that has approved it for bipolar depression.

Table 1 and 2 summarizes the current approved indications for both QTP IR and QTP XR.

Table 1: QTP fumarate immediate release - QTP IR (Seroquel) [NDA 20-639]

Indication	Date of Approval
Schizophrenia (acute)	9/26/1997
Depressive Episodes associated with Bipolar Disorder	10/20/2006
Acute Manic Episodes associated with Bipolar I Disorder monotherapy or adjunct therapy to lithium or valproex	1/12/2004
Maintenance Treatment of Bipolar I Disorder as adjunct therapy to lithium or divalproex	5/13/2008

Table 2: QTP fumarate extended release - QTP XR (Seroquel XR) [NDA 22-047]

Indication	Date of Approval
Schizophrenia (acute)	5/17/2007
Schizophrenia (maintenance)	11/15/2007 [under NDA 22-172]

Under NDA 22-047, a supplement (S-010, 011, 012) was submitted for MDD treatment (monotherapy, adjunctive therapy, maintenance) with QTP XR on 2/27/2008 and was reviewed by the Division. Recently, the Division has issued a complete response letter regarding this set of NDA supplements for MDD (dated 12/22/2008).

The 3 short-term GAD clinical trials (studies 09, 10, and 11) and one maintenance GAD trial (study 12) were conducted under IND 73851 (submitted on 12/21/05).

2.2 Currently Available Treatment for Indications

Several classes of drugs (SSRIs, SNRIs, BZD) have demonstrated efficacy in the treatment of anxiety disorders, including GAD. Currently, no atypical antipsychotic has been approved for the treatment of GAD in the United States (US).

The approved drugs in the U.S. for the treatment of GAD are as follows:

For acute therapy - alprazolam, venlafaxine XR, duloxetine, paroxetine, escitalopram.

For maintenance therapy - buspirone, venlafaxine XR, duloxetine, paroxetine.

2.3 Availability of Proposed Active Ingredient in the United States

QTP fumarate was first approved on September 26, 1997. QTP XR was first approved on 5/17/2007 for the acute treatment of schizophrenia. QTP XR is currently available as 200, 300 and 400 mg extended-release tablets. A 150 mg extended-release tablet was approved in August 2008. A 50 mg extended-release tablet was previously approved but never marketed – the Sponsor is going to market this new strength now.

2.4 Important Issues with Pharmacologically Related Products

Atypical antipsychotics have been associated with several safety issues. Among the major safety issues are increased mortality in elderly patients with dementia-related psychosis, suicidality in children and adolescents, clinical worsening and suicidality, neuroleptic malignant syndrome, tardive dyskinesia (TD), orthostatic hypotension, hyperglycemia and diabetes mellitus.

The sponsors of atypical antipsychotics have been asked to provide additional data and pooled analyses for the metabolic profile safety signals. This includes AstraZeneca who have been asked to provide data and analyses for quetiapine IR and quetiapine XR for effects on lipids (cholesterol, HDL, LDL, triglycerides), glucose (glucose, HbA1c, UA glucose), and weight for both adults and pediatric subjects (see Division letter January 8, 2008). The Sponsor recently provided these data on 6/26/08 and they are currently under review.

Prior to this supplemental NDA submission for GAD, the Division has asked the Sponsor to provide a benefit/risk assessment including TD. Although the sponsor acknowledged this request, no such assessment report was found in current submission.

2.5 Pre-Submission Regulatory Activity

For the GAD clinical development program for QTP XR, the following were included as part of discussion at end of Phase 2 (EOP2) meeting on 5/13/05:

- Two positive studies would be required for approval
- The benefit/risk assessment must include tardive dyskinesia and agranulocytosis.
- A deferral of pediatric studies.
- Q-Les-Q was an acceptable secondary endpoint of special interest.
- A non-inferiority hypothesis would need to be tested for CSFQ data.
- Columbia-like approach for suicidality would be acceptable.
- PSQI would not be acceptable for the labeling claim.

On 8/3/05, there was a teleconference meeting on follow-up to EOP2 meeting of 5/13/05 to clarify FDA requirements for the stabilization period in the long term GAD studies. The FDA indicated that the Psychopharmacological Drugs Advisory Committee (PDAC) would provide

recommendations on the regulatory requirements. The FDA accepted sponsor proposals to include elderly patients up to 70 years in the GAD program.

On 10/25/05, the FDA at the PDAC meeting discussed the need for long term data at the time of initial filing for chronic psychiatric disorders. PDAC strongly support the need for long-term data but not at the time the initial application is submitted. PDAC recommended further discussion regarding the stabilization period and optimal study design in collaborative working groups with industry academia and others.

Following the PDAC meeting of 10/25/05, the sponsor then asked the FDA additional questions on 11/15/05. These questions/answers were discussed at the 12/5/05 FDA meeting and it was confirmed that sponsor would proceed to previously agreed clinical development plans for the GAD program with a minor change to the stabilization period of GAD Study 12 increased to three months, as per the new PDAC recommendations. Subsequently, the Agency sent the sponsor written correspondence on 12/12/05.

The protocols for the proposed studies were submitted to IND 73851 on:

- 2/8/06 for study 9
- 2/1/06 for studies 10 and 11
- 12/21/05 for the maintenance study 12

The GAD pre-sNDA briefing package was submitted on 4/5/07. Questions sought agreement on the content and format of the planned sNDA. On 5/3/07, FDA provided preliminary responses to questions posed in the GAD pre-sNDA briefing package. Key responses of that correspondence included:

- FDA agreed with the basic statistical analysis models.
- FDA agreed to the pooling strategy and requested results of exploratory subgroup analyses by country/region for international trials.
- For CSFQ, FDA informed the sponsor to set the non-inferiority margin of 0.75 units.
- FDA requested the raw data with key demographic variables (Age, Sex and Race) merged onto each dataset as well as all the derived datasets for the efficacy analyses.
- The eCTD format and the proposed table of contents.

On 4/5/07, FDA requested clarification on the Q-LES-Q analysis. On 5/10/07, there was a FDA Type B teleconference meeting. Key responses included:

- FDA agreed to the sponsor's proposed analyses of primary and key secondary outcome variable (Q-LES-Q). Regarding time of onset claim, the Division is reconsidering a policy position but could not yet confirm this would be acceptable.

On 7/18/07, through written correspondence to FDA, the sponsor stated they understand the Division is interested in the CSFQ results for the total MDD/GAD combined pooled data and these results of the CSFQ analysis would be provided in the GAD sNDA.

This GAD sNDA supplement was submitted to FDA on 5/6/08. The Filing Meeting was held on 6/24/08 and it was concluded that this set of supplements was fileable. The mid-cycle meeting was held on 10/30/2008. The PDUFA date is 3/7/2009.

2.6 Post-Submission Regulatory Activity

A 4-Month Safety Update (4MSU) to the NDA was submitted on 9/4/08. It included two 11-week short-term, double blind, randomized, placebo controlled trials. The protocols for both these trials were submitted to IND 45456. The full study report including efficacy data from Study D1448C00015 was submitted on 11/25/08, this will be the focus of a separate NDA submission.

Study D1448C00015 (hereafter referred to as Study 15) was a study of the efficacy and safety of QTP XR flexible dosing (50 mg/day to 300 mg/day) as monotherapy compared to matching placebo in the treatment of elderly patients with GAD. Safety data analyses (deaths, SAEs, AE dropout rate) from a total of 450 patients (223 exposed to QTP XR and 227 exposed to placebo) are included in this review in section 7.

Study D1441L00016 (hereafter referred to as Study 16) was a study to evaluate the efficacy and safety of QTP XR as an adjunct to treatment in patients with GAD who demonstrate partial or no response to selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) alone or in combination with a benzodiazepine. Safety data analyses (deaths, SAEs, AE dropout rate) from a total of 409 randomized patients are included in this review.

2.7 Other Relevant Background Information

The sponsor did not report any withdrawal of this product in other countries, or on submission of marketing authorization applications to foreign regulatory agencies for the GAD indication.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Julia Pinto, Ph.D., is the CMC reviewer for this submission. An Environmental Assessment of QTP XR was requested as approval of this NDA supplement will likely result in an increased usage associated with the new dosage (50 mg) form and the new indication (GAD).

The new proposed strength of 50 mg of QTP XR has been previously reviewed with the original NDA and was considered for approval but the sponsor had decided not to market that strength at the time of initial approval. The sponsor stated in their bipolar efficacy NDA supplements that

they intend to re-introduce the 50 mg strength. Thus, this was approved by the division in October 2008.

The environmental assessments, as submitted by the sponsor, have been reviewed by Raanan Bloom. The increased use is predicted to result from metabolites rather than active moiety. Since the new indication does not increase the active moiety, a request was made for categorical exclusion under 21 CFR 25.31 (a), and this was concurred. As there are no new changes to the CMC for QTP XR, the chemistry review notes that they recommend approval of this supplement (review dated 10/29/2008).

3.2 Animal Pharmacology and Toxicology

This application contains no new information pertaining to animal Pharm/Tox of QTP XR.

3.3 Statistical Review and Evaluation

John Lawrence, Ph.D., is the statistical reviewer for this NDA supplement. In his statistical review, he notes that all three short term studies correctly handled all the multiplicity issues related to multiple doses and multiple endpoints. The baseline demographics of all three short term studies did not show any significant differences between the groups with respect to these variables. He confirmed the sponsor's primary efficacy results and key secondary variable (QLES-Q) results. Please refer to his statistical review dated 1/6/2009 for detail. Please also see section 6 of this clinical review for discussion of efficacy findings.

3.4 DSI Clinical Site Inspections

Four sites were selected for Division of Scientific Investigations (DSI) inspection. These sites were chosen because of their large enrollment in each of the studies.

On 11/20/2008 DSI provided a brief update of inspectional findings through email which stated that sites for Study 10 in Alabama, USA and Study 12 in QC, Canada would be classified as NAI (No Action Indicated). One site for study 09 is currently being inspected, and the remaining site will be inspected in early January secondary to investigator availability. The DSI inspection summary report is pending.

Table 3: DSI Sites Selected For Inspection

Study	Country	Center No.	Investigation Name	Center Address	Patients Enrolled
Study 09	USA	1026	Lora McGill	CNS Healthcare, Inc. 6401 Poplar Ave., Suite 420 Memphis, TN 38119	53
Study 09	USA	1054	Mario S Cuervo	Aurora – Cuervo Clinical Trials 7000 SW 62nd Street Suite 545 Miami, FL 33143	75
Study 12	Canada	2002	Richard Bergeron	20 Pharand St Gatineau J9A 1K7, QC, Canada	51
Study 10	USA	1021	H. Edward Logue	Birmingham Psychiatry Pharmaceutical Studies 100 Century Park, Suite 214 Birmingham, AL 35226	57

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The efficacy of QTP XR in the treatment of adult patients with GAD is based on three short term placebo–controlled Studies (Studies 09, 10, and 11) and one randomized withdrawal maintenance Study (study 12).
The primary safety database is comprised of pooled data of the three short term GAD studies (study 09, 10, 11,) and one randomized withdrawal maintenance Study (study 12). The 4 month safety update included data from studies 15 (elderly) and 16 (adjunctive treatment).

4.2 Table of Clinical Studies

A total of four completed clinical Studies (studies 09, 10, 11 and 12) comprise this application. There are two studies in 4MSU (studies 15 and 16) submitted to this supplement. The clinical study reports for study 15 and 16 will be submitted under a separate efficacy supplement. These trials are summarized in the table below.

Table 4: Summary of All QTP XR Studies

Completed Short Term Studies	
Study 09	Multicenter (63 USA), double-blind, randomized, parallel-group, placebo-controlled; 2-week post-treatment follow-up period; Evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms with HAM-A total score changes observed from baseline to day 57 in patients with GAD (DSM-IV-TR); QTP XR 50 mg/Day (n=219) ,QTP XR 150 mg/Day (n=226), QTP XR 300 mg/Day (n=224), Placebo (n=225).
Study 10	Multicenter (64 USA), double-blind, randomized, parallel-group, placebo-controlled, active-controlled (escitalopram); 2-week post-treatment follow-up period; Evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms with HAM-A score changes observed from baseline to day 57 in patients with GAD (DSM-IV-TR); QTP XR 150 mg/Day (n=212), QTP XR 300 mg/Day (n=201), Placebo (n=203), Escitalopram 10 mg/Day (n=212).
Study 11	Multicenter (113 centers in Europe, North America, South Africa, and South America), double-blind, randomized, parallel-group, placebo-controlled, active-controlled (paroxetine); 2-week post-treatment follow-up period; Evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms with HAM-A score changes observed from baseline to day 57 in patients with GAD (DSM-IV-TR) QTP XR 50 mg/Day (n=212), QTP XR 150 mg/Day (n=201), Placebo (n=203), Paroxetine 20 mg/Day (n=212).
Completed Maintenance study	
Study 12	International (128 centers in Asia, Australia, Europe, and North America), multicenter, double-blind, parallel-group, placebo-controlled, randomized withdrawal with open label run-in and stabilization periods; Evaluate the efficacy of QTP XR compared to placebo in decreasing the risk of recurrence of anxiety symptoms in patients with GAD (DSM-IV-TR); 4-8 weeks of open-label run-in treatment with QTP XR; 12-18 weeks of open label stabilization treatment with QTP XR; up to 52 weeks of double-blind treatment with QTP XR or placebo with N = 216 patients each group; Flexible dosing of QTP XR 50 mg/Day, 150 mg/Day, 300 mg/Day, or Placebo.
Completed Elderly study	
Study 15	11-week clinical studies of QTP XR in the treatment of elderly patients with GAD “A Multicenter, Double-blind, Randomized, Parallel Group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release as Mono-therapy in the Treatment of Elderly Patients with GAD”.
Ongoing Adjunct Therapy Study	
Study 16	An adjunct therapy study entitled "A Multicenter, Randomized, Double-blind, Parallel-group, Placebo controlled Study of the Efficacy and Safety of QTP XR Compared with Placebo as an Adjunct to Treatment in Patients with GAD who Demonstrate Partial or No Response to a SSRI or S-NRI SNRI Alone or in Combination with a Benzodiazepine".

4.3 Review Strategy

For efficacy each Study (studies 09, 10 ,11 and 12) will be reviewed individually and for the safety review, there will be pooling of the safety data among the three short term Studies (studies 09, 10, 11) and one maintenance Study (study 12). A listing of the items examined during the course of this review is provided in Table 5.

Table 5: Items Utilized In the Review

Submission Date	Items Reviewed
May 6 , 2008	Clinical Study Reports: Studies 9, 10, 11 and 12, Proposed Labeling, Application Summary, Financial Disclosure Certification, Case Report Tabulations (.xpt files), Case Report Forms

4.4 Data Quality and Integrity

See sections 3.3 (Statistical Review and Evaluation) and 3.4 (DSI Clinical Site Inspections) for other comments regarding data quality and integrity.

I conducted a brief audit of adverse event safety data by comparing case report forms, narratives and line listings for consistency on reporting. Overall, there was good consistency of adverse event information across these sources of data. Adverse event coding (verbatim to preferred terms) appeared to be appropriate. No significant deficiencies were noted.

4.5 Compliance with Good Clinical Practices

Per study protocols, these clinical trials were "performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Committee on Harmonization/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics".

4.6 Financial Disclosures

Among the clinical investigators in all four studies, one was identified by the sponsor as having financial arrangements that require disclosure and one was identified as not having provided financial disclosure information.

Dr. Jelena Kunovac was listed as the investigator at one site (No. 1020) among the total 63 US sites for study D1448C00009. She received sums greater than $25,000 from AstraZeneca LP. This center enrolled twenty-four (24) patients into the trial. It is unlikely that these arrangements biased the study results since this was a controlled, randomized, multicenter study.

One clinical investigator among the total four studies was identified by the sponsor as not having provided financial disclosure information, and having left the facility with no forwarding address. The investigator was identified as Dr. Danielle Bordeau. She was listed as a Co-Investigator for Dr. Arun Ravindran for the QTP XR study D1448C00011, site (No. 2046) in Toronto, Canada. This center enrolled five (5) patients to the trial. This trial was a controlled, randomized, multicenter Study. This in combination with the low number of patients recruited by Dr. Ravindran's site should prevent any bias that possibly could have affected the outcome of the trial.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new PK data submitted in this sNDA.

5.2 Pharmacodynamics

No new PD data in this submission.

5.3 Exposure-Response Relationships

There is no data regarding a dose or exposure-response relationship of QTP XR in the treatment of patients with GAD.

6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION - Acute Treatment of GAD

6.1.1 Methods

The Sponsor conducted three multicenter, double-blind, randomized, placebo-controlled studies (09, 10 and 11) to evaluate the efficacy and safety of QTP XR in acute treatment of GAD in adult patients.

Study 09	QTP XR 50, 150 and 300 mg compared to Placebo
Study 10	QTP XR 150 and 300 mg compared to Placebo with Escitalopram (ESC) 10 mg as active control
Study 11	QTP XR 50 and 150 mg compared to Placebo with Paroxetine (PAR) 20 mg as active control

6.1.2 General Discussion of Endpoints

The primary efficacy variable for three acute short-term studies (09, 10 and 11) is change from randomization of HAM-A total score on day 57.

A teleconference was conducted between the Sponsor and FDA on 5/10/07 discussing several secondary efficacy variables. Key responses from that meeting correspondence are as follows.

<u>Q-LES-Q</u>

The Division required a clarification if the Q-LES-Q analysis (applied only to short-term Studies and not intended for longer-term studies) is intended to focus on change from randomization in total score or on "percentages of maximum total score". The Sponsor explicated they would focus on change from randomization in percentages of maximum total score. The percentages of total maximum in Q-LES-Q was derived from the following formula: 100*(Q-LES-Q Total

Score - 14) / 42. This was acceptable by the Division. Of note, in the analysis plan, the formula incorrectly reads 100* (Q-LESQ Total Score - 14) / 56.

CSFQ

As per the divisions request, the sponsor agreed to pool the results of CSFQ data for GAD and MDD studies and submit the result to the GAD supplement. The sponsor also agreed to the divisions request to employ an already established precedent of non-inferiority margin of 0.75 units for the CSFQ results. Individual studies will also be looked at to see for effects of Escitalopram (study 4 and 10), Duloxetine (study 2), and Paroxetine (study 11) vs. placebo for assay sensitivity, as a way of validating the pooled approach for QTP XR vs. placebo.

Time of Onset

The Sponsor wanted the claim that improvement in GAD symptoms was observed as early as Day 4 when measuring change from randomization in HAM-A scores compared with Placebo. The Division commented that "Displaying such data would constitute a time of onset claim, and there is no agreement in the community as yet on the optimal approach for such claims".

6.1.3 Study Design and Efficacy Findings

Below is an individual review of each of the three short term placebo controlled Studies (study 09, 10 and 11).

STUDY 09

Design

Protocol D1448C00009: An 8-Week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, phase III outpatient study of the efficacy and safety of QTP XR 50 mg/Day, 150 mg/Day, and 300 mg/Day compared with placebo in the acute treatment of GAD in adults.

First patient enrolled: 4/19/2006 Last patient enrolled: 5/14/2007

After the initial evaluation visit there was an enrollment period of up to 28 days, during which a washout for all psychotropic medication occurred before randomization. Patients were randomized to one of the four treatment arms (QTP XR 50 mg, QTP XR 150 mg, QTP XR 300 mg, or placebo) on Day 1, followed by a titration period and a fixed dose double-blind treatment period. The study drug was administered once daily in the evening.

The post-treatment consisted of a 2 week follow up period. Patients were encouraged not to take anxiety medication during the 14 day post treatment period. Patients who took QT XR dose of 300 mg were weaned off during the 14 day post treatment period. If patients were discontinued prematurely, the Day 57 (final visit) assessments were performed at end of their discontinuation.

Figure 1: Dose Initiation and Visit Schedule (extracted from the sponsor's submission)

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8		Visit 9	Visit 10
-28 to -1[d]	1	8	15	22	29	43	57[e]	☎[f]	7[g]	14[h]
Enrollment	Randomize						Final	Post	Post	Post

[a] No Titration: Days 1-56 quetiapine XR 50 mg.
[b] Titration: Days 1–2 quetiapine XR 50 mg; Days 3–56 quetiapine XR 150 mg.
[c] Titration: Days 1–2 quetiapine XR 50 mg; Days 3–4 quetiapine XR 150 mg; Days 5–56 quetiapine XR 300 mg. Down-titration: Days 57–63 quetiapine 150 mg.
[d] Enrollment period is a maximum of 28 days prior to randomization.
[e] Last treatment dose of 8-week treatment period is Day 56; final treatment assessments are Week 8.
[f] TDSS by telephone remote from the study center on post-treatment Days 1, 3, and 5.
[g] End of down-titration (post-treatment Days 0–6 [Week 8–63]) visit
[h] End of study post-treatment (post-treatment Days 7–14 [Days 64–71]) visit

Investigators/Sites

A total of sixty three principal investigators conducted this study at 63 sites throughout the U.S.

Objectives

Primary: To demonstrate superior efficacy of QTP XR for the three doses, 50 mg/Day, 150 mg/Day and 300 mg/Day, compared with placebo in the treatment of anxiety symptoms in patients with GAD. Evaluation was conducted by measuring change from randomization of Hamilton Anxiety Scale (HAM-A Total Score) at Week 8 (Day 57).

During development stage of this protocol, FDA agreed to measurement of change from randomization at Week 8 of Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q% maximum total score) as a key secondary. However, after the protocol was written, the sponsor opted to designate Q-LES-Q as a "secondary variable of particular interest" rather than identifying it as a "key secondary" efficacy assessment. It is my impression that these terms are interchangeable.

Secondary: To evaluate the effects of QTP XR versus placebo by evaluating change from randomization of:

- Quality of Life Enjoyment and Satisfaction Questionnaire item 15 and 16 (Q-LES-Q)
- Clinical Global Impression-Global Improvement (CGI-I)
- Clinical Global Impression-Severity of Illness (CGI-S)
- Sleep quality measured by Pittsburgh Sleep Quality Index (PSQI)
- Early efficacy of QTP XR on day 8 (Time of Onset)

Study Population

The inclusion/exclusion criteria are similar for all three short-term acute treatment studies 09, 10 and 11. Important criteria are as follows.

Inclusion criteria:

- Male or female aged 18 to 65 years with a clinical diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for GAD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI).
- A HAM-A total score of ≥ 20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥ 2 at both enrollment and randomization. A CGI-S score of ≥ 4 and MADRS total score ≤ 16 at both enrollment and randomization.
- Female patients must have had a negative serum pregnancy test at enrollment and had to be willing to use a reliable method of birth control during the study.

Exclusion criteria:

- Meeting the criteria for any other DSM-IV Axis I, Axis II, concomitant organic mental disorder or mental retardation.
- A current serious suicidal or homicidal risk or a suicide attempt within past 6 months.
- Evidence of a clinically relevant medical illness and/or evidence of clinically abnormal laboratory results including positive pregnancy test.
- A substance abuse or dependence disorder as defined by DSM-IV and not in full remission. Positive urine toxicology results before randomization.
- A known lack of response to QTP of atleast 50 mg for 4 weeks.
- Previous enrollment/randomization to treatment in any other GAD Studies.
- Use of ECT treatment, depot or oral antipsychotic, mood stabilizer, antidepressant (fluoxetine in particular), anxiolytic, hypnotic, potent P450 3A4 inducers, potent P450 3A4 inhibitors, or other psychoactive drugs within 7 days before randomization and throughout the treatment period (except medications specified in *Concomitant Medications* chart below).

Permitted, Restrictive, and Prohibited Medications

Table 1 below lists permitted, restricted and prohibited medications. This was similar for all 3 sort-term acute treatment studies 09, 10 and 11.

Table 6: Permitted, Restrictive, and Prohibited Medications/Treatments during the Study (extracted from sponsor's submission)

Use category	Type of medication/treatment
Permitted	• Nonpsychoactive medications, including over-the-counter medications that were required to treat nonpsychiatric concurrent conditions or illnesses. • Contraceptives (ie, oral contraceptive, implant, dermal contraception, long-term injectable contraceptive, intrauterine device).
Restricted	• From randomization until Day 14 only, 1 of the following could be used for insomnia, maximum 2 times per week, up to the specified dosage per night; hypnotic use not allowed on the night prior to conducting study assessments: zolpidem 10 mg, chloral hydrate 1 g, zaleplon 20 mg, and zolpiclone 7.5 mg. • Anticholinergics could be used to treat extrapyramidal symptoms (EPS). • Psychotherapy was only allowed if it has been ongoing since at least 3 months prior to randomization.
Prohibited	• Use of drugs that induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes (eg, carbamazepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine, St. John's wort) and inhibitors (eg, ketoconazole [except for topical use], itraconazole, fluconazole, erythromycin, clarithromycin, fluvoxamine, nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir, saquinavir). • Use of any psychoactive drugs including the following classes, other than those allowed in a restricted manner: Antidepressants, Anxiolytic, Hypnotic, Mood stabilizing, Antipsychotic, or Sedatives. • Prophylactic use of Anticholinergics for EPS. • ECT throughout the randomized treatment period. • Abuse or dependence according to the DSM-IV TR criteria of Alcohol, Opiates, amphetamine, barbiturate, cocaine, cannabis, or hallucinogen.

Efficacy Assessments

Primary efficacy variable was change from randomization in the HAM-A total score at Week 8 (Day 57).

As described in the objectives section the term "secondary variable of particular interest" was change from randomization of the Q-LES-Q% maximum total score at Week 8.

Other secondary efficacy variables measuring change from randomization at Week 8, included HAM-A somatic cluster, HAM-A Response and Rate, Q-LES-Q item 15 and 16, CGI-I, CGI-S, PSQI, and Time of Onset.

Efficacy Analysis Plan

The analysis of all primary efficacy, "secondary objective of particular interest", secondary efficacy variables and Patient Reported Outcome (PRO) variables were performed using the modified intent-to-treat (MITT) analysis set.

MITT analysis set: Patients who were randomized, took study drug, and had a randomization HAM-A total score assessment and at least 1 HAM-A total score post-randomization.

LOCF analysis set: If a patient dropped out before the Day 57 assessment, the HAM-A total score for the actual last study assessment of that patient (if post baseline) was moved forward using Last Observation Carried Forward (LOCF). The LOCF approach was used as the primary method for handling of missing data. An alternative analysis using Observed Cases (OC) data was also carried out.

For the analysis of HAM-A total score and Q-LES-Q% maximum total score, comparing QTP XR and placebo, levels of significance were determined using the multiple testing procedure (MTP) as described below. All statistical tests were 2-sided with an overall significance level of 5% unless otherwise specified. For comparisons between each dose of QTP XR and placebo, 95% confidence intervals (CIs) were reported. P-values were controlled for multiplicity only at Week 8.

The multiplicity problem concerning the false-positive error rate for the 50 mg/Day and 150 mg/Day, and 300 mg/Day dose comparisons with placebo in the primary analysis was handled by utilizing the Bonferroni-Hommel procedure. This procedure was demonstrated to control the overall Type I error at α. This ensured that the probability of getting a "false" success in any of the 3 comparisons was at most 5%; i.e., $\alpha=0.05$.

The analysis of change from baseline to final assessment (LOCF) in all primary, "secondary objective of particular interest", secondary efficacy variable, and Patient Reported Outcome (PRO) variables total scores at week 8 tested the superiority of each dose level of QTP XR using an analysis of covariance (ANCOVA) with the baseline total scores as the covariates and included treatments as a fixed effects and centers as random effects in the model. The contrasts of interest were the treatment differences between each dose of QTP XR and placebo.

Patient Disposition

Thirteen hundred and sixty four (1364) patients were screened. Four hundred thirteen (413) were screen failures. Nine hundred and fifty one (951) patients were randomized in this study. Nine (9) were not treated. The ITT population (942) consisted of 232 patients receiving QTP XR 50 mg, 238 patients receiving QTP XR 150 mg, 238 patients receiving QTP XR 300 mg and 234 patients receiving placebo. A total of 895 patients were included in the MITT analysis after 47 patients were excluded because they did not have valid baseline or post-baseline HAM-A scores.

Approximately 65% of randomized patients completed the 8 Week randomized period of the study, with higher rates of completion in the placebo group compared to the QTP XR groups.

Those who completed the Study:
In the QTP XR 50 mg group - 69% (162/232 patients)
In the QTP XR 150 mg group of - 64% (154/238 patients)
In the QTP XR 300 mg group - 58% (139/238 patients)
In the placebo group - 70% (165/234 patients)

The Overall dropout rate from the 8 Week randomized period consisted of:
In the QTP XR 50 mg group - 31% (72/232 patients)
In the QTP XR 150 mg group - 36 % (87/238 patients)
In the QTP XR 300 mg group - 42% (102/238 patients)
In the placebo group - 30% (70/234 patients)

The adverse event dropout rates included:
In the QTP XR 50 mg group – 15% (36/232 patients)
In the QTP XR 150 mg group - 17% (41/238 patients)
In the QTP XR 300 mg group – 24% (58/238 patients)
In the placebo group -24% (58/238 patients)

Other significant reason for dropout included patients "lost to follow up" and "patients not willing to continue Study". QTP XR treatment discontinuations rates ranged from 7% to 9% across all groups compared with 9% of the placebo group. The sponsor did not further identify and include if dropouts were due to lack of efficacy.

Baseline Demographic Characteristics

The baseline demographics of all three short term studies do not show any significant differences between the groups with respect to age, gender, or race variables. The mean age was about 40; the majorities were Caucasian and female.

Table 7: Baseline Demographics Characteristics Study 09 - MITT Population

Treatment	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Oriental	Other
QTP XR 50 mg (n = 219)	39.0	18-65	43	57	80	16	0	3.2
QTP XR 150 mg (n = 226)	40.7	18-65	37	63	84	12	0.4	3.5
QTP XR 300 mg (n = 224)	41.0	18-65	39	61	81	14	1.8	3.1
Placebo (n = 225)	39.2	18-65	34	66	80	16	0	3.1

Information obtained from Sponsor Table 11.1.6.1 in Clinical Study Report

Baseline Severity of Illness

Treatment groups had no major differences with respect to mean baseline HAM-A total scores:
In the QTP XR 50 mg group – mean score of 24.6
In the QTP XR 150 mg group – mean score of 24.5
In the QTP XR 300 mg group – mean score of 24.5
In the placebo group - mean score of 24.9

The mean Q-LES-Q total score was 52 to 53, the CGI-S score was approximately 4, and the MADRS total score was about 13.

Concomitant Medication

Sleep medication use was low overall. The most commonly used sleep medication was lorazepam. The percentage of patients using sleep medication decreased over the course of the study for all groups.

Overall anticholinergic use was low (≤ 4.8% in any treatment group) during the randomized treatment period for all treatment groups.

Based on the safety population, the protocol violators (prohibited medication used) were:
In the QTP XR 50 mg group - 9.6% (21/219 patients)
In the QTP XR 150 mg group - 9.3% (21/226 patients)
In the QTP XR 300 mg group - 8.9% (20/224 patients)
In the Placebo group - 5.8% (13/225 patients)

Dosing Information

A fixed dose study utilizing QTP XR doses of 50 mg/Day, 150 mg/Day and 300 mg/Day.

Results

Primary efficacy variable results

1. HAM-A total score

QTP XR doses of 50 mg/Day and 150 mg/Day (but not 300 mg/Day) are significantly superior to placebo as demonstrated by the mean change from randomization at Week 8 in HAM-A total score after adjustment for multiplicity.

Table 8: HAM-A total score change from randomization to endpoint Study 09 - LOCF, MITT analysis

		Baseline	Endpoint	LSMean Change *	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	225	24.9(4.0)	13.7(8.1)	-11.10	-	-
QTP XR 50 mg/Day	219	24.6(3.8)	11.3(7.0)	-13.31	-2.21	< 0.001
QTP XR 150 mg/Day	226	24.5(3.4)	11.1(6.5)	-13.54	-2.44	< 0.001
QTP XR 300 mg/Day	224	24.5(3.4)	12.7(7.5)	-11.87	-0.77	0.240

Information obtained from Sponsor Table 18 in Clinical Study Report
* = LS mean change from randomization

Key Secondary efficacy variable results

1. Q-LES-Q % maximum total score

Q-LES-Q % maximum total score mean change from randomization at Week 8 was "Secondary variable of particular interest". The efficacy of QTP XR 50 mg/Day, 150 mg/Day, and 300

mg/Day over placebo was not established for improvement in health-related quality of life based on the change from randomization to Week 8 in the Q-LES-Q % maximum total score.

Table 9: Q-LES-Q % maximum total score change from randomization to endpoint in Study 09 - LOCF, MITT

	N	Baseline Mean(SD)	Endpoint Mean(SD)	LSMean Change*	LSMean Difference	P-value vs. Placebo
Placebo	204	51.76(16.14)	63.60(15.74)	10.96	-	-
QTP XR50 mg/Day	207	52.20(14.23)	63.10(15.76)	10.36	-0.60	0.661
QTP XR 150 mg/Day	212	53.30(14.89)	64.37(16.01)	11.11	0.15	0.913
QTP XR 300 mg/Day	206	52.71(15.29)	62.29(16.48)	9.27	-1.69	0.220

Information obtained from Sponsor Table 19 in Clinical Study Report
* = LS mean change from randomization

Efficacy Conclusions

QTP XR doses of 50 mg/Day and 150 mg/Day are significantly superior to placebo as demonstrated by the mean change from randomization at Week 8 in HAM-A total score after adjustment for multiplicity. However, the QTP XR dose of 300 mg/Day was not statistically superior to placebo after adjustment for multiplicity. For Q-LES-Q% maximum total score, none of the QTP XR dose groups showed a statistically significant improvement compared to placebo after adjustment for multiplicity.

STUDY 10

Design

Protocol D1448C00010: An 8-Week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, phase III outpatient study of the efficacy and safety of QTP XR 150 mg/Day, 300 mg/Day, and ecitalopram 10 mg/Day (active control) compared with placebo in the acute treatment of GAD in adults.

First patient enrolled: 4/17/2006 Last patient enrolled: 6/14/2007

After the initial evaluation visit there was an enrollment period of up to 28 days, during which a washout for all psychotropic medication occurred before randomization. Patients were randomized to one of the four treatment arms (QTP XR 150 mg, QTP XR 300 mg, ecitalopram 10 mg, or placebo) on Day 1, followed by a titration period and a fixed dose period of treatment. The treatment was administered once daily in the evening.

The post-treatment consisted of a 2 week follow up period. Patients were encouraged not to take anxiety medication during the 14 day post treatment period. Patients who took QT XR dose of 300 mg were weaned off during the 14 day post treatment period. Unsolicited AE reports occurring up to 14 days after last dose of investigational product were recorded together with concomitant medications in appropriate sections of the Paper Case Report Forms (PCRF). Patients were asked to return to the study center on Day 7 (Visit 9) and Day 14 (Visit 10) of post treatment to complete

assessments including the final Treatment Discontinuation Signs and Symptoms (TDSS) assessment. If patients were discontinued prematurely, the Day 57 (final visit) assessments were performed at end of their discontinuation.

Figure 2: Dose Initiation and Visit Schedule (extracted from the sponsor's submission)

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9		Visit 10	Visit 11
-28 to -1[c]	1	4	8	15	22	29	43	57[d]	[e]	7	14[f]
Enrollment	Randomize							Final	Post	Post	Post

[a] Titration: Days 1-2 quetiapine XR 50 mg; Days 3-56 quetiapine XR 150 mg
[b] Titration: Days 1-2 quetiapine XR 50 mg; Days 3-4 quetiapine XR 150 mg; Days 5-56 quetiapine XR 300 mg
[c] Enrollment period was a maximum of 28 days prior to randomization
[d] Last dose was Day 56; final treatment assessments were Day 57
[e] TDSS by telephone from a location remote from the study center on Post-treatment Days 1, 3, and 5
[f] End of study post-treatment visit

Investigators/Sites

A total of 68 principal investigators conducted this study at 64 sites throughout U.S.A.

Objectives

Primary: To demonstrate superior efficacy of QTP XR for the three doses, 150 mg/Day, 300 mg/Day and active control ecitalopram 10 mg/Day, compared with placebo in the treatment of anxiety symptoms in patients with GAD. Evaluation was conducted by measuring change from randomization of Hamilton Anxiety Scale (HAM-A Total Score) at Week 8 (Day 57).

During development stage of this protocol, FDA approved measurement of change from randomization at Week 8 of Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q% maximum total score) as a key secondary. However, after the protocol was written, the sponsor opted to designate Q-LES-Q as a "secondary variable of particular interest" rather than identifying it as a "key secondary" efficacy assessment. It is my impression that these terms are interchangeable.
Secondary: To evaluate the effects of QTP XR versus placebo by evaluating change from randomization of:

- Quality of Life Enjoyment and Satisfaction Questionnaire item 15 and 16 (Q-LES-Q)
- Clinical Global Impression-Global Improvement (CGI-I)
- Clinical Global Impression-Severity of Illness (CGI-S)
- Sleep quality measured by Pittsburgh Sleep Quality Index (PSQI)
- Early efficacy of QTP XR on day 8 (Time of Onset)

Study Population

The inclusion/exclusion criteria are similar for all three short-term acute treatment studies 09, 10 and 11 (see this section under study 09).

Permitted, Restrictive, and Prohibited Medications

This is similar for all three sort-term acute treatment studies 09, 10 and 11 (see study 09 in section 6 for reference).

Efficacy Assessments

Primary efficacy variable was change from randomization in the HAM-A total score at Week 8 (Day 57).

As described in the objectives section the term "secondary variable of particular interest" was measuring change from randomization of the Q-LES-Q% maximum total score at Week 8. Other secondary efficacy variables measuring change from randomization at Week 8, included HAM-A somatic cluster, HAM-A Response and Rate, Q-LES-Q item 15 and 16, CGI-I, CGI-S, PSQI, and Time of Onset.

Efficacy Analysis Plan

The analysis of all primary efficacy, "secondary objective of particular interest", secondary efficacy variables and Patient Reported Outcome (PRO) variables were performed using the modified intent-to-treat (MITT) analysis set.

MITT analysis set: Patients were randomized, took study drug, and had a randomization HAM-A total score assessment and at least 1 HAM-A total score post-randomization.

LOCF analysis set: If a patient dropped out before the Day 57 assessment, the HAM-A total score for the actual last study assessment of that patient (if post baseline) was moved forward using Last Observation Carried Forward (LOCF). The LOCF approach was used as the primary method for handling of missing data. An alternative analysis using Observed Cases (OC) data was also carried out.

For the analysis of HAM-A total score and Q-LES-Q% maximum total score, comparing QTP XR and placebo, levels of significance were determined using the multiple testing procedure (MTP) as described below. All statistical tests were 2-sided with an overall significance level of 5% unless otherwise specified. For comparisons between each dose of QTP XR and placebo, 95% confidence intervals (CIs) were reported. P-values were controlled for multiplicity only at Week 8.

The multiplicity problem concerning the false-positive error rate for the 50 mg/Day and 150 mg/Day, and 300 mg/Day dose comparisons with placebo in the primary analysis was handled

by utilizing the Bonferroni-Hommel procedure. This procedure was demonstrated to control the overall Type I error at α. This ensured that the probability of getting a "false" success in any of the 3 comparisons was at most 5%; i.e., α=0.05.

The analysis of change from baseline to final assessment (LOCF) in all primary, "secondary objective of particular interest", secondary efficacy variable, and Patient Reported Outcome (PRO) variables total scores at week 8 tested the superiority of each dose level of QTP XR using an analysis of covariance (ANCOVA) with the baseline total scores as the covariates and included treatments as a fixed effects and centers as random effects in the model. The contrasts of interest were the treatment differences between each dose of QTP XR and placebo.

Patient Disposition

Thirteen hundred and thirty four (1334) patients were screened. Four hundred eighty (480) were screen failures. Eight and fifty four (854) patients were randomized in this study. Eight (8) were not treated. The ITT population (846) consisted of 217 patients receiving QTP XR 150 mg, 206 patients receiving QTP XR 300 mg, 209 patients receiving escitalopram 10 mg and 214 patients receiving placebo treatment. A total of 828 patients were included in the MITT analysis after 18 patients were excluded because they did not have valid baseline or post-baseline HAM-A scores.

Approximately 71% of randomized patients completed the 8 Week randomized period of the study, with higher rates of completion in the placebo group compared to the QTP XR groups.

Those who completed the Study:
In the QTP XR 150 mg group - 71% (156/217 patients)
In the QTP XR 300 mg group of - 60% (126/206 patients)
In the ecitalopram 10 mg group -72% (154/209 patients)
In the placebo group - 79% (169/214 patients)

The Overall dropout rate from the 8 Week randomized period consisted of:
In the QTP XR 150 mg group - 29% (61/217 patients)
In the QTP XR 300 mg group - 40% (80/206 patients)
In the ecitalopram 10 mg group - 28% (55/209 patients)
In the placebo group - 21% (45/214 patients)

The adverse event dropout rates included:
In the QTP XR 150 mg group – 17% (38/217 patients)
In the QTP XR 300 mg group - 25% (51/206 patients)
In the ecitalopram 10 mg group – 9% (19/209 patients)
In the placebo group - 6% (13/214 patients)

Other significant reason for dropout included patients "lost to follow up" and "patients not willing to continue Study". QTP XR treatment discontinuations rates ranged from 4% to 8% across all groups compared with same rates for the placebo group. The sponsor did not further identify and include if dropouts were due to lack of efficacy.

Baseline Demographic Characteristics

The baseline demographics of all three short term studies do not show any significant differences between the groups with respect to age, gender, or race variables. The mean age was about 40; the majorities were Caucasian and female.

Table 10: Baseline Demographic Characteristics Study 10- Mitt Population for Study 10

Treatment	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Oriental	Other
QTP XR 150 mg (n = 219)	38.2	19 to 64	33	68	81	13	0.5	5.7
QTP XR 300 mg (n = 226)	39.0	18 to 66	29	71	80	10	2.0	7.5
Escitalopram 10 mg (n =224)	40.4	20 to 64	35	66	79	15	0.5	5.9
Placebo (n = 225)	36.6	18-65	36	64	82	11	0.9	6.6

Information obtained from Sponsor Table 11.1.6.1 in Clinical Study Report

Baseline Severity of Illness

Treatment groups had no major differences with respect to mean baseline HAM-A total scores:
In the QTP XR 150 mg group – mean score of 25.0
In the QTP XR 300 mg group – mean score of 25.2
In the escitalopram 10 mg group – mean score of 24.6
In the placebo group - mean score of 25.3

Concomitant Medication

Sleep medication use was low in all treatment groups. It was lower in the QTP XR 150 mg/Day and 300 mg/Day groups (≤ 1.7% and ≤ 2.3%, respectively, at any week) compared with the escitalopram 10 mg/Day group (≤ 3.0% at any week) and higher than the placebo group (≤ 1.1% at any week).

Anticholinergic use was lower in the QTP XR 150 group (≤ 1.8% at any week) compared with the escitalopram (≤ 2.2% at any week) and placebo groups (≤ 4.1% at any week). It was highest in the QTP XR 300 group (≤ 6.1%).

Based on the safety population, the protocol violators (prohibited medication used) were:
In the QTP XR 150 mg group - 0% (0/212 patients)
In the QTP XR 300 mg group - 2.0% (4/201 patients)
In the escitalopram 10 mg group - 0.5% (1/224 patients)
In the Placebo group - 0.5% (1/203 patients)

Dosing Information

This was a fixed dose study including QTP XR does of 150 mg/Day, 300 mg/Day and escitalopram 10 mg/Day.

Dosing Information

A fixed dose study utilizing QTP XR doses of 50 mg/DAY, 150 mg/Day and 300 mg/Day.

Results

Primary efficacy variable results

1. HAM-A total score

QTP XR doses of 150 mg/Day and 300 mg/Day were superior to placebo, as demonstrated by change from randomization to Week 8 in HAM-A total score after adjustment for multiplicity. The difference between escitalopram 10 mg/Day and placebo at Week 8 was statistically significant (no multiplicity adjustment). QTP XR 150 mg/Day, but not 300 mg/day, was significantly better than escitalopram 10 mg/day.

Table 11: HAM-A total score change from randomization to endpoint in Study 10 - LOCF, MITT analysis

		Baseline	Endpoint	LSMean Change *	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	212	25.3 (4.3)	14.2 (8.3)	-11.0	-	-
QTP XR 150 mg/Day	212	25.0 (4.3)	11.0 (7.5)	-14.0	-3.20	<0.001
QTP XR 300 mg/Day	201	25.2 (3.9)	12.6 (7.2)	-12.6	-1.60	0.025
ESC 10 mg/Day	203	24.6 (4.0)	12.4 (7.7)	-12.2	-1.55	0.030

Information obtained from Sponsor Table 17 in Clinical Study Report
* = LS mean change from randomization

Key secondary efficacy variable results

1. Q-LES-Q % maximum total score

Q-LES-Q % maximum total score mean change from randomization at Week 8 was "Secondary variable of particular interest". QTP XR dose of 150 mg/Day, but not 300 mg/Day, was superior to placebo with regard to change from randomization to Week 8 in Q-LES-Q % maximum total score after adjustment for multiplicity (QTP XR 150 mg/Day versus placebo: $p \leq 0.025$). The difference between escitalopram and placebo at Week 8 was statistically significant (no multiplicity adjustment).

Table 12: Q-LES-Q % maximum total score change from randomization at Week 8 in Study 10 - LOCF, MITT

		Baseline	Endpoint	LSMean Change *	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	200	52.46 (13.89)	61.48 (15.17)	9.14	-	-
QTP XR 150 mg/Day	198	52.87 (13.80)	65.29 (16.37)	12.25	3.48	0.012
QTP XR 300 mg/Day	190	54.61 (13.46)	61.58 (16.49)	7.11	-0.94	0.502
ESC 10 mg/Day	191	54.05 (15.07)	65.61 (15.15)	11.35	3.14	0.025

Information obtained from Sponsor Table 18 in Clinical Study Report
* = LS mean change from randomization

Efficacy Conclusions

QTP XR doses of 150 mg/Day and 300 mg/Day are significantly superior to placebo as demonstrated by the mean change from randomization to endpoint in HAM-A total score after adjustment for multiplicity. For Q-LES-Q % maximum total score, the quetiapine XR 150 mg/day dose group showed a statistically significant improvement compared to placebo after adjustment for multiplicity, but the 300 mg/day dose did not show any significant difference.

STUDY 11

Design

Protocol D1448C00011: An 8-Week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, phase III outpatient study of the efficacy and safety of QTP XR 50 mg/Day, 150 mg/Day, and paroxetine 20 mg/Day (active control) compared with placebo in the acute treatment of GAD in adults.

First patient enrolled: 5/18/2006 Last patient enrolled: 2/15/2007

After the initial evaluation visit there was an enrollment period of up to 28 days, during which a washout for all psychotropic medication occurred before randomization. Patients were randomized to one of the four treatment arms (QTP XR 50 mg, QTP XR 150 mg, paroxetine 20 mg, or placebo) on Day 1, followed by a titration period and a fixed dose period of treatment. The treatment was administered once daily in the evening.

The post-treatment consisted of a 2 week follow up period. Patients were encouraged not to take anxiety medication during the 14 day post treatment period. If patients were discontinued prematurely, the Day 57 (final visit) assessments were performed at end of their discontinuation.

Figure 3: Dose initiation and visit schedule (extracted from the sponsor's submission)

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10		Visit 11
-28 to -1[c]	1	4	8	15	22	29	43	57[d]	☎[e]	7	14[f]
Enrollment	Randomize							Final	Post	Post	Post

[a] Titration: Days 1-56 quetiapine XR 50 mg
[b] Titration: Days 1-2 quetiapine XR 50 mg; Days 3-56 quetiapine XR 150 mg
[c] Enrollment period is a maximum of 28 days prior to randomization
[d] Last dose on Day 56; final treatment assessments on Day 57
[e] TDSS by telephone remote from the study center at Day 1, 3, and 5, post-treatment
[f] End of study post-treatment visit

Investigators/Sites

A total of 114 principal investigators conducted this study at 113 sites: Czech Republic (10), Denmark (4), Finland (6), France (11), Germany (8), Mexico (4), Norway (4), Romania (5), Bulgaria (9), and South Africa (7), Spain (4), Sweden (6), Slovakia (6), Argentina (11), and Canada (17).

Objectives

Primary: To demonstrate superior efficacy of QTP XR for the three doses, 50 mg/Day, 150 mg/Day and active control paroxetine 20 mg/Day, compared with placebo in the treatment of anxiety symptoms in patients with GAD. Evaluation was conducted by measuring change from randomization of Hamilton Anxiety Scale (HAM-A Total Score) at Week 8 (Day 57).

During development stage of this protocol, FDA concurred measurement of change from randomization at Week 8 of Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q% maximum total score) as a key secondary. However, after the protocol was written, the sponsor opted to designate Q-LES-Q as a "secondary variable of particular interest" rather than identifying it as a "key secondary" efficacy assessment. It is my impression that these terms are interchangeable.

Secondary: To evaluate the effects of QTP XR versus placebo by evaluating change from randomization of:

- Quality of Life Enjoyment and Satisfaction Questionnaire item 15 and 16 (Q-LES-Q)
- Clinical Global Impression-Global Improvement (CGI-I)
- Clinical Global Impression-Severity of Illness (CGI-S)
- Sleep quality measured by Pittsburgh Sleep Quality Index (PSQI)
- Early efficacy of QTP XR on day 8 (Time of Onset)

Study Population

The inclusion/exclusion criteria are similar for all three short-term acute treatment studies 09, 10 and 11 (see study 09 section for reference).

Permitted, Restrictive, and Prohibited Medications

This is similar for all three sort-term acute treatment studies 09, 10 and 11 (see study 09 section for reference).

Efficacy Assessments

Primary efficacy variable was change from randomization in the HAM-A total score at Week 8 (Day 57).

As described in the objectives section the term "secondary variable of particular interest" was measuring change from randomization of the Q-LES-Q% maximum total score at Week 8.

Other secondary efficacy variables measuring change from randomization at Week 8, included HAM-A somatic cluster, HAM-A Response and Rate, Q-LES-Q item 15 and 16, CGI-I, CGI-S, PSQI, and Time of Onset. Change from randomization of HAM-A psychic cluster was evaluated at Weeks 1, 8 and 8.

Efficacy Analysis Plan

The analysis of all primary efficacy, "secondary objective of particular interest", secondary efficacy variables and Patient Reported Outcome (PRO) variables were performed using the modified intent-to-treat (MITT) analysis set.

MITT analysis set: Patients were randomized, took study drug, and had a randomization HAM-A total score assessment and at least 1 HAM-A total score post-randomization.

LOCF analysis set: If a patient dropped out before the Day 57 assessment, the HAM-A total score for the actual last study assessment of that patient (if post baseline) was moved forward using Last Observation Carried Forward (LOCF). The LOCF approach was used as the primary method for handling of missing data. An alternative analysis using Observed Cases (OC) data was also carried out.

For the analysis of HAM-A total score and Q-LES-Q% maximum total score, comparing QTP XR and placebo, levels of significance were determined using the multiple testing procedure (MTP) as described below. All statistical tests were 2-sided with an overall significance level of 5% unless otherwise specified. For comparisons between each dose of QTP XR and placebo, 95% confidence intervals (CIs) were reported. P-values were controlled for multiplicity only at Week 8.

The multiplicity problem concerning the false-positive error rate for the 50 mg/Day and 150 mg/Day, and 300 mg/Day dose comparisons with placebo in the primary analysis was handled by utilizing the Bonferroni-Hommel procedure. This procedure was demonstrated to control the overall Type I error at α. This ensured that the probability of getting a "false" success in any of the 3 comparisons was at most 5%; i.e., α=0.05.

The analysis of change from baseline to final assessment (LOCF) in all primary, "secondary objective of particular interest", secondary efficacy variable, and Patient Reported Outcome (PRO) variables total scores at week 8 tested the superiority of each dose level of QTP XR using an analysis of covariance (ANCOVA) with the baseline total scores as the covariates and included treatments as a fixed effects and centers as random effects in the model. The contrasts of interest were the treatment differences between each dose of QTP XR and placebo.

Patient Disposition

One thousand and fifty four (1054) patients were screened. One hundred eighty one (181) were screen failures. Three (3) were not treated. Eight and seventy three (873) patients were randomized in this study. The ITT population (870) consisted of 220 patients receiving QTP XR 50 mg, 218 patients receiving QTP XR 150 mg, 215 patients receiving paroxetine 20 mg and 217 patients receiving placebo. A total of 866 patients were included in the MITT analysis after 4 patients were excluded because they did not have valid baseline or post-baseline HAM-A scores.

Approximately 77% of randomized patients completed the 8 Week randomized period of the study, with higher rates of completion in the placebo group compared to the QTP XR groups.

Those who completed the Study:
In the QTP XR 50 mg group - 74% (164/220 patients)
In the QTP XR 150 mg group of - 75% (163/218 patients)
In the paroxetine 20 mg group -80 % (173/215 patients)
In the placebo group - 81% (176/217 patients)

The Overall dropout rate from the 8 Week randomized period consisted of:
In the QTP XR 50 mg group - 26% (57/220 patients)
In the QTP XR 150 mg group - 25% (55/218 patients)
In the paroxetine 20 mg group - 20% (44/215 patients)
In the placebo group - 19% (41/217 patients)

The adverse event dropout rates included:
In the QTP XR 50 mg group – 11% (25/220 patients)
In the QTP XR 150 mg group - 15% (32/218 patients)
In the paroxetine 20 mg –7% (16/215 patients)
In the placebo group - 3% (8/217 patients)

Discontinuations due to "lost to follow-up" were similar across all four treatment groups ($\leq$ 1.4%). Discontinuations due to patient 'not willing to continue" were in the range of 3 to 6% among QTP XR group, 7% in paroxetine group and 6% in the placebo group. The paroxetine group had the higher rates of patients not willing to continue compared to QTP XR and placebo groups. Discontinuations due to lack of efficacy were most frequent in the placebo group 6% (13/217 patients), followed by QTP XR 50 mg group were 4% (9/220 patients), paroxetine group were 2% (4/217 patients) and QTP XR 150 mg group were 0.5% (1/218 patients).

Baseline Demographic Characteristics

The baseline demographics of all three short term studies do not show any significant differences between the groups with respect to age, gender, or race variables. The mean age was about 40; the majorities were Caucasian and female.

Table 13: Baseline Demographic Characteristics Study 11 - Mitt Population

Treatment	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Oriental	Other
QTP XR 50 mg(n = 219)	40.7	18-65	32	68	93	4.1	0.5	3.2
QTP XR 150 mg (n = 216)	42.3	18-65	33	67	95	4.2	0	0.5
Paroxetine 20 mg (n = 214)	41.6	19-64	36	64	96	4.2	0	0
Placebo(n = 217)	41.2	18-65	38	62	94	4.6	0	1.4

Information obtained from Sponsor Table 11.1.6.1 in Clinical Study Report

Baseline Severity of Illness

Treatment groups had no major differences with respect to mean baseline HAM-A total scores:
In the QTP XR 50 mg group – mean score of 26.9
In the QTP XR 150 mg group – mean score of 26.6
In the paroxetine 20 mg group – mean score of 27.1
In the placebo group - mean score of 27.3

Concomitant Medication

Sleep medication use was lower in the QTP XR patients than in the placebo patients. Sleep medication use at any week (Week 1 to Week 8) was noted for ≤ 1.5% of QTP XR 50 mg/Day patients, ≤ 3.2% of QTP XR 150 mg/Day patients, ≤3 .3% of paroxetine 20 mg/Day patients, and ≤ 3.8% of placebo patients.

Anticholinergic use was low in all of the treatment groups. It was lower in the QTP XR groups (≤ 0.6% at any week) compared to paroxetine (≤ 1.1% at any week), and similar to the placebo group (≤ 0.5% at any week).

Based on the safety population, the protocol violators (prohibited medication used) were:
In the QTP XR 50 mg group - 5.5% (12/219 patients)
In the QTP XR 150 mg group - 7.4% (16/216 patients)
In the paroxetine 20 mg group - 6.5% (14/214 patients)
In the Placebo group - 7.8% (17/217 patients)

Dosing Information
This was a fixed dose study including QTP XR does of 50 mg/Day, 150 mg/Day and paroxetine 20 mg/Day.

Primary efficacy variable results

1. HAM-A total score

QTP XR doses of 50 mg/Day and 150 mg/Day were superior to placebo, as demonstrated by change from randomization to Week 8 in HAM-A total score after adjustment for multiplicity. The difference between paroxetine 20 mg/Day and placebo at Week 8 was statistically

significant (no multiplicity adjustment). QTP XR 150 mg/Day, but not 50 mg/day, was significantly better than paroxetine 20 mg/Day.

Table 14: HAM-A total score change from randomization to endpoint Study 11 - LOCF, MITT analysis

		Baseline	Endpoint	LSMean Change *	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	217	27.3 (4.4)	14.8 (9.5)	-12.5	-	-
QTP XR 50 mg/Day	219	26.9 (4.2)	12.8 (8.6)	-14.1	-1.65	0.027
QTP XR 150 mg/Day	206	26.6 (4.2)	10.6 (7.8)	-16.0	-3.66	<0.001
PAR 20 mg/Day	214	27.1 (4.0)	12.4 (9.3)	-14.7	-2.15	0.004

Information obtained from Sponsor Table 17 in Clinical Study Report
* = LS mean change from randomization

Secondary efficacy variable results

1. Q-LES-Q % maximum total score

Q-LES-Q % maximum total score mean change from randomization at Week 8 was "Secondary variable of particular interest". QTP XR dose of 150 mg/Day, but not 50 mg/Day, was superior to placebo with regard to change from randomization to Week 8 in Q-LES-Q % maximum total score after adjustment for multiplicity (QTP XR 150 mg/Day versus placebo: $p \leq 0.025$). The difference between escitalopram and placebo at Week 8 was statistically significant (no multiplicity adjustment).

Table 15: Q-LES-Q % maximum total score change from randomization at Week 8 in Study 11 - LOCF, MITT

		Baseline	Endpoint	LSMean Change *	LSMean Difference	P value vs. placebo
	N	Mean(SD)	Mean(SD)			
Placebo	209	48.91 (15.71)	55.56 (17.04)	6.48	-	-
QTP XR 50 mg/Day	207	48.00 (13.53)	57.05 (16.18)	9.08	1.83	0.198
QTP XR 150 mg/Day	203	46.88 (14.76)	60.08 (15.61)	13.58	5.75	<0.001
PAR 20 mg/Day	204	46.36 (14.93)	57.53 (18.17)	11.35	3.4	0.017

Information obtained from Sponsor Table 18 in Clinical Study Report
* = LS mean change from randomization

Efficacy conclusions

QTP XR doses of 50 mg/Day and 150 mg/Day are significantly superior to placebo as demonstrated by the mean change from randomization to end point in HAM-A total score after adjustment for multiplicity. For Q-LES-Q % maximum total score, only the 150 mg/day QTP XR dose group showed a statistically significant improvement compared to placebo after adjustment for multiplicity.

6.1.4 Other Important Efficacy Issues

Predictors of Response in subgroup analysis

The subgroup analyses evaluated the effect of the following variables on treatment response (HAM-A total score change from randomization at Week 8) for all three short term studies.

- Age (18-39 y/o, 40-65 y/o)
- Gender (M/F)
- Race (Caucasian, Black, Oriental and Other)
- baseline severity of illness (HAM-A total score $\leq$ 29 or $\geq$ 29)
- geographic region (by continent for study 11)

Of note, the sponsor performed a subset analysis to evaluate the effect of treatment response on these subgroups for pooled short-term studies. Data showed that among the different races, the treatment effects were less pronounced in the Blacks. The subgroup analysis of baseline disease severity showed that the patients with a HAM-A total score of $\geq$ 29 at study entry demonstrated greater treatment effects. The differential treatment effect appears to be driven mainly by the reduced effect seen in placebo patients with a severe disease at baseline, rather than by an increased effect of QTP XR in this subgroup. The effect of QTP XR appeared to be consistent across geographic regions.

Dr. Lawrence in his statistical review covered the exploratory subgroup analysis within each of these three short-term studies.

Size of Treatment Effect

Treatment effect size was examined in terms of HAM-A total score change from baseline at Day 57. Results are summarized in Table 4 below for studies 09, 10, and 11.

Table 16: Treatment Effect Size as Expressed by HAM-A Total Score, LS Mean Change from Baseline to endpoint in Three Short Term Studies (09, 10 and 11) - LOCF, MITT Population

Study	QTP XR 50 mg/Day	QTP XR 150 mg/Day	QTP XR 300 mg/Day	ESC 10 mg/Day	PAR 20 mg/Day	Placebo
09	-13.31[a]	-13.54[a]	-11.87	NA	NA	-11.10
10	NA	-13.92[a]	-12.32[c]	-12.27[c]	NA	-10.72
11	-13.95[c]	-15.96[a]	NA	NA	-14.45[b]	-12.30

a = p<0.001 compared with placebo
b = p<0.01 compared with placebo
c = p<0.05 compared with placebo

Table 17: Summary of Efficacy Results (Statistical Significance of Drug/Placebo Differences at Day 57 (LOCF, Mitt Population))

Variable	Dataset	Study 09 QTP XR mg/Day Dose			Study 10 QTP XR and Escitalopram (ESC) mg/Day Dose			Study 11 QTP XR and Paroxetine (PAR) mg/Day Dose		
		50	150	300	150	300	ESC 10	50	150	PAR 20
Mean Δ in HAM-A total score	LOCF	*	*	NS	**	*	*	*	**	*

* = significant (0.01<p≤ 0.05)
**= highly significant (p≤ 0.01)
NS= Not Significant (p>0.10)
NP= not provided

Duration of Treatment

Study 12 addressing the longer-term efficacy of QTP XR in GAD has been completed. See section 6.2.

Key Secondary Variables and Other Secondary Variables

For the endpoint change in the Q-LES-Q% (the key secondary endpoint in the three short term studies) the 50 mg/day dose was not better than placebo in any study, the 150 mg/day dose was better than placebo in two out of three studies, and the 300 mg/day dose was not better than placebo in any study. Other secondary variables that the sponsor proposed to claim in the labeling are listed below. None of these are pre-specified key secondary variables. Refer to appendix for these results.

Clinical Global Impression-Global Improvement (CGI-I)
- Clinical Global Impression-Severity of Illness (CGI-S)
- Sleep quality measured by Pittsburgh Sleep Quality Index (PSQI)
- Early efficacy of QTP XR on day 8 (Time of Onset)
- Montgomery-Åsberg Depression Rating Scale (MADRS)

6.1.5 Clinical Microbiology

Since QTP XR is a solid oral formulation, this section is not applicable.

6.1.6 Efficacy Conclusions (Studies 09, 10 and 11)

In summary, the sponsor has provided evidence that supports the claim of short-term primary efficacy for the 50 and 150 mg dose of QTP XR in GAD as measured by change in baseline to endpoint in HAM-A total score.

Short-term efficacy for the 300 mg dose of QTP XR was seen only in study 10 while study 9 did not show any statistically significant treatment effect for this dose. No additional benefit was seen at 300 mg dose based on the positive results from study 10. In both studies, a slightly larger percentage (40-42%) dropped out from the study in this 300 mg dose group as compared to the other two dose groups (25-36%). The percentage of dropouts due to adverse events was slightly larger as well.

6.2 INDICATION – Maintenance Treatment of GAD

6.2.1 Methods

The Sponsor conducted one multicenter, double-blind, randomized, placebo-controlled study (12) to evaluate the efficacy and safety of QTP XR in maintenance treatment of GAD in adult patients.

6.2.2 General Discussion of Endpoints

The primary efficacy variable for randomized-withdrawal, parallel-group, double-blind, placebo-controlled Study is time to occurrence of an anxiety event.

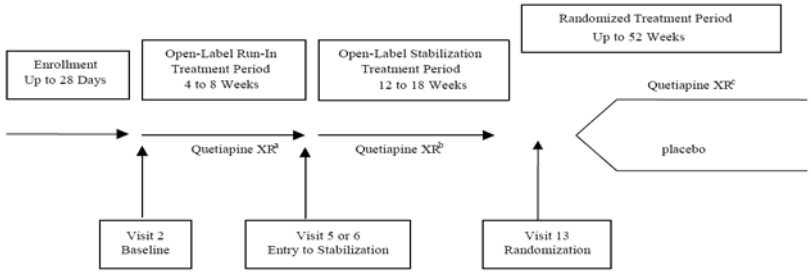
6.2.3 Study Design and Efficacy Findings

STUDY 12

Design

Study 12 was a multicenter, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study preceded by an Open-Label Run-In Treatment (OLRT) and Open-Label Stabilization Treatment (OLST) phases. Both open label treatment phases were designed for 16 to 26 weeks. The randomized treatment period was designed for up to 52 weeks. The QTP XR employed flexible dosing 50 mg/Day, 150 mg/Day, 300 mg/Day and placebos.

Figured 4: Flow Chart of Study 12 (extracted form sponsors submission)



[a] The dose of quetiapine XR was titrated as 50 mg on Day 1 to Day 2 and then 150 mg on Day 3 to Day 4. On Day 5 and thereafter, the dose was adjusted as clinically indicated to 50 mg, 150 mg, or 300 mg.
[b] The dose of quetiapine XR was adjusted to 50 mg, 150 mg, or 300 mg as based upon the clinical judgment of the Investigator.
[c] Patients were randomized to quetiapine XR or matching placebo at the same dose as taken at the last study visit in the Open-Label Stabilization Treatment Period. During the Randomized Treatment Period, quetiapine XR was adjusted to 50 mg, 150 mg, or 300 mg as based upon the clinical judgment of the investigator.

Investigators

Study was conducted by 127 principal investigators at 127 sites throughout Australia (6), Canada (9), Finland (6), Germany (10), Hungary (7), Indonesia (3), Korea (4), Philippines (4), Russia (8), UK (13), and USA (57).

Study Objective

The primary objective in Study 12 was to evaluate the efficacy of QTP XR compared to placebo in increasing time from randomization to an anxiety event in adult patients with GAD.

An anxiety event was described as more than one of the following:

- Initiation of medical treatment by the investigator to treat anxiety symptoms.
- Initiation of medical treatment by the patient for at least 1 week to treat anxiety symptoms.
- HAM-A total score ≥ 15 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinued.
- A suicide attempt or discontinuation from study due to imminent risk of suicide.
- Hospitalization for anxiety symptoms.
- A CGI-S score ≥ 5

Inclusion criteria

The inclusion criteria included:
- A male or female, 18 to 65 years of age with a diagnosis of GAD.
- The HAM-A total score should be > 20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥ 2, and a CGI-S score > 4.
- Female patients of childbearing potential must have a negative serum pregnancy test at enrollment and be willing to use a reliable method of birth control.

Exclusion criteria

The following were relevant exclusion criteria:
- Meeting the criteria for any other DSM-IV Axis I, Axis II diagnosis, concomitant organic mental disorder or mental retardation.
- A current serious suicidal or homicidal risk or a suicide attempt within past 6 months.
- Evidence of a clinically relevant medical illness and/or clinically abnormal laboratory results including positive pregnancy test.
- A substance abuse or dependence disorder as defined by DSM-IV and not in full remission. Positive urine toxicology results before randomization.
- A known lack of response to QTP of atleast 50 mg for 4 weeks.
- Previous enrollment/randomization to treatment in following GAD studies (10, 11 & 12).

Enrollment and Washout phase

The enrollment period preceded the OLRT phase by 7 to 28 days and consisted of a washout period of psychoactive medication. Patient eligibility was established at Visit 1 and patients who met all inclusion criteria and no exclusion criteria entered the OLRT phase at Visit 2.

OLRT phase (4 to 8 weeks)

During the OLRT phase, patients received QTP XR 50 mg/Day on Days 1 and 2, and then the dose increased to 150 mg/Day on Days 3 and 4. The dose of QTP XR could be increased to 300 mg/Day on Day 5 or thereafter, based on the clinical judgment of the investigator. Patients who met the criteria of HAM-A ≤ 12 and CGI-S score ≤ 3 by 4 weeks would enter into OLST phase. If they did not meet criteria they would be treated for up to 4 more weeks. Patients in the OLRT phase who did not meet the OLST criteria by Week 8 were discontinued from the study.

OLST phase (12 to 18 weeks)

The purpose of the OLST was to maintain stabilization after acute treatment of anxiety before Randomization to double-blind treatment. The prescribed QTP XR dosage could be adjusted subsequently to 50 mg/Day, 150 mg/Day, or 300 mg/Day once daily to maximize efficacy and tolerability. Patients in the OLST phase who met the criteria of a HAM-A ≤ 12, CGI-S score ≤ 3 and MADRS score < 16 could enter into RTP phase. The HAM-A score could not be more than > 15 at two sequential visits or a score of CGI > 5 at any one visit. If these criteria were not met at the 12-week visit, the patient could stay for up to 6 more weeks to meet the criteria. Patients who did not meet the eligibility criteria for Randomization by Week 18 were discontinued from the study.

Randomized Treatment Period

Patients meeting Randomization criteria (i.e., patients who remained stable and tolerated QTP XR doses of 50 mg/Day, 150 mg/Day or 300 mg/Day for at least 12 weeks) were allocated to a double-blind treatment to continue with blinded QTP XR or switch to matching placebo of the same dose as taken at the last visit of the OLST. There will be no tapering of the QTP XR treatment before patient is randomized on placebo. As per the investigators clinical judgement the dose can be adjusted. Patients could continue in the randomized treatment period for up to 52 weeks. Patients experiencing an anxiety event (relapse) were required to discontinue the study, and when the total number of required relapses (44 anxiety events) 14 or more days after Randomization occurred, the sponsor terminated the study.

Permitted, Restrictive, and Prohibited Medication

Table 18: Permitted, Restrictive, and Prohibited Medication/Treatments during the Study

Use category	Type of medication/treatment
Permitted	• Nonpsychoactive medications, including OTC medications that were required to treat nonpsychiatric concurrent conditions or illnesses. • Contraceptives (ie, oral contraceptive, implant, dermal contraception, long-term injectable contraceptive, intrauterine device).
Restricted	• From randomization until Day 14, 1 of the following could be used for insomnia, maximum 2 times per week; hypnotic use not allowed on the night prior to conducting study assessments: zolpidem 10 mg, chloral hydrate 1g, zaleplon 20 mg, and zolpiclone 7.5 mg. • Ach could be used to treat EPS and proranolol for emergent akathisia. • Psychotherapy was only allowed if it has been ongoing since at least 3 months prior to randomization.
Prohibited	• Use of drugs that induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes (eg, carbamazepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine, St. John's wort) and inhibitors (eg, ketoconazole [except for topical use], itraconazole, fluconazole, erythromycin, clarithromycin, fluvoxamine, nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir, saquinavir). • Use of any psychoactive drugs including the following classes, other than those allowed in a restricted manner: Antidepressants, Anxiolytic, Hypnotic, Mood stabilizing, Antipsychotic, or Sedatives. • Prophylactic use of Anticholinergics for EPS. • ECT throughout the randomized treatment period. • Abuse or dependence according to the DSM-IV TR criteria of Alcohol, Opiates, amphetamine, barbiturate, cocaine, cannabis, or hallucinogen.

Efficacy Assessments

The primary efficacy variable included time from randomization to an anxiety event.

Efficacy Analysis Plan

The randomized safety (RS) analysis set included all patients who received treatment during the RTP, classified according to actual treatment taken. The intention-to-treat (ITT) analysis set included all randomized patients who received study treatment during the RTP, classified according to their randomized treatment. The ITT analysis set was used for Primary variable analysis. The per protocol (PP) analysis set was based on a subset of data from the ITT patients. The treatment discontinuation signs and symptoms (TDSS) analysis set was a subset of the ITT analysis set.

The primary variable is the time to relapse performed with Cox proportional hazards Model comparing QTP XR to placebo with a hazard ratio (HR) and associated 95% CI. A 2-sided Wald test of null hypothesis of equivalent hazards was performed. Time to anxiety event is presented graphically using Kaplan-Meier curves representing the QTP XR and placebo group.

The following time periods were analyzed:

- ≥ 14 days after randomization (censoring all anxiety events occurring < 14 days after randomization ensured that the anxiety events analyzed were not due to the immediate effects of QTP XR treatment discontinuation in the placebo group).
- Randomization through Week 4, Week 12, and Week 28.

TDSS Scale

Subjects randomized to placebo group encountered an abrupt discontinuation of QTP XR, evidenced by withdrawal symptoms. The TDSS scale (Treatment Discontinuation Signs and Symptoms) was developed by Michelson et al to study emergent discontinuation symptoms of SSRI treatments. The 17 items of the scale used by Michelson are based on the 43-item Discontinuation Emergent Signs and Symptoms (DESS) scale. The TDSS scale uses similar terms for signs and symptoms as used in the Michelson scale, with the addition of "vomiting".

The 18-item TDSS scale was measured at baseline and on Days 1, 3, and 5 information was obtained by a phone interview and Days 7, and 14 were assessed in an office interview. It assessed symptoms as 'present' or 'absent' based upon a yes/no response from the patient. If a symptom was present at a post-baseline visit and it was also present at baseline, the patient was asked whether the symptom was better, unchanged, or worse as compared to baseline. A greater number of symptoms recorded as "new" or "old but worse" indicated greater levels for discontinuation syndrome.

TDSS Results

Mean TDSS scores were higher in the placebo group compared with the QTP XR group. Worsening symptoms potentially related to withdrawal in the placebo group ≥ 1.5 times the rates of the QTP XR group were: insomnia, anxiety, agitation, irritability, mood swings, difficulty concentrating, sweating, muscle tension, chills, nausea, tearfulness, diarrhea, and vomiting. TDSS total score at final visit were higher in the early-relapse group (8.8) than the late-relapse group (5.0) and the non-relapse group (2.4).

Subject Disposition

A total of 1811 patients were screened. Patients enrolled were 1248. Patients randomized to QTP XR and placebo treatments for the open label phase (both OLRT and OLST) were 1224.

By the end of open label phase (both OLRT and OLST), 615 patients had discontinued of reason stated in Table 15. When the total number of required relapses (46 anxiety events) 14 or more days after Randomization occurred, the sponsor terminated the Study, leaving 200 patients continuing to participate in the study without ever being randomized. Thus the total number of patients that did not enter the randomized phase was 815. Equaling to 432 patients that did get randomized to RTP phase and received either QTP XR or placebo treatment. Both the QTP XR and placebo treatment groups had 216 patients in each group.

By the end of the RTP phase, a total of 60% (259 patients) were participating in the QTP XR group (162 patients) and placebo group (97 patients). A total of 25 % of patients relapsed with an anxiety event: QTP XR group had 22 patients and placebo group had 84 patients relapse. Patients discontinuing for reasons other than an anxiety event in the QTP XR and placebo group was 15%. The study was terminated, as specified in the protocol, after more than 46 late anxiety events occurred. No patients completed 52 weeks of randomized treatment.

Table 19: Most Common Reasons for Discontinuations at end of the Open Label Phase (both OLRT and OLST).

Study 12	
Reason for discontinuation	**Number of patients**
Adverse Events	235 patients
Patient Not Willing To Continue	147 patients
Eligibility Criteria Not Fulfilled	83 patients
Lost To Follow Up	82 patients
Lack Of Efficacy	29 patients
Noncompliance To Treatment	27 patients
Other	12 patients
Total No. of discontinued patients at end of open label phase	615 patients
Patients Were Participating Up To Termination Of The Study By The Sponsor, But Were Not Randomized	200 patients
Total No. of patients not randomized	815 patients

Baseline Demographic Characteristics

Overall, QTP XR and placebo groups were similar in baseline demographic Characteristics.

Table 20: Baseline Demographics - Study 12- ITT Population

Treatment	**Age (yrs)**		**Sex (%)**		**Race (%)**			
	Mean	**Range**	**Male**	**Female**	**White**	**Black**	**Oriental**	**Other**
QTP XR (n = 216)	44.7	21-65	32.9	67.1	84.7	6.0	7.4	1.9
Placebo (n = 216)	41.6	18-64	36.6	63.4	81.9	6.5	9.3	2.3

Baseline Severity of illness

Overall, the randomization baselines mean HAM-A total scores were similar in Baseline Severity of illness.

Table 21: Baseline Disease Characteristics (HAM-A Total Score) - ITT Population

Study 12	
QTP XR (n = 216)	5.9
Placebo (n = 216)	6.2

Concomitant Treatments

Nine patients (4.1%) from the QTP XR and eight patients (3.7%) from the placebo RTP groups received the prohibited concomitant medication. Following is a list of the prohibited Benzodiazepine use in Study 14.

Table 22: List of Prohibited Medications/Treatments used in Study 12.

Study 12		
Drug name	No. of patients receiving drug in Placebo group	No. of patients receiving drug in QTP XR group
Alprozolam	2	0
Clozaprate	1	0
Clonazepam	0	1
Diazepam	2	0
Lorazepam	3	1
Temazepam	1	0
Phenazepam*	1	0

* = Foreign drug with diazepam like properties.

Dosing Information

Dosing was flexible throughout the study with patients taking either QTP XR 50 mg/Day, 150 mg/Day, and 300 mg/Day administered orally in the evening.

At the end of the OLST (*mean duration of 15.3 weeks*) distributions of doses were:
For 50 mg/Day group - 26%
For 150 mg/Day group - 49%
For 300 mg/Day group - 25%

At time of randomization, 93% patients were on the same dose of QTP XR as at end of OLST phase with matching placebos. Mean daily dosing during the OLST was 140.4 ($\pm$75.9) mg.

The mean dose at randomization was 160.4 mg/Day, while the mean dose of QTP XR during RTP was 163.2 mg/day. Each dose of QTP XR was significant in increasing the time to occurrence of an anxiety event when compared to Placebo. The mean duration of stabilization prior to randomization was 14.7 weeks in the QTP XR group and 15.9 weeks in the placebo group. Randomized exposure was about 56% greater in the QTP XR group (106.9 mean days in the QTP XR group compared with 68.6 days in the placebo group).

Of the 216 patients in the QTP XR group, a total of 107 patients received at least 12 weeks of randomized treatment with QTP XR, and a total of 44 patients received at least 24 weeks of randomized treatment with QTP XR. During randomized treatment, 58 patients experienced an anxiety event at 14 or more days after randomization, and the study was stopped according to the analysis plan.

Table 23: Efficacy Results of Different Doses

Study 12			
QTP XR Dose	Hazard ratio	CI	p- value

50 mg/day	0.21	95% CI=0.08 to 0.51	p=0.0006
150 mg/day	0.17	95% CI=0.08 to 0.36	p<0.0001
300 mg/day	0.22	95%CI=0.09 to 0.51	p=0.0005

Information obtained from Table 20 from sponsor clinical study 12 report.

Primary Efficacy Variable Results

Analysis of all anxiety events

QTP XR when used as monotherapy, of maintenance treatment of patients with GAD significantly increased the time to occurrence of an anxiety event when compared with the placebo group. Analysis of time to recurrence of an anxiety event (including all events) results showed the estimated HR (QTP XR versus placebo) of 0.19 (95% CI=0.12 to 0.31). The numbers of patients with anxiety events was 84/216 (38.9%) and 22/216 (10.2%) in the placebo and QTP XR treatment groups, respectively.

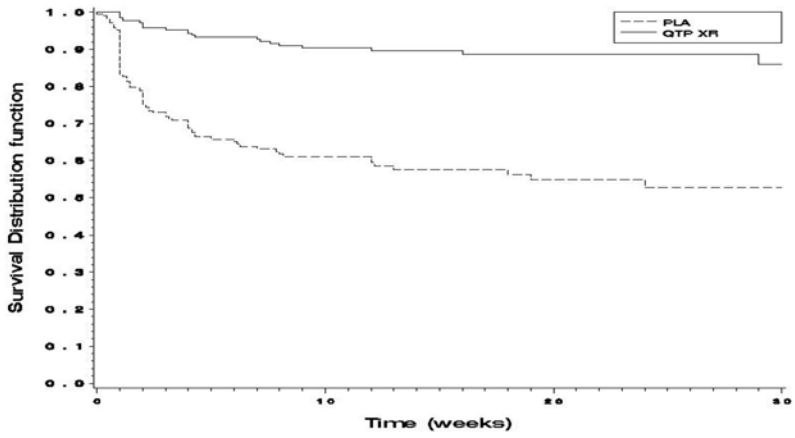
Table 24: Analysis of Time to Occurrence of an Anxiety Event - ITT Analysis Set

Study 12 - QTP XR (N = 216) VS. Placebo (N = 216)		
Hazard ratio	**CI**	**p- value**
0.19	95% CI = 0.12 to 0.31	P < 0.0001

CI = Confidence Interval **ITT** = Intention to treat **N** = Number of patients in RTP

Information obtained from Table 19 from sponsor clinical study 12 report.

Figure 5: Time to Occurrence of an Anxiety Event, Kaplan-Meier Curves – ITT Analysis Set, Randomized Phase (extracted from sponsor submission)



Analysis of anxiety events (after censoring events occurred during the first 13 days of randomized period)

In this analysis after censoring events occurred during the first 13 days, results still showed the anxiety event rates in QTP XR group were lower than the placebo group. The estimated HR

(QTP XR versus placebo) was 0.27 (95% CI=0.15 to 0.47), demonstrating continued effectiveness after the first 13 days of randomized treatment of QTP XR versus placebo in delaying the time to an anxiety event (p-value <0.0001). The number of anxiety events was 41 (24.7%) in placebo and 17 (8.1%) in the QTP XR treatment groups.

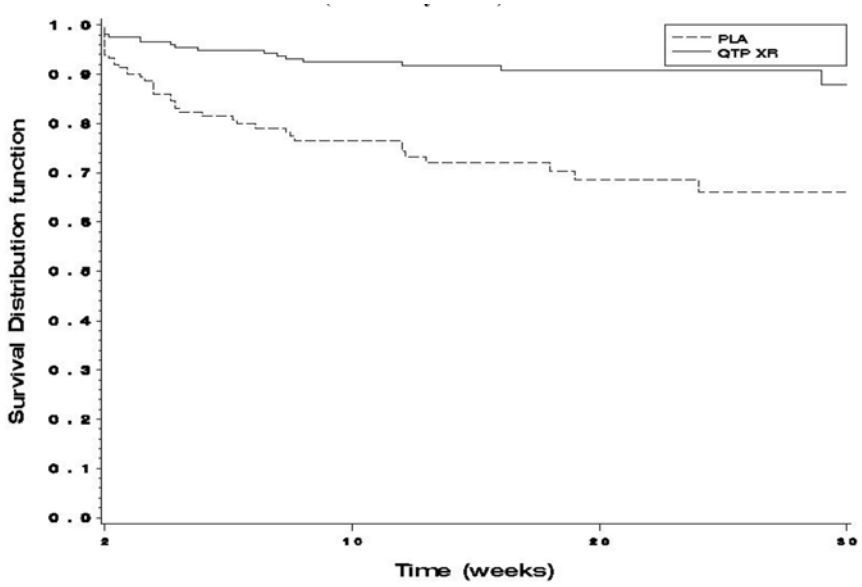
This seemed to demonstrate that the effect of QTP XR in increasing the time to occurrence of an anxiety event was not likely driven by withdrawal symptoms or rebound phenomena for the first 13 days after open-label treatment with QTP XR in the placebo group.

Table 25: Analysis of Time to Occurrence of an Anxiety Event censoring events that occurred during the first 13 days - ITT Analysis Set

Study 12 - QTP XR (N = 166) VS. Placebo (N = 210)		
Hazard ratio	**CI**	**p- value**
0.27	95% CI = 0.15, 0.47	P < 0.0001

CI = Confidence Interval **ITT** = Intention to treat **N** = Number of patients in RTP
Information obtained from Table 21 from sponsor clinical study 12 report.

Figure 6: Time to Occurrence of an Anxiety Event, Kaplan-Meier Curves – ITT Analysis Set, Randomized Phase (extracted from sponsor submission)



Statistical review results

Statistical reviewer John Lawrence Ph.D., notes that, there was a significant difference in the time to an anxiety event after the randomized withdrawal (the primary endpoint). The baseline demographics of the maintenance study do not show any significant differences between the groups with respect to these variables except age (the subjects in the placebo group tended to be younger). The mean age is about 40; the majorities are Caucasian and female.

For Study 12, the primary endpoint (time to anxiety event), QTP XR was statistically significantly better than placebo. The estimated hazard ratio was 0.19 with a 95% CI of (0.12, 0.31) and the p-value was smaller than 0.0001 (from Study Report and confirmed by FDA). Approximately the same number of the subjects dropped out early in the withdrawal period for reasons other than relapse in both the QTP XR and placebo groups (35 vs. 32 subjects). The most common reason for dropout in the treatment groups was "patient not willing to continue".

Efficacy Conclusions

Study 12 demonstrates a longer time to relapse an anxiety event in patients who had been stable in an open-label QTP XR treatment phase for approximately 15.3 weeks as compared to placebo.

6.2.4 Other Important Efficacy Issues

Predictors of Response in subgroup analysis

The effect of treatment with QTP XR on the time to occurrence of an anxiety event compared with placebo across the patient subgroups investigated (age, gender, race, baseline of severity and region) were consistent with the general pattern of results in the overall study population. Statistically significant differences were not observed among the racial subgroups secondary to small number of non-Caucasian patient enrollment. The majority of subjects were females (63.0% to 67.1%) and the overall mean age ranged from 41.7 to 44.8 years, with a higher proportion of QTP XR patients in the older age distribution (40 to 65 years) compared with placebo. These minor differences between randomized groups did not impact interpretation of study results.

The Percentage of Patients with Anxiety Events as Part of Secondary Analysis

The number of patients with an anxiety event was 84 (39%) in the placebo group and 22 (10%) in the QTP XR treatment group.

Of the 216 patients in the QTP XR group, a total of 107 patients received at least 12 weeks of randomized treatment with QTP XR, and a total of 44 patients received at least 24 weeks of randomized treatment with QTP XR. The median dose of QTP XR was 164 mg/day. During randomized treatment, 58 patients experienced an anxiety event at 14 or more days after randomization, and the study was stopped according to the analysis plan. Randomized exposure was about 56% greater in the quetiapine XR group (106.9 mean days in the QTP XR group compared with 68.6 mean days in the placebo group).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The primary safety database for QTP XR treatment of GAD is comprised of three short- term, randomized, double-blind, placebo-controlled studies (studies 09, 10 and 11) and one longer-term randomized withdrawal maintenance study (study 12).

This safety review entailed an examination of the occurrence of deaths, non-fatal serious adverse events, and premature discontinuations due to adverse events across all four trials. Additionally, analyses of common adverse events, vital signs, laboratory test data, and ECG results were conducted on the pool of the three short-term studies.

Also, Study 15 and Study 16 were the two studies as part of 4-month safety update (4MSU) submitted on 9/4/08. These were short- term, randomized, double-blind, placebo-controlled studies. Study 15 enrolled elderly patients with GAD and QTP XR was given as flexible dosing (50 to 300 mg/day). In Study 16, QTP XR was given as an adjunctive treatment in patients with GAD who demonstrated partial or no response to SSRI/SNRI alone or in combination with a benzodiazepine.

7.1.1 Deaths

There were three deaths: Patient E1010712 (study 09) died 60 days post last QTP XR dose, Patient E4510701 (study 11) died before randomization and Patient E6605501 (study 15) in the placebo group died secondary to cardiomyopathy. The deaths in study 09 and study 11 can not be directly attributed to treatment with QTP XR, as neither death occurred during or shortly after treatment with drug. There were no deaths in studies 10, 12, and 16. The death after QTP XR treatment is summarized below.

Patient E1010712 (study 9)

The patient was a 53 year old Caucasian male with a history of acute liver failure and gout. Patient's past medical history included anemia, thrombocytopenia, hemorrhoids, constipation, seasonal allergies, hyperinsulinemia, lymphopenia, and heart burn. He had been randomized on 3/13/2007 to the QTP XR 300 mg/Day group. The patient stopped randomized treatment on 5/17/2007. The patient was lost to follow up. Per subject's daughter (and her mother), subject was found deceased on 7/9/2007 at his home. Patient died approximately 65 days after their final dose of the study drug. The cause of death is unknown.

7.1.2 Other Serious Adverse Events

A serious adverse event met one or more of the following criteria:

- Death
- immediately life-threatening
- required inpatient hospitalization or prolonged existing hospitalization
- resulted in persistent or significant disability or incapacity
- congenital abnormality or birth defect, and/or an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the above outcomes

The table below shows a line listing of SAEs in patients on placebo, Escitalopram (ESC), Paroxetine (PAR) and QTP XR.

Table 26: A line listing of patients with Serious Adverse Events (Other Than Death) on placebo

Patient	Age	Sex	Drug	Serious Adverse Events
Study 10				
E1013815	21	F	placebo	Syncope
E1032814	54	F	placebo	Aspergilloma
E1057823	32	F	placebo	Cholecystitis
Study 11				
E3207712	53	F	placebo	Hemorrhoids, anal abscess
E6204705	53	F	placebo	Peritonitis
Study 12				
E1013602	57	F	placebo	Ovarian cyst
E1042609	36	M	placebo	Pancreatitis
E1210604	33	F	placebo	Appendicitis
Study 15				
E1706514	69	M	placebo	Cholelithiasis
E1712504	84	F	placebo	Cellulites

Table 27: A line listing of patients with Serious Adverse Events (Other Than Death) on ESC or PAR

Patient	Age	Sex	Drug	Serious Adverse Events
Study 10				
E1009814	39	F	ESC 10	Pneumonia
E1022806	26	M	ESC 10	Hemangioma
E1026803	53	M	ESC 10	Hyperlipedemia

Table 28: A line listing of patients with Serious Adverse Events (Other Than Death) on QTP XR

Patient	Age	Sex	Drug	Serious Adverse Events
Study 09				
E1026775	41	M	150	Hematuria, Coumadin toxicity, cardiac pacemaker malfunction
E1045714	40	M	150	Congestive heart failure
E1021702	31	M	300	Suicidal ideation
E1021716	57	F	300	Acute coronary syndrome, gastritis
E1026751	53	M	300	Diabetes mellitus, acute renal failure
E1043735	59	F	300	Suicidal ideation
E1074740	41	F	300	Cholelithiasis
Study 10				
E1009816	57	F	150	Non cardiac chest pain
E1013842	39	F	150	Syncope
E1009802	28	F	300	Herpes, esophagitis
E1021869	33	M	300	Vomiting
Study 11				
E3405713	48	F	50	Acute stress disorder
E3405720	26	F	50	Suicide attempt
E6202701	65	F	50	Wrist fracture
E3405719	24	F	150	Anxiety
Study 12				
E1055610	21	F	150	Suicidal behavior
E1107602	61	M	300	Bladder cancer
E2002604	52	F	300	Cholelithiasis
Study 15				
E6611509	66	F	300	Broncho-pneumonia
Study 16				
E1034023	45	M	QTP	Benzodiazepine withdrawal
E1047007	28	M	QTP	Left leg injury

I reviewed the individual narrative summaries of patients with SAEs. In summary, there were no serious adverse events that are judged to be unexpected and reasonably attributable to treatment with QTP XR. However, three cases from study 09 merit further discussion.

Patient E1045714, a 40 year old black male receiving QTP XR 150 mg/Day had an SAE of "Cardiac failure congestive". The patient had a medical history of diabetes and hypertension. The event occurred after being on study drug for 64 days. The event resolved after 3 days and the patient continued on the study drug without recurrence. Thus, this event seems unlikely quetiapine–related.

Patient E1026775, a 41 year old male receiving QTP XR 150 mg/Day had SAEs of cardiac pacemaker malfunction, drug toxicity, and flank pain, haematuria and coumadin toxicity. The patient's current medical history included hypertension, seasonal allergies, and headache. The SAE event of coumadin toxicity occurred on Day 34 of taking QTP XR treatment, the drug was withdrawn and the event resolved after two days. There is no known interaction between QTP XR and coumadin.

Patient E1026751, a 53-year-old Black male receiving QTP XR 300 mg/day experienced hyperglycemia and newly diagnosed with diabetes mellitus during study treatment (Day 37). He was hospitalized on Day 45 for hyperglycemia (>900 mg/dL) and acute renal failure. He received IV Fluid and insulin treatment and was discharged from hospital on Day 50. He returned for study discontinuation visit on Day 52. A further description of this SAE is referred under section 7.1.4.1 Diabetes Mellitus.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile of Dropouts

Studies 09, 10, and 11

The pooled data of the three short-term acute treatment studies (09, 10 and 11) showed that the completion rates were lower in the QTP XR groups (69%) compared with the placebo group (78%). Among QTP XR treated patients, the most common reason for discontinuation was "Adverse event". This appeared to be dose-related. For placebo patients, the most common reason for discontinuation was "Subject not willing to continue study".

Table 29: Incidence (%) of study completion of dose groups and reasons for dropouts among the pooled studies (09, 10, and 11)

	QTP XR mg/Day						
	50 N=452	150 N=673	300 N=444	Total N=1569	ESC 10 N=203	PAR 20 N=214	Pla N=665
Completed Treatment	74%	72%	62%	69%	76%	81%	78%
Premature Discontinuation	26%	28%	38%	31%	24%	19%	22%
Adverse Event	13%	17%	24%	18%	9%	8%	5%
Subject Not Willing to continue	5%	4%	6%	5%	6%	7%	8%
Lost to Follow-up	3%	4%	4%	4%	6%	1%	4%
Lack of Therapeutic Response	2%	1%	0%	1%	1%	2%	2%
Severe noncompliance	2%	2%	0%	1%	1%	1%	2%
Other Reason	1%	0%	1%	1%	1%	1%	1%
Eligibility Criteria Not Met	0%	1%	1%	1%	0%	0%	1%

Study 12

The most common reasons for discontinuation from the randomized phase of study 12 were "terminated by sponsor" (after at least 44 anxiety events occurred ≥14 days after randomization) and "subject not willing to continue". With the exception of "terminated by sponsor" and "anxiety event", the discontinuation rates and reasons for discontinuation were similar in the QTP XR and placebo groups. The incidence of AEs leading to discontinuation during the randomized treatment phase was 2.3% and 3.7% in the QTP XR and placebo groups, respectively, and 19.4% during open-label QTP XR treatment.

Table 30: Incidence (%) of study completion and reasons for dropouts in the randomized phase of maintenance study (12)

	QTP XR 50- 300 mg/Day (N=216)	Placebo (N=216)
Completed treatment of up to 52 weeks	0%	0%
Sponsor discontinued	76%	46%
Premature discontinuation due to an anxiety event	10%	39%
Subject Not Willing to Continue Study	6%	7%
Lost to Follow-up	3%	3%
Other Reason	2%	1%
Adverse Event	2%	4%
Severe noncompliance	1%	0%

7.1.3.2 Adverse Events Associated With Dropouts

Study 09, 10 and 11

Adverse events leading to dropout in at least 1% of patients during the acute treatment phase are presented in Table 6. Other events leading to premature discontinuation during this phase (by MedDRA preferred term) were dry mouth, dysarthria, irritability, nausea, asthenia, allergy, suicidal ideation, tachycardia, abdominal pain, akathisia, anxiety, balance disorder, disturbance in attention, dyspnea, headache, heart rate increases, myalgia, restlessness, sluggishness, palpitations, and depression.

Table 31: Incidence of Dropouts due to Adverse Events in Study 09, 10, and 11

	QTP XR				
	50 mg/Day N=452	150 mg/Day N=673	300 mg/Day N=444	Total N=1569	Placebo N=665
Sedation	2%	5%	10%	6%	1%
Somnolence	4%	5%	7%	5%	0%
Fatigue	2%	3%	3%	2%	0%
Dizziness	2%	1%	2%	1%	1%

Study 12

The QTP XR AE dropouts in the randomized phase will be biased by dropouts that occurred in the open-label phase, I don't think this information can be easily interpreted. Nonetheless, there were no unexpected, potentially serious events that led to dropout during open-label or blinded treatment with QTP XR.

7.1.3.3 Other Significant Adverse Events

No other significant adverse events.

7.1.4 Other Search Strategies

7.1.4.1 Diabetes Mellitus

An integrated search for diabetes mellitus was based on both a search for related MedDRA terms (see the listing at the end of this subsection) in AE reports and the change from baseline of glucose regulation laboratory data. The results presented in this section are fasting samples with results obtained only from documented fasting samples (at least 8 hours since the last meal). Separate analyses of patients with pre-existing diabetes, patients with risk for diabetes and non-diabetic patients were performed. Diabetes risk factors included: fasting glucose ≥ 100 and < 126 mg/dL at randomization, history of diabetes or obesity or BMI > 35 kg/m2. The criteria for treatment emergent clinically important glucose lab values included the following.

- Glucose - ≤ 2.5 mmol/L ≤45 mg/dL and ≥ 7 mmol/L ≥ 126 mg/dL
- HbA1c - >7.5%

There were 2 cases of diabetes mellitus reported in study 9 (Patient E1045714 and Patient E1026751). One of these events (Patient E1026751, quetiapine XR 300 mg/day group) was considered serious and related to the study drug. The patient withdrew from the study due to the SAE event. This patient E1026751, a 53-year-old Black male receiving QTP XR 300 mg/day experienced severe hyperglycemia and newly diagnosed with diabetes mellitus during

study treatment (Day 37). Medical history included hypertension and chronic pancreatitis; there was no family history of diabetes. Concomitant medications included atenolol, clonidine, valsartan hydrochlorothiazide, and acetylsalicylic acid. The patient did not use tobacco or alcohol. At study entry, patient's body weight was 75.9 kg (BMI 20.5 kg/m^2), fasting blood glucose was 120 mg/dL, and HbA_{1c} was 6.5%. On Day 31 of randomized treatment, fasting blood glucose was 147 mg/dL. On Day 37, the patient experienced dizziness, numbness in right hand, hot and cold flashes, blurred vision, a loss of appetite, increased urination, nausea, and vomiting. The patient was hospitalized on Day 45 due to high blood sugar (>900 mg/dL). Blood urea nitrogen and creatinine were elevated at 39 and 2.8, respectively. BP was 180/110. With IV fluid and insulin treatment, patient's condition improved and was discharged from hospital on Day 50. Patient discontinued from study. At the discontinuation visit, Day 52, no fasting blood glucose was reported; however, HbA_{1c} was 10.6% with ongoing insulin treatment. The investigator considered this event to be severe and related to the study drug.

The other event (Patient E1045714, quetiapine XR 150 mg/day group) was considered not serious and was not considered related to study drug. This patient E1045714, a 40-yr old obese 196.4 kg, BMI 58.6 kg/m^2) Black male, with history of hypertension and family history of diabetes was noted to have a baseline fasting glucose of 128 mg/dL and HbA1c 5.6%. He received QTP XR 150 mg/day. The fasting blood glucose was 137 mg/dL and HbA1c 5.8% on Day 58. This patient had a weight increase of 13.4 kg during the study. He was diagnosed with diabetes and initiated treatment with metformin 100 mg on Day 64.

The pooled short-term acute treatment study data showed the incidence of AEs potentially associated with diabetes mellitus was low and similar in across all treatment groups.

Table 32: Incidence of AEs potentially associated with diabetes mellitus in studies 9, 10, and 11

	All QTP XR N=1569	QTP XR50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
DM-related event* (%)	8 (0.5%)	1(0.2%)	4(0.6%)	3(0.7%)	7 (1.1%)

* - Patients with multiple events are counted only once in the total
Information obtained from Sponsor table SA037 in Clinical Study Report

The mean change from baseline to end of treatment in glucose related laboratory data are summarized below. The QTP XR 150 mg and 300 mg treatment group had a slight mean increase in fasting glucose data as compared to placebo.

Table 33: Mean change from randomization to end of treatment in glucose, HbA1c and insulin - Study 9, 10, 11

	PLA		ALL QTP XR		QTP XR 50		QTP XR 150		QTP XR 300	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Glucose (mg/dl)	572	1.67 (14)	1348	1.71 (16)	380	-0.52 (15)	578	2.27 (15)	300	3.06 (18)
HbA1c (%)	560	-0.018 (0.22)	1282	0.003(0.28)	365	0.0 (0.3)	547	-.015 (0.25)	370	0.031(0.31)
Insulin (pmol/L)	575	2.5 (19)	1337	3.3 (20)	386	1.99 (12)	569	3.08 (21)	382	4.97 (23)

Information obtained from Sponsor table S032 in Clinical Safety Summary Report

The proportion of patients with treatment emergent clinically important glucose and glycated Hb shift during the short-term studies is summarized below.

Table 34: The proportion of patients with fasting glucose and HbA1c shifts to clinically important values in studies 9, 10, and 11

	PLA N=665			ALL QTP XR N=1569			QTP XR 50 N=452			QTP XR 150 N=673			QTP XR 300 N=444		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Glucose ≤45 mg/dL	572	0	(0.0)	1348	2	(0.1)	380	1	(0.3)	578	0	(0.0)	390	1	(0.3)
Glucose ≥126 mg/dL	562	19	(3.4)	1331	47	(3.5)	375	11	(2.9)	569	17	(3.0)	387	19	(4.9)
HbA1c (%) >7.5%	559	0	(0.0)	1277	4	(0.3)	363	1	(0.3)	545	0	(0.0)	369	3	(0.8)

N number of patients at risk, ie not fulfilling the criteria at randomization.

n Number of patients in the analysis subset. PLA Placebo. QTP XR Quetiapine extended-release.

Note: Percentages in total column are calculated as $n/N_a \times 100$.

Information obtained from Sponsor table SA095 in Clinical Safety Summary Report

The proportion of patients with treatment emergent clinically important glucose and glycated Hb shift for patients with diabetes, patients at risk for diabetes and patients with no known risk is summarized below. The highest incidence of patients with clinically important elevated glucose levels occurred in the QTP XR 300 mg group. Few cases of HbA1c values shifting to clinically important levels were noted: 1 case in the QTP XR 50 mg group and 3 cases in the QTP XR 300 mg group. However, all instances of clinically important HbA1c values occurred in the diabetic subgroup of patients.

Table 35: The proportion of patients with fasting glucose and HbA1c shifts to clinically important values based on DM risk status in studies 9, 10, and 11

	Placebo N=665			All QTP XR N=1569			QTP XR 50 mg/Day N=452			QTP XR 150 mg/Day N=673			QTP XR 300 mg/Day N=444		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	%
Fasting Glucose															
≤45 mg/dL Diabetic	38	0	(0.0)	102	0	(0.0)	31	0	(0.0)	42	0	(0.0)	30	0	(0.0)
≤45 mg/dL Diabetic risk	200	0	(0.0)	455	2	(0.4)	126	1	(0.8)	193	0	(0.0)	136	1	(0.7)
≤45 mg/dL NonDiabetic	334	0	(0.0)	791	0	(0.0)	224	0	(0.0)	343	0	(0.0)	224	0	(0.0)
≥126 mg/dL Diabetic	33	7	(21.2)	86	17	(19.8)	26	3	(11.5)	33	4	(12.1)	27	10	(37.0)
≥126 mg/dL Diabetic risk	198	6	(3.0)	454	18	(4.0)	125	8	(6.4)	193	5	(2.6)	136	5	(3.7)
≥126 mg/dL NonDiabetic	331	6	(1.8)	791	12	(1.5)	224	0	(0.0)	343	8	(2.3)	224	4	(1.8)
HbA1c															
>7.5% Diabetic	36	0	(0.0)	98	4	(4.1)	31	1	(3.3)	38	0	(0.0)	30	3	(10.0)
>7.5% Diabetic risk	200	0	(0.0)	427	0	(0.0)	121	0	(0.0)	178	0	(0.0)	128	0	(0.0)
>7.5% NonDiabetic	323	0	(0.0)	752	0	(0.0)	212	0	(0.0)	329	0	(0.0)	211	0	(0.0)

Information obtained from Sponsor table S035 in Clinical Safety Summary Report

Diabetic: Patients with pre-existing diabetes; Diabetic risk: Patients with risks for diabetes; Non-Diabetic: patients with no known risks for diabetes.

Following are MedDRA terms related to Diabetes Mellitus		
ANTI-INSULIN ANTIBODY INCREASED	DIABETES MELLITUS INSULIN-DEPENDENT	HYPERGLYCAEMIA HYPERGLYCAEMIC
ANTI-INSULIN ANTIBODY POSITIVE	DIABETES MELITTUS NONINSULIN-DEPENDENT	HYPEROSMOLAR NONKETOTIC SYNDROME
BLOOD GLUCOSE ABNORMAL	DIABETES WITH HYPEROSMOLARITY	HYPERINSULINAEMIA HYPERINSULINISM
BLOOD GLUCOSE FLUCTUATION	DIABETIC COMA DIABETIC COMPLICATION	HYPERPHAGIA IMPAIRED FASTING
BLOOD GLUCOSE INCREASED	DIABETIC HYPERGLYCAEMIC COMA	GLUCOSE IMPAIRED INSULIN
BLOOD INSULIN ABNORMAL	DIABETIC HYPEROSMOLAR	SECRETION
BLOOD INSULIN DECREASED	DIABETIC KETOACIDOSIS DIABETIC KETOACIDOTIC	INCREASED INSULIN REQUIREMENT
BLOOD INSULIN INCREASED	HYPERGLYCAEMIC COMA	INSULIN C-PEPTIDE
BLOOD PROINSULIN ABNORMAL	GLUCOSE TOLERANCE DECREASED	ABNORMAL INSULIN C-PEPTIDE
BLOOD PROINSULIN DECREASED	GLOCOSE TOLERANCE IMPAIRED	DECREASED INSULIN C-PEPTIDE
BLOOD PROINSULIN INCREASED	GLUCOSE TOLERANCE TEST ABNORMAL	INCREASED INSULIN RESISTANCE
DAWN PHENOMENON	GLUCOSE URINE PRESENT	INSULIN RESISTANCE
DIABETES MELLITUS	GLYCOSOLATED	SYNDROME
DIABETES MELLITUS	HAEMOGLOBIN INCREASED	INSULIN RESISTANT
INADEQUATE CONTROL	POLYDIPSIA	DIABETES
INSULIN-REQUIRING TYPE II	POLYURIA	GLYCOSURIA DURING
DIABETES MELLITIS	THIRST	PREGNANCY
INSULIN TOLERANCE TEST	BLOOD KETONE BODY	GESTATIONAL DIABETES
ABNORMAL	PRESENT	GLUCOSE TOLERANCE
METABOLIC DISORDER	BLOOD KETONE BODY	IMPAIRED IN PREGNANCY
NEONATAL DIABETES MELLITIS	INCREASED	SOMOGYI PHENOMENON

7.1.4.2 Weight data

The mean change from randomization to end of treatment in weight (kg) BMI categorical change from randomization, mean change in waist circumference from randomization to end of treatment was reviewed.

In the short term pooled studies results showed that at the end of treatment increase in mean weight were observed in all groups, although greater weight increases were observed in the QTP XR groups than placebo: 0.58 kg, 0.82 kg and 0.93 kg for the 50 mg, 150 mg and 300 mg QTP XR groups, respectively, compared to 0.16 kg in the placebo group. Changes in median body weight were smaller (0.3 kg, 0.7, kg and 0.5 kg for the 50 mg, 150 mg and 300 mg QTP XR groups, respectively, compared to no change in the placebo group). There was no clear pattern of weight gain based on initial BMI category, and mean weight gain was similar in males and females. Small increases in mean waist circumference were observed in all QTP XR treatment groups (0.2 cm, 0.7 cm and 0.4 cm for the 50 mg, 150 mg and 300 mg QTP XR groups, respectively, compared to a 0.5 cm decrease in the placebo group, although there was no change in median waist circumference in any of the treatment groups.

In the pooled studies the percentage of patients with a clinically important weight gain from randomization to end of treatment (≥7% increase from baseline to last visit) was higher for QTP XR-treated patients (4.3% in the QTP XR 50 mg group, 6.0% in the QTP XR 150 mg group, and 4.7% in the QTP XR 300 mg group) compared with placebo-treated patients (2.4%). Clinically

important weight increases were observed at higher percentages in the lower BMI categories than in the higher categories for both QTP XR and placebo treated patients

7.1.4.3 Extrapyramidal Symptoms (EPS)

An integrated search for EPS is based on both AE reports (see list of MedDRA terms below) and the results of the SAS and BARS.

The assessment of parkinsonian symptoms was based on change from baseline of SAS total score to the end of study. The results showed that majority of the patients were in the "no change" category. Patient's "improved" rates with QTP XR were 16% and with placebo were 18%. Patient's "worsened" rates with QTP XR were 7.3% and with placebo were 7.1%. There were no notable differences across QTP XR dose groups.

Change from baseline of BARS total score to the end of study showed that majority of the patients were in the "no change" category. Patient's "improved" rates with QTP XR were 15.3% and with placebo were 14.8%. Patients with "worsened" rates with QTP XR were 4.4% and with placebo were 3.6%. There were no notable differences across QTP XR dose groups. Similar results were seen for study 12.

The pooled short-term acute treatment study data showed the incidence of AEs associated with EPS did not exceed 6 % in any of the treatment groups. The incidence was higher in the QTP XR treatment groups than in the Placebo group. None of the EPS were SAEs. Akathisia was reported more in the QTP XR groups than in the Placebo group.

Table 36: Incidence of AEs potentially associated with EPS in studies 9, 10, and 11

	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
EPS-related event [a] (%)	77 (4.9 %)	17 (3.8 %)	34 (5.1 %)	26 (5.9 %)	21 (3.2%)
Akathisia	23 (1.5%)	4 (0.9 %)	11 (1.6 %)	8 (1.8 %)	3 (0.5 %)

a- Patients with multiple events are counted only once in the total.
Information obtained from Sponsor table SA038 in Clinical Study Report

Following are MedDRA terms related to safety area of EPS		
AKATHISIA	DYSKINESIA	MASKED FACIES
AKINESIA	DYSKINESIA OESOPHAGEAL	MICROGRAPHIA
ATHETOSIS	DYSTONIA	MOVEMENT DISORDER
BRADYKINESIA	EXTRAPYRAMIDAL	MUSCLE CONTRACTIONS
BUCCOGLOSSAL	DISORDER	INVOLUNTARY
SYNDROME	FREEZING PHENOMENON	MUSCLE RIGIDITY
CHOREA	GRIMACING	NUCHAL RIGIDITY
CHOREOATHETOSIS	HYPERKINESIA	OCULOGYRATION
COGWHEEL RIGIDITY	HYPERTONIA	OPISTHOTONUS
DROOLING	HYPOKINESIA	PARKINSONIAN GAIT
PARKINSONISM	POSTURING	TARDIVE DYSKINESIA
PLEUROTHOTONUS	PSYCHOMOTOR	TORTICOLLIS
RESTLESSNESS	HYPERACTIVITY	TREMOR

7.1.4.4 Tardive Dyskinesia

There were no assessments done to evaluate the long term risk such as tardive dyskinesia in the short term trial subject population.

In study 12 (maintenance study), the sponsor stated that there were no AE reports of tardive dyskinesia were observed at any time during the study. During the open-label phase, a small mean increase in AIMS total score was observed (0.1). During the randomized phase, mean change in AIMS total score (Items 1 to 7) for the QTP XR group and the placebo group was minimal (0-0.1). For a large majority of patients in the study 12, there was either no change or an improvement in SAS or BARS total scores over the treatment period. However, because of the study design, the results from this study would be difficult to interpret.

Although we have asked the sponsor in the 2005 meeting that the benefit/risk assessment must include tardive dyskinesia for this patient population, no additional assessment by the sponsor was identified in this submission.

7.1.4.5 Neutropenia and Agranulocytosis

An integrated search for neutropenia and agranulocytosis is based on both AE reports (see MedDRA terms below) and the laboratory data included:

Neutropenia: < $1.5x10^3$/UL
- Severe Neutropenia: < $0.5x10^3$/UL
- Agranulocytosis: < $0x10^3$/UL

The pooled short-term acute treatment study data showed the percentage of patients who had shifts to clinically important value for neutropenia were 1.5% patients in the QTP XR 50 mg group, 2.0% patients in the QTP XR 150 mg group, 0.8% patients in the QTP XR 300 mg group, and 2.3% patients in the placebo group. No patients discontinued the study secondary to neutropenia. No specific dose relatedness observed. No patient had treatment-emergent severe neutropenia.

The numbers and percentage of patients with shifts to clinically important values is presented in the laboratory data section 7.1.6.2.1, Table 45.

Table 37: Incidence of AEs potentially associated with neutropenia/agranulocytosis in studies 9, 10, 11

	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
Neutropenia [a,b] (%)	1 (0.1%)	1 (0.2%)	0	0	1 (0.2 %)

a- Neutropenia: < $1.5x10^3$/UL
b - Patients with multiple events are counted only once in the total.
Information obtained from Sponsor table SA041 in Clinical Study Report

Following are MedDRA terms for safety area of neutropenia/agranulocytosis		
BAND NEUTROPHIL COUNT DECREASED	NEUTROPENIC INFECTION	GRANULOCYTE COUNT DECREASED
BAND NEUTROPHIL PERCENTAGE DECREASED	NEUTROPENIC SEPSIS	GRANULOCYTOPENIA
FEBRILE NEUTROPENIA	NEUTROPHIL COUNT DECREASED	IDIOPATHIC NEUTROPENIA
NEUTROPHIL PERCENTAGE ABNORMAL NEUTROPENIA	NEUTROPHIL PERCENTAGE DECREASED	NEUTROPHIL COUNT ABNORMAL
	AGRANULOCYTOSIS	

7.1.4.6 Suicidality

The sponsor conducted an integrated search for suicidality based on AEs (see the list below), a score of ≥ 4 on MADRS Item 10, and a Columbia-type suicidality analysis using the following categories:

- No event (code 0)
- Completed suicide (code 1)
- Suicide attempt (code 2)
- Preparatory acts toward imminent suicidal behavior (code 3)
- Suicidal ideation (code 4)
- Self-injurious behavior, intent unknown (code 5)
- Not enough information, death(code 6)
- Self-injurious behavior, no suicidal intent (code 7)
- Other (code 8)
- Not enough information, non-fatal (code 9)

The pooled short-term acute treatment study data showed the incidence of AEs associated with suicidality were similar for all dose groups and did not exceed 0.7%. Most adverse events were of suicidal ideation.

Table 38: Patients with suicidal behavior/ideation in Studies 9, 10, and 11 - Columbia-type analysis

Classification (codes)	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
Suicidal behavior (1, 2, 3)	2 (0.1%)	1 (0.2%)	0	1 (0.2%)	0
Suicidal ideation (4)	5 (0.3%)	2 (0.4%)	1 (0.1%)	2 (0.5%)	2 (0.3%)
Possible suicidal behavior/ideation (5, 6, 9)	6 (0.4%)	2 (0.4%)	2 (0.3%)	2 (0.5%)	4 (0.6%)

Information obtained from Sponsor table SU3 in Clinical Study Report

Table 39: Incidence of MADRS item 10 score ≥ 4 associated with suicidality in studies 9, 10, and 11

	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
Patients with MADRS Item 10 Score ≥ 4	2 (0.1%)	0	0	2(0.5 %)	1(0.2 %)

Information obtained from Sponsor table SA052 in Clinical Study Report

Table 40: Incidence of AEs potentially associated with suicidality in studies 9, 10, and 11

	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
Suicidality [b] (%)	8 (0.5%)	3 (0.7 %)	2 (0.3 %)	3 (0.7 %)	2 (0.3 %)
Suicidal behavior	0	0	0	0	1 (0.2 %)
Suicidal ideation	7 (0.4 %)	2 (0.4 %)	2 (0.3 %)	3 (0.7 %)	1 (0.2 %)
Suicide attempt	1 (0.1 %)	1 (0.2 %)	0	0	0

b - Patients with multiple events are counted only once in the total.
Information obtained from Sponsor table SA051 in Clinical Study Report

Following are MedDRA terms related to safety area of suicidality		
COMPLETED SUICIDE	SUICIDAL BEHAVIOUR	INTENTIONAL SELF-INJURY
SUICIDE ATTEMPT	SUICIDAL IDEATION	SELF INJURIOUS BEHAVIOR
SELF MUTILATION	SELF-INJURIOUS IDEATION	

7.1.4.7 Syncope

The pooled short-term acute treatment study data showed the incidence of AEs associated with syncope (see table), were slightly higher in the QTP XR treatment groups (0.9%, 0.4% and 1.4% in the 50 mg, 150 mg and 300 mg groups, respectively) than in the placebo group (0.2%). No dose relatedness observed.

Following are MedDRA terms related to safety area of syncope		
FAINT	SYNCOPE	ORTHOSTATIC COLLAPSE
FAINTING	SYNCOPE POSTURAL	SYNCOPE CONVULSIVE
LIPOTHYMIA	SYNCOPE AGGRAVATED	CARDIAC SYNCOPE
SYNCOPAL ATTACK		SYNCOPE HYPOTENSIVE

7.1.4.8 Somnolence

An integrated search for somnolence and sedation is based on reviewing MedDRA termed AEs (see the list below).

The pooled short-term acute treatment study data showed the incidence rates of AEs associated with somnolence were higher in the QTP XR treatment groups than in the placebo group and appeared to be dose-related. AEs associated with somnolence led to discontinuation in 6.2%, 10.4% and 17.1% of patients in the QTP XR 50 mg/Day, 150 mg/Day and 300 mg/Day groups, respectively. The majority of discontinuations occurred after Day 7, and they were associated with more severe somnolence.

The incidence, intensity, and time of onset of somnolence and sedation AEs in the QTP XR treatment group were consistent with the known pharmacological profile of QTP. Updated incidence numbers of somnolence and sedation as combined terms are in the proposed annotate label.

Table 41: Incidence of AEs potentially associated with somnolence in studies 9, 10, and 11

	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Pla N=665
Combined somnolence-sedation events [b] (%)	804(51.2%)	172(38.1%)	352(52.3%)	280(63.1%)	110(16.5%)
Somnolence	477 (30.4)	117 (25.9)	214 (31.8)	146 (32.9)	70 (10.5)
Sedation	320 (20.4)	56 (12.4)	133 (19.8)	131 (29.5)	33 (5.0)

b- Patients with multiple events are counted only once in the total.
Information obtained from Sponsor table SA045 in Clinical Study Report

Following are MedDRA terms related to safety area of somnolence			
SOMNOLENCE	SEDATION	SLUGGISHNESS	LETHARGY

7.1.4.9 Nausea

An integrated search of nausea is based on reviewing MedDRA termed AE's (see list of MedDRA terms below).

The pooled short-term acute treatment study data showed the incidence of AEs associated with nausea were higher in the QTP XR 300 mg/Day group (9 %) than the QTP XR 150 mg/Day group (6.1 %), QTP XR 50 mg/Day group (5.8 %) and the placebo group (6.3 %). Slight dose relatedness observed. In the QTP XR group, 13 patients (0.8%) were withdrawn from the study due to an AE of nausea and 3 patients (0.2%) due to an AE of vomiting, similar to the numbers and percentages of patients in the placebo group. One AE vomiting in the QTP XR 300 mg treatment group was classified as an SAE.

Table 42: Incidence of AEs potentially associated with nausea or vomiting in studies 9, 10, and 11

	All QTP XR N=1569	QTP XR 50 mg/Day N=452	QTP XR 150 mg/Day N=673	QTP XR 300 mg/Day N=444	Placebo N=665
Nausea or vomiting [b] (%)	196 (12.5%)	42 (9.3 %)	88 (13.1 %)	66 (14.9 %)	68(10.2%)
Nausea	173(11.0%)	36 (8.0%)	78 (11.6%)	59 (13.3%)	55 (8.3%)
Vomiting	61 (3.9%)	10 (2.2%)	27 (4.0%)	24 (5.4%)	21 (3.2%)

b Patients with multiple events are counted only once in the total.
Information obtained from Sponsor table SA039 in Clinical Study Report

Following are MedDRA terms related to safety area of nausea			
NAUSEA	VOMITING	REGURGITATION	RETCHING

7.1.5 Common Adverse Events

7.1.5.1 Eliciting Adverse Events Data in the Development Program

In the five short-term studies (studies 9, 10 and 11) the adverse events were collected on a weekly basis from spontaneous reports from the patient, patient reports after prompting with a general question and observations by the study staff.

7.1.5.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse event terms used by the study investigators to describe adverse experiences in all the studies were coded to MedDRA terminology. In order to ascertain the acceptability of the adverse event coding in the placebo-controlled database, the adverse event datasets (.xpt files) for all the studies were examined. In particular, the investigator terms were compared to the MedDRA preferred term (variable PT_NAME for all studies) for each event listed in the dataset in each of the studies. This process was performed twice, once after sorting by CRF term and once after sorting by preferred (coded) term. This audit revealed no significant deficiencies in the coding process, which was judged to be acceptable.

7.1.5.3 Incidence of common adverse events

For purposes of identifying the adverse experiences commonly observed with QTP XR, the pool of short-term placebo-controlled studies were examined in terms of the proportions of patients in each treatment group (QTP XR and placebo) who reported specific events by MedDRA preferred term.

7.1.5.4 Common adverse event tables

Table 43: Common Adverse Events (events reported ≥ 2% in all QTP XR patients) studies 9, 10, and 11

MedDRA Preferred Term	QTP XR	Placebo
	N=1569	N=665
Gastrointestinal Disorders		
Dry Mouth	31%	10%
Constipation	7%	3%
Diarrhea	6%	7%
Vomiting	4%	3%
Nausea	11%	8%
Abdominal pain upper	2%	2%
Nervous System Disorders		
Somnolence [1]	50%	15%
Dizziness	15%	9%
Headache	13%	18%
Insomnia	6%	6%
Dysarthria	4%	0%
Myalgia	3%	2%
Abnormal dreams	3%	2%
Back pain	3%	2%
Asthenia	2%	1%
Metabolism and Nutrition Disorders		
Increased appetite	5%	4%
Weight increased	2%	1%
Decreased appetite	2%	3%
General disorders		
Fatigue	11%	7%
Nasopharyngitis	4%	3%
Irritability	3%	2%
Vision blurred	2%	1%
Upper respiratory tract infection	2%	3%

Information obtained from Sponsor table S 11 in Clinical Study Report
[1] - Combines the AE term sedation

7.1.5.5 Identifying common and drug-related adverse events

Common and drug-related adverse events are typically defined as those occurring in at least 5% of active drug patients and at an incidence at least twice that in the placebo group.

Applying this definition to the above data, the following three events are considered common and drug-related (QTP XR incidence, placebo incidence).

Table 44: Common Adverse Events (events reported ≥ 5% of QTP XR and incidence twice the rate of placebo) studies 9, 10 and 11

MedDRA Preferred Term	QTP XR	PLACEBO
	N=1569	N=665
Somnolence [1]	50%	15%
Dry Mouth	31%	10%
Dizziness	15%	9%
Nausea	11%	8%
Constipation	7%	3%

Information obtained from Sponsor S 18 in Clinical Study Report
[1] - Combines the AE term sedation

7.1.5.6 Additional Analyses and Explorations

7.1.5.6.1 Dose-Dependency of Common Adverse Events

The incidence of the above identified common, drug-related adverse events by randomized QTP XR dose group in the pool of placebo-controlled studies is shown in table 22.

The Sponsor conducted a Jonckheere-Terpstra analysis on adverse events pooled from the short-term studies. The analysis indicated that when the placebo group is excluded from the analysis the following adverse events exhibit a "dose effect" relationship with QTP XR (p-value < 0.05): Dry mouth, somnolence, sedation, nausea, constipation, dyspepsia, vomiting, weight increased, dysarthria and nasal congestion.

Table 45: Adverse event incidence by dose group placebo-controlled study pool of studies 9, 10 and 11

MedDRA preferred term [a, b]	QTP XR Dose Group		
	50 mg/Day N=452	150 mg/Day N=673	300 mg/Day N=444
Somnolence [c]	167 (37%)	335 (50%)	271 (61%)
Dry mouth	94 (21%)	208 (31%)	172 (39%)
Nausea	26 (6%)	50 (7%)	43 (10%)
Constipation	19 (4%)	38 (6%)	38 (9%)

a - MedDRA-encoded AE occurring at an incidence ≥5% in any active treatment group and at least twice the placebo rate
b - Patients with multiple events falling under the same preferred term are counted only once under that term
Information obtained from Sponsor table S 13 in Clinical Study Report
c – Combines the AE term sedation

7.1.5.6.2 Demographic Interactions with Adverse Events

For each of the common, drug-related adverse events identified above, the incidence of these events in the placebo-controlled study pool, stratified by age, gender, and race subgroups, is reviewed below. The sponsor states a Breslow-Day analysis on the incidence of the common drug related adverse events and common adverse events pooled from the short-term studies for the demographic variables of gender, age and race was conducted. This analysis was run on both common AEs (with a 2% incidence in any group and twice placebo rate).

Gender
With respect to gender, all p-values for the homogeneity test exceeded 0.05 with the exception Of "dysarthria". Dysarthria was reported in males at a frequency of 1.2% (n=7) in subjects randomized to receive QTP XR compared to 0.8% (n=2) in subjects in the placebo group. For females, the frequencies were at 1.8% (n=18) and 0.0% (n=0) in the QTP XR and placebo-randomized groups, respectively. The incidence of "dysarthria" was somewhat higher in females. There were no cases of dysarthria in females randomized to placebo, which is likely a chance finding. Based on the above analysis, presentations of common drug-related adverse events do not depend on gender.

Age
All p-values for the homogeneity test exceeded 0.05 for age and hence for the AEs listed there is no indication that the odds ratios were unequal for patients aged 18-49 years old and patient's 50 years old or older.

Race
Due to the lower number of non-Caucasian subjects, the racial groups 'Black', 'Oriental' and 'Other' were grouped into one category (non-Caucasian) in order to facilitate analysis. Hence, for the purpose of these analyses, race was classified as Caucasian and non-Caucasian.

In instances when no patient in a treatment group had an adverse event classification, an odds ratio was not calculated. For the variable of 'race', all p-values for the homogeneity test exceeded 0.05 except for the AE terms of "vomiting" and "somnolence". "Vomiting" was reported in Caucasians at a frequency of 2.0% (n=26) in subjects randomized to receive QTP XR compared to 0.9% (n=5) in the placebo group. For the non-Caucasian group, the frequencies were also low at 0.4% (n=1) and 2.0% (n=2) in the QTP XR and placebo randomized groups, respectively.

As with the other demographic analyses above, taking into account the very low incidence involved, this is not likely to represent a clinically important difference between these groups. "Somnolence" was reported in Caucasians at a frequency of 29.6% (n=393) in subjects Randomized to QTP XR compared to 8.5% (n=48) in the placebo group. For the non-Caucasian group, the frequency of "somnolence", 28.3% (n=68), was similar to that seen in the Caucasian group for QTP XR, while the frequency of this event in placebo-randomized Subjects, 17.2% (n=17), was somewhat higher than that seen in Caucasians.

Hence, the overall incidence of "somnolence" is quite similar between the Caucasian and non-Caucasian groups. The higher frequency of somnolence in non-Caucasians randomized to receive placebo is likely a chance finding, perhaps related to the small numbers involved. Furthermore, the event of "sedation" was reported at generally similar rates in the Caucasian and non-Caucasian groups (RR of 4.2 and 3.1, respectively), suggesting that this AE (which is similar to "somnolence") is evenly distributed in frequency between these groups. Taking into account these factors, the potential finding of a relative increase in "somnolence" in the Caucasian group is not felt to represent a clinically meaningful difference. Based on the above analysis presentations of common drug-related adverse events do not depend on race

7.1.5.6.2 Comparison of Common Adverse Events with Quetiapine XR versus Quetiapine IR

The same criteria for common and drug-related adverse events (occurring in at least 5% of active drug patients at an incidence at least twice that in the placebo group) was applied to the pool of the QTP IR treatment groups in the placebo-controlled studies. A side-by-side comparison of the common and drug-related adverse experiences with QTP XR versus QTP IR is provided in Table 23. Overall, there is considerable overlap in the profiles of common, drug-related adverse events.

Table 46: Common, Drug-Related Adverse Events for QTP XR versus QTP IR

QTP XR	QTP IR
Dry mouth	Dry mouth
Somnolence	Somnolence
Dizziness	Dizziness
Dyspepsia	Sedation
Sedation	Tachycardia

7.1.5.7 Less Common Adverse Events

A listing of all adverse events from the placebo-controlled studies, regardless of reporting frequency, was examined to identify any that might be potentially clinically important and possibly related to QTP XR. After excluding cases of serious adverse events which are discussed above in this review there were no others identified as such.

7.1.6 Laboratory Findings

7.1.6.1 Overview of Laboratory Testing in the Development Program

Analyses of laboratory data were examined for the pool of the three placebo-controlled studies (09, 10 and 11). The analyses most helpful in determining whether QTP XR was associated with significant abnormalities in laboratory test parameters are the incidence of outliers (i.e., the proportion of patients with clinically important values at any time point) and premature discontinuations due to laboratory abnormalities.

Laboratory testing in all studies was conducted as follows:

Hematology – hemoglobin, leukocyte count, leukocyte differential count, platelet count, neutrophil count, red blood cells, hematocrit. Hematology panel was performed at Day -28 to -1, Day 29 and Day 57.

Chemistry – creatinine, urea, bilirubin (total), albumin, alkaline phosphatase, ALT, AST, potassium, calcium, sodium, chloride, bicarbonates, glucose (fasting), insulin (fasting), hemoglobin A1C, lipids (fasting) including total cholesterol, triglycerides, HDL, LDL; thyroid

function tests including free T3, free T4, TSH; prolactin; and beta-HCG. Chemistry panel was performed at day -28 to -1, Day 29 and Day 57.

Urinalysis – urine toxicology conducted at baseline only.

7.1.6.2 Standard Analyses and Explorations of Laboratory Data

7.1.6.2.1 Analyses Focused on Measures of Abnormal Hematology Values

Tables below depict the numbers and percentages of QTP XR and placebo patients in all pooled studies with potentially clinically important (PCI) values at any time, as defined by the criteria indicated. The numbers of patients at risk were those who did not meet the specified criterion pre-treatment. Hematology and chemistry analytes were reviewed and the most significant "outliers" are noted in this sub-section and the other sub-sections that follow.

Table 47: Hematology shifts to clinically important values at any time - Study 9, 10, 11

	PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Hgb															
M ≤11.5g/dL	215	1	(0.5)	498	3	(0.6)	156	0	(0.0)	212	2	(0.9)	130	1	(0.8)
M ≥18.5g/dL	215	0	(0.0)	503	0	(0.0)	157	0	(0.0)	212	0	(0.0)	134	0	(0.0)
F ≤10.5g/dL	387	4	(1.0)	890	5	(0.6)	246	0	(0.0)	384	2	(0.5)	260	3	(1.2)
F ≥16.5g/dL	390	2	(0.5)	902	5	(0.6)	248	3	(1.2)	387	2	(0.5)	267	0	(0.0)
Platelets															
≤100x10^9 cells/L	598	1	(0.2)	1387	0	(0.0)	400	0	(0.0)	592	0	(0.0)	395	0	(0.0)
≥600x10^9 cells/L	598	0	(0.0)	1388	4	(0.3)	400	2	(0.5)	592	1	(0.2)	396	1	(0.3)
Basophils															
≥0.5x10^9 cells/L	605	0	(0.0)	1399	0	(0.0)	403	0	(0.0)	536	0	(0.0)	400	0	(0.0)
Eosinophils															
≥1x10^9 cells/L	604	3	(0.5)	1397	3	(0.2)	403	0	(0.0)	594	2	(0.3)	400	1	(0.3)
Leucocytes															
≤3x10^9 cells/L	605	6	(1.0)	1405	7	(0.5)	405	0	(0.0)	599	5	(0.8)	401	2	(0.5)
≥16x10^9 cells/L	605	3	(0.5)	1403	4	(0.3)	405	0	(0.0)	596	2	(0.3)	401	2	(0.5)
Lymphocytes															
≤0.5x10^9 cells/L	604	0	(0.0)	1399	0	(0.0)	403	0	(0.0)	596	0	(0.0)	400	0	(0.0)
≥6x10^9 cells/L	605	0	(0.0)	1399	0	(0.0)	403	0	(0.0)	596	0	(0.0)	400	0	(0.0)
Monocytes															
≥1.4x1099cells/L	605	0	(0.0)	1399	0	(0.0)	403	0	(0.0)	596	1	(0.2)	400	0	(0.0)
Neutrophils															
<0.5x103/UL	605	0	(0.0)	1399	0	(0.0)	403	0	(0.0)	596	0	(0.0)	400	0	(0.0)
≥0x103/UL	604	8	(1.3)	1389	1	(0.6)	400	2	(0.5)	591	3	(0.5)	398	0	(0.8)
Neutrophils, Particle Concentration															
<1.5x10^3/UL	605	14	(2.3)	1399	21	(1.5)	403	6	(1.5)	595	12	(2.0)	400	3	(0.8)
≥10x10^3/UL	604	8	(1.3)	1389	8	(0.6)	400	2	(0.5)	591	3	(0.5)	398	3	(0.8)

Note: Percentages in total column are calculated as n/Na x 100.
Information obtained from Sponsor Table SA066 and Table SA071 in Clinical Study Report.

Regarding mean changes from baseline to end of treatment in hematology assessments in the QTP XR groups, the changes were very small and similar to placebo. There were no notable clinically significant differences among the treatment groups in mean change from baseline in hematology laboratory data during short-term treatment.

7.1.6.2.2 Erythrocyte (volume fraction)

There were few differences between treatments, although shifts from normal to clinically low erythrocyte (volume fraction) values were observed more often in the QTP XR 300 mg group at all visits. In the QTP XR 300 mg group 9 (2.3%) patients had a shift from to a clinically important erythrocyte volume fraction at any time during the study, compared with 8 (1.3%) patients in the placebo group, 3 (0.8%) patients in the QTP XR 50 mg group and 9 (1.5%) patients in the QTP XR 150 mg group.

7.1.6.2.3 Hepatic laboratory data

There were no notable clinically significant differences between treatment groups in mean change from baseline in hepatic laboratory data during short-term treatment. There were no cases of jaundice or liver failure. Changes in hepatic assessments in the QTP XR groups at the end of treatment were small and similar to placebo.

Table 48: Hepatic shifts to clinically important values at any time - Study 9, 10, 11

	PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
ALT≥3 ULN	558	1	(0.2)	1280	4	(0.3)	366	2	(0.5)	546	2	(0.4)	368	0	(0.0)
AP ≥3 ULN	561	0	(0.0)	1283	0	(0.0	366	0	(0.0)	547	0	(0.0)	370	0	(0.0)
APT ≥3 ULN	560	0	(0.0)	1283	3	(0.2)	366	1	(0.3)	547	2	(0.4)	370	0	(0.0)
Bilirubin, total ≥1.5 ULN	555	1	(0.2)	1267	4	(0.3)	358	0	(0.0)	542	2	(0.4)	367	2	(0.5)

Note: Percentages in total column are calculated as n/N x 100.
Information obtained from Sponsor Table SA029 in Clinical Study Report.

7.1.6.2.4 Renal laboratory data

Two cases of renal function values shifted to clinically important levels were noted. The cases were one in each of the QTP XR 150 mg and 300 mg groups. The creatinine mean changes were less than ≤0.03 mg/dL.

Table 49: Renal function shifts to clinically important values at any time - Study 9, 10, 11

	PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Creatinine ≥1.58 mg/dL	552	0	(0.0)	1268	2	(0.2)	360	0	(0.0)	543	1	(0.2)	365	1	(0.3)

Note: Percentages in total column are calculated as n/Na x 100.
Information obtained from Sponsor Table S 30 in Clinical Study Report.

7.1.6.2.5 Electrolyte laboratory data

Electrolyte laboratory values shifting to clinically important levels at any time during the studies were infrequent, and the incidence was similar across treatments. There were clinically significant differences in mean changes from baseline to endpoint among the QTP XR and placebo groups.

7.1.6.2.6 Glucose laboratory data

Refer to section of Diabetes Mellitus in 7.1.4 Other Search Strategies.

7.1.6.2.7 Lipids

The results presented in this section are results obtained using only documented fasting samples, ie, only those samples taken at least 8 hours since the last meal. A decrease in mean HDL cholesterol values was noted in all treatment groups, with larger change in the QTP XR groups (-1.5 mg/dL in the QTP XR 50 mg group, -2.0 g/dL in the QTP XR 150 mg group and –2.9 mg/dL in the QTP XR 300 mg group, compared with a –0.5 mg/dL change in mean HDL cholesterol value in the placebo group). A median decrease of 2.0 mg/dL was recorded in all QTP XR groups, compared with no change in median HDL cholesterol value in the placebo group. There were no notable differences between treatment groups in changes in LDL or total cholesterol values.

Triglycerides exhibited higher increases from baseline for QTP XR treated patients than for placebo treated patients, with the highest increase in the QTP XR 300 mg group. The mean change was 5.6 mg/dL in the QTP XR 50 mg group, 11.3 mg/dL in the QTP XR 150 mg group and 17.2 mg/dL in the QTP XR 300 mg group, compared with a 4.9 mg/dL mean decrease in triglyceride value in the placebo group. These results show high variability in all treatment groups.

Table 49: Lipid lab values shifts to clinically important values at any time - Study 9, 10, 11

	PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Cholesterol ≥240 mg/dL	495	19	(3.8)	1125	65	(5.8)	312	20	(6.4)	475	28	(5.9)	338	17	(5.0)
HDL ≤40 mg/dL	470	42	(8.9)	1086	108	(9.9)	315	26	(8.3)	468	43	(9.2)	303	39	(12.9)
LDL ≥160 mg/dL	511	18	(3.5)	1175	47	(4.0)	330	16	(4.8)	496	23	(4.6)	349	8	(2.3)
Triglycerides ≥200 mg/dL	479	34	(7.1)	1107	131	(11.8)	319	28	(8.8)	476	59	(12.4)	312	44	(14.1)

Note: Percentages in total column are calculated as n/Na x 100.
Information obtained from Sponsor Table SA127 in Clinical Study Report.

7.1.6.2.8 Thyroid

There were 3 cases with treatment emergent clinically important shifts in total/free thyroxine in relation to clinically important high TSH values, 1 in each of the placebo group, QTP XR 50 mg and QTP XR 150 mg groups. One patient in the QTP XR 50 mg/Day group also reported the only AE of hypothyroidism. The AE was considered mild in intensity and did not lead to discontinuation. The results show no clinical significant differences of total/free thyroxine and TSH lab values at the end of treatment compared to placebo.

The total/free thyroxine and TSH lab changes from baseline were analyzed. Mean increase in TSH was observed in the QTP XR group than the placebo group (0.272 mIU/mL compared with 0.091 mIU/mL, respectively), with similar mean changes seen across the QTP XR dose groups. QTP XR treated patients also exhibited a greater mean decrease in thyroxine compared with placebo-treated patients (0.029 ng/dL in the QTP XR 50 mg group, 0.054 ng/dL in the QTP XR 150 mg group and 0.067 ng/dL in the QTP XR 300 mg group, compared to 0.010 ng/dL in the placebo group).

7.1.6.2.9 Prolactin

Prolactin changes from randomization to end of treatment in mean prolactin laboratory data were small, with large variation in scores, although a larger increase in mean prolactin values was noted with increasing dose of QTP XR (0.21 ng/mL, 0.37 ng/mL and 0.80 ng/mL for the quetiapine XR 50 mg, 150 mg and 300 mg groups, respectively, compared to 0.24 ng/mL for the placebo group).

Table 50: Prolactin lab values shifts to clinically important values at any time - Study 9, 10, 11

	PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Prolactin															
Male >20 ng/mL	194	0	(0.0)	451	5	(1.1)	141	0	(0.0)	184	3	(1.6)	126	2	(1.6)
Female >30 ng/mL	356	8	(2.2)	820	9	(1.1)	221	2	(0.9)	357	4	(1.1)	242	3	(1.2)

Note: Percentages in total column are calculated as n/Na x 100.
Information obtained from Sponsor Table SA127 in Clinical Study Report.

7.1.6.2.10 Vital Signs

The following vital sign outlier criteria were used.

- Pulse (bpm) - ≥120, ≤ 50, more than 15 bpm of difference
- Systolic blood pressure (mmHg) - ≥ 180, ≤ 90 mmhg
- Diastolic blood pressure (mmHg) - ≥ 105, ≤ 50 mmhg

Pooled short term study vital sign results data showed there were no clinically significant differences between treatment groups in mean change from randomization in vital sign data In QTP XR group compared with placebo

Table 51: Vital sign values shifts to clinically important values at any time - Study 9, 10, 11

	PLA(N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Pulse (bpm)															
> 120	655	2	0.3	1519	3	0.2	438	0	0	654	0	0	427	3	0.7
≥15 Increase	655	125	19.1	1520	399	26.3	438	88	20.1	655	176	26.9	427	135	31.6
<50	652	7	1.1	1509	8	0.5	434	3	0.7	650	3	0.5	425	2	0.5
≥15Decrease	655	83	12.7	1520	148	9.7	438	49	11.2	655	64	9.8	427	35	8.2
SBP (mmHg)															
≥180	655	4	0.6	1517	1	0.1	437	1	0.2	655	0	0	425	0	0
≥20 Increase	655	80	12.2	1519	200	13.2	438	56	12.8	655	91	13.9	426	53	12.4
≤90	647	16	2.5	1504	48	3.2	433	18	4.2	651	23	3.5	420	7	1.7
≥20Decrease	655	102	15.6	1519	192	12.6	438	48	11.0	655	88	13.4	426	56	13.1
DBP (mmHg)															
≥105	652	11	1.7	1516	12	0.8	437	6	1.4	654	3	0.5	425	3	0.7
≥30 Increase	655	5	0.8	1519	7	0.5	438	5	1.1	655	1	0.2	426	1	0.2
≤50	654	13	2.0	1517	29	1.9	438	11	2.5	654	11	1.7	425	7	1.6
≥20Decrease	655	35	5.3	1519	78	5.1	438	24	5.5	655	28	4.3	426	26	6.1

Note: Percentages in total column are calculated as n/Na x 100.
Information obtained from Sponsor Table SA132 in Clinical Study Report.

7.1.6.2.11 ECG Data

An integrated search for QT prolongation is based on both AE reports and the ECG. The criteria of cutoff for QT interval (msec) are as follows: QT interval (msec): $\geq$ 500 msec, $\leq$ 200 msec, $\geq$ 60 msec increase difference

Results of ECG tests showed only a few cases of QT prolongation in the short term (studies 9, 10 and 11), and there were no notable differences between the treatment groups. No dose relatedness observed. No AEs potentially associated with QT prolongation were reported. Also, shifts to clinically important ECG values were similar for placebo and the QTP XR groups.

Table 52: Shifts to clinically important ECG findings at any time (pooled Study 9, 10, 11)

		PLA (N=665)			ALL QTP XR (N=1569)			QTP XR 50 (N=452)			QTP XR 150 (N=673)			QTP XR 300 (N=444)		
	Cut offs	N[a]	n	%	N[a]	n	%	N[a]	n	%	N[a]	n	%	N[a]	n	%
Heart rate (bpm)	>120	553	0	0	1279	1	0.1	371	0	0	543	1	0.2	365	0	0
	<50	538	12	2.2	1246	11	0.9	365	3	0.8	527	4	0.8	354	4	1.1
	≥15 Increase	553	40	7.2	1279	156	12.2	371	25	6.7	543	63	11.6	365	68	18.6
	≥15 Decrease	553	32	5.8	1279	46	3.6	371	20	5.4	543	17	3.1	365	9	2.5
PR interval (msec)	≥210	547	3	0.5	1261	4	0.3	365	0	0	533	3	0.6	363	1	0.3
QRS interval (msec)	≥120	544	1	0.2	1269	0	0	369	0	0	539	0	0	361	0	0
	≤50	553	0	0	1279	0	0	371	0	0	543	0	0	365	0	0
QT interval (msec)	≥500	553	0	0	1279	0	0	371	0	0	543	0	0	365	0	0
	≤200	553	0	0	1279	0	0	371	0	0	543	0	0	365	0	0
	≥60 Increase	553	2	0.4	1279	5	0.4	371	2	0.5	543	1	0.2	365	2	0.5
QTc Fridericia (msec)	≥450	540	5	0.9	1261	14	1.1	369	6	1.6	534	5	0.9	358	3	0.8
	≥60 Increase	553	0	0	1279	1	0.1	371	0	0	543	0	0	365	1	0.3

a-Number of patients in treatment group at risk (ie, not fulfilling the criteria at baseline)
n Number of patients in analysis subgroup
PLA Placebo. QTP XR Quetiapine extended-release
Note: Percentages in total column are calculated as n/Na x 100
Information obtained from Sponsor Table S 40 in Clinical Study Report

Following are MedDRA terms related to safety area of QT prolongation		
LONG QT SYNDROM	ELECTROCARDIOGRAM QT PROLONGED	CARDIAC DEATH
ELECTROCARDIOGRAM QT CORREECTED INTERVAL PROLONGED	LONG QT SYNDROM CONGENTIAL	SINUS ARREST
TORSADES DE POINTES	CARDIO-RESPIRATORY ARREST	ELECTROMECHANICAL DISOCIATION
		CARDIAC ARREST

7.1.7 Special Assessment

Changes in Sexual Dysfunction Assessment based on Sexual Functioning Questionnaire (CSFQ)

An integrated search for sexual dysfunction is based on both AE reports and Changes in Sexual Functioning Questionnaire (CSFQ) total score evaluating the change from randomization to end of treatment. A pooled meta-analysis of CSFQ Data from approximately 4031 patients (GAD and MDD studies) was analyzed by the sponsor using an ANCOVA model. The pooled CSFQ results were submitted to NDA 22047 (S-14 and S-15) GAD supplement.

The CSFQ is a 36-item clinical and research instrument identifying five scales of sexual functioning. CSFQ-14, more commonly used in Day to Day clinical practice yields scores for three scales corresponding to the phases of the sexual response cycle (i.e., desire, arousal, and orgasm) as well as the five scales of the original CSFQ. The five original scales include: (a) Desire/Frequency (b) Desire/Interest (c) Arousal/Excitement (d) Orgasm/Completion (e) Pleasure. In the CSFQ-14, questions 2 through 6 relate to the desire phase, questions 7 though 9 to the arousal phase, and questions 11 through 13 to the orgasm or completion phase. CSFQ and AEs assessment was done on Day 1, Day 29 and final visit. Males and females completed separate versions of the questionnaire. Higher scores indicate higher sexual functioning or lower impairment.

The journal article "Reliability and Construct Validity of the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)" by Adrienne Keller et.al, was published in Journal of Sex

& Marital Therapy, 2006. It confirms the construct validity and internal reliability of the CSFQ-14 as a global measure of sexual dysfunction.

The CSFQ Data Source

Analyses were done within individual studies as well as across pooled studies. All the studies were multicenter, fixed dose, double-blind, randomized, parallel-group, placebo-controlled. The table below highlights treatment arms and duration of these studies.

Table 53: Studies included in CFSQ analysis

Study	Type	Treatment arms and Duration
Study 09	GAD	compared QTP XR (50, 150 and 300 mg/Day) versus placebo x 8 weeks
Study 10	GAD	compared QTP XR (150 and 300 mg/Day) versus placebo with active comparator of Escitalopram 10 mg/day x 8 weeks
Study 11	GAD	compared QTP XR (50 and 150 mg/Day) versus placebo with active comparator of Paroxetine 20 mg/Day x 8 weeks
D1448C00001	MDD	compared QTP XR (50, 150 and 300 mg/Day) versus placebo x 6 weeks
D1448C00002	MDD	compared QTP XR (150 and 300 mg/Day) versus placebo with active comparator of Duloxetine 60 mg/day x 6 weeks
D1448C00003	MDD	compared QTP XR (150 and 300 mg/Day) versus placebo x 6 weeks
D1448C00004	MDD	compared QTP XR (150 and 300 mg/Day) versus placebo with active comparator of Escitalopram at 10 and 20 mg/day

CSFQ Data Results

The sponsor claims that non-inferiority to placebo is demonstrated since the lower limit of the confidence interval when pooling Studies 09, 10 and 11, is -0.54 and is larger than -0.75 (non-inferiority margin set by FDA).

Studies that had an active treatment arm such as studies 10 and 11 (GAD), studies 02 and 04 (MDD) and when studies 04 and 10 (ESC groups) are combined, the results of the active treatment group's CSFQ was not significantly different from placebo [i.e. not statistically significant at two-sided level $\alpha=0.05$]. This suggests that either both active controls are similar to placebo for this endpoint or that there was no assay sensitivity to compare arms within any study. See table below

Table 54: Analysis of CSFQ data (as conducted by Dr. Lawrence):

Study or Studies	Treatment group	N (Trt)	N (Pla)	LS Mean†	SE	95% CI LS Mean ± SE
02	QTP XR 150	152	157	-0.58	0.79	(-2.13, 0.97)
02	QTP XR 300	152	157	0.18	0.79	(-1.37, 1.73)
02	DUL 60	149	157	0.18	0.80	(-1.39, 1.75)
04	QTP XR	157	155	0.9	0.99	(-0.98, 2.90)
04	ESC	156	155	0.16	0.98	(-1.76, 2.08)
10	QTP XR 150	217	214	-0.24	0.67	(-1.07, 1.55)
10	QTP XR 300	206	214	-0.0	0.68	(-1.36, 1.30)
10	ESC 10	209	214	-0.62	0.67	(-1.93, 0.69)
11	QTP XR 50	220	217	0.21	0.64	(-1.04, 1.46)
11	QTP XR 150	218	217	-0.84	0.64	(-0.41, 2.09)
11	PAR 20	215	217	-0.36	0.64	(-1.61, 0.89)
04+10	ALL QTP XR	580	369	-0.63	0.51	(-0.37, 1.63)
04+10	ESC	365	369	-0.3	0.56	(-1.40, 0.80)
09+10+11	ALL QTP XR	1462	633	0.07	0.31	(-0.54, 0.68)
01+02+03+04 +09+10+11	ALL QTP XR	2482	1208	0.12	0.24	(-0.35, 0.59)

Trt – Treatment
Pla – Placebo
†Estimated placebo-subtracted LS Mean Change. Negative values suggest worsening of sexual dysfunction compared to placebo.

The incidence of AEs (anorgasmia, libido increase, libido decrease, loss of libido, premature ejaculation, vulvovaginal dryness) related to sexual dysfunction in GAD patients ranged from 1.3% (for the 50 mg/day dose) to 3.8% (for the 300 mg/day dose) for QTP XR versus 2.1% for Placebo during short-term treatment. Libido decrease was the most commonly reported AE in both genders.

7.1.8 Additional Analyses and Explorations

No additional analyses or explorations which would substantially impact on the safety profile of this drug were conducted.

7.1.9 Immunogenicity

No immunogenicity studies were performed.

7.1.10 Human Carcinogenicity

No carcinogenicity study data was submitted with this application.

7.1.11 Special Safety Studies

There was no special safety studies conducted.

7.1.12 Withdrawal Phenomena and/or Abuse Potential.

Signs and symptoms associated with treatment discontinuation were analyzed over a 2-week post-treatment period by recording the incidence of AEs and administering the Treatment Discontinuation Signs and Symptoms (TDSS) scale. During the first week following

Randomized treatment in Studies 9, 10, and 11, patients returned to the study site and could report spontaneous AEs and take the TDSS, which posed specific questions about discontinuation symptoms. Most common abrupt treatment discontinuation AE seen during that time were insomnia, nausea, headache, vomiting, and diarrhea during the first week post-treatment. However, after the first week, these symptoms resolved. The sponsor referred to the supplemental NDA for MDD submitted in February 2008 regarding the safety summary data for this section for withdrawal, as they proposed to add labeling language in Warnings and Precautions, section 5.20, Withdrawal, in that submission.

There were no reports of abuse of QTP XR in the conducted studies.

7.1.13 Human Reproduction and Pregnancy Data

The inclusion criteria required female patients to have a negative serum pregnancy test at enrollment and to be willing to use a reliable method of birth control during the study.

There were 8 pregnancies reported during the short-term studies, 3 in the placebo group, 3 in the QTP XR 50 mg group and 1 in each of the QTP XR 150 mg and 300 mg QTP XR groups. None of these events were considered an AE. Of these 8 pregnancies, 2 resulted in a healthy birth, 3 were ended through elective termination. The outcome of the other 3 pregnancies is unknown due to incomplete information or the patient being lost to follow-up.

In the maintenance study a total of 4 pregnancies were reported, 2 after the start of the open-label run in period and 2 during stabilization period (1 of whom discontinued 5 days after starting the randomized treatment period). One of the pregnancies resulted in a healthy full–term baby, 2 resulted in elective termination, and 1 pregnancy outcome is unknown.

7.1.14 Assessment of Effect on Growth

The effect of QTP XR on growth was not assessed in these trials, which were conducted in adult patients.

7.1.15 Overdose Experience

The QTP XR development program for the treatment of GAD defined overdose as any dose taken that exceeded the number of tablets prescribed for that day, or for unblinded data, a QTP XR dose greater than 800 mg/day. Investigators were instructed not to report overdose as an adverse event unless there were associated symptoms or signs.

Short-term studies (studies 9, 10 and 11)

In the short-term studies there were 66 reports of overdose and no deaths. No overdose was judged as "suicidal intent" as per Columbia-type classifications system, majority of them involved the patient taking a small number of additional tablets.

There were 2 SAEs in patients who took concomitant medications. Patient E3405720, a 26 year old who took intentional overdose after an argument with a boyfriend. This overdose was classified as a suicide attempt according to the Columbia-type classification system. The subject was hospitalized and received a gastric lavage. Patient E6204707, a 42 year old female, prior to randomization had a severe anxiety crisis and took several doses of clonazepam with the intention to control her anxiety. Patient was hospitalized. This patient failed screening and did not receive the study drug.

Table 55: Overdoses in the short term studies (studies 9, 10 and 11)

	PLA (N=667)	QTP XR total (N=1581)	ESC (N=209)	PAR (N=215)	Concomitant Medication
Overdose	17 (2.5%)	40 (2.5%)	5 (2.4%)	2 (0.9%)	2

Information obtained from Sponsor Table 2 in Clinical Study Report.

Maintenance study (study 12)

In the maintenance study there were 31 reports of overdose. The majority of these overdoses (28 out of 31) occurred while the patient was in the open label phase of the study during which time all patients were administered QTP XR. Three overdoses were reported during the randomized phase of the study, two of which were in the placebo group and one in the QTP XR group. No patient who took an overdose of QTP XR died as a result of his or her overdose. There was a single serious adverse event that was associated with overdose. Patient E1210619, a 64-year-old Caucasian male took an intentional overdose of an unknown amount of QTP XR during the open label phase of the study. The patient was admitted to hospital, the event was not considered related to treatment by the investigator and the subject was withdrawn from the trial.

7.1.16 Postmarketing Experience

QTP IR is approved for the treatment of schizophrenia, for mania, and for bipolar depression in many countries. QTP IR is currently the only atypical antipsychotic approved by the FDA for both mania and bipolar depression. QTP XR is approved for schizophrenia. QTP XR is under review for bipolar and major depressive disorder indications. QTP IR or QTP XR is not approved in any country for the indication of GAD.

Sponsor's "post marketing data search" results

Post-marketing data for QTP IR and QTP XR have been submitted as Periodic Safety Update Reports (PSURs) to all relevant regulatory authorities. All relevant safety issues from PSUR covering the report period of 1/8/2006 – 31/7/2007 were taken into consideration for this submission. The referenced PSUR was submitted to the FDA on 04/10/ 2007. A thorough search of the scientific/medical literature (from 1/8/2006 – 31/7/2007) for quetiapine was performed for the PSUR. Following a comprehensive review of the AE reports in the PSUR line listing and the scientific/medical literature received during the reporting period, no new

significant safety issues bearing on the established overall safety profile of quetiapine were identified.
Patient-years of quetiapine use have been calculated from the number of tablets delivered to wholesalers worldwide during the PSUR period. A daily dose of 300 to 450 mg/patient/Day has been assumed based upon a 1-year exposure. There have been an estimated 2,035,069 to 1,356,713 patient-years (respectively) of quetiapine use during this reporting period, based on those average daily doses.

It has been estimated that about 22.8 million patients worldwide have been exposed to quetiapine IR and XR since launch through the end of February 2008. This estimate is based upon:

1. Assumptions as to the number of prescriptions per patient, based upon 2007 United States market research.
2. Projections of prescriptions since launch based upon information available in the US (dispensed prescriptions from retail, long-term-care and mail order) and 12 other countries (Australia, Belgium, Canada, Egypt, Germany, Italy, Japan, Netherlands, Saudi Arabia, Spain, & UK; written prescriptions from office based physicians) in which QTP IR and XR is marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study Type and Design/Patient Enumeration

Study design and description for all QTP XR studies reviewed for GAD is as follows.

Table 56: Summary of All QTP XR Studies

Completed Short Term Studies	
Study 09	Multicenter (63 USA), double-blind, randomized, parallel-group, placebo-controlled; 2-week post-treatment follow-up period; Evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms with HAM-A total score changes observed from baseline to day 57 in patients with GAD (DSM-IV-TR); QTP XR 50 mg/Day (n=219) QTP XR 150 mg/Day (n=226), QTP XR 300 mg/Day (n=224), Placebo (n=225).
Study 10	Multicenter (64 USA), double-blind, randomized, parallel-group, placebo-controlled, active-controlled (escitalopram); 2-week post-treatment follow-up period; Evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms with HAM-A score changes observed from baseline to day 57 in patients with GAD (DSM-IV-TR); QTP XR 150 mg/Day (n=212), QTP XR 300 mg/Day (n=201), Placebo (n=203), Escitalopram 10 mg/Day (n=212).
Study 11	Multicenter (113 centers in Europe, North America, South Africa, and South America), double-blind, randomized, parallel-group, placebo-controlled, active-controlled (paroxetine); 2-week post-treatment follow-up period; Evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms with HAM-A score changes observed from baseline to day 57 in patients with GAD (DSM-IV-TR) QTP XR 50 mg/Day (n=212), QTP XR 150 mg/Day (n=201), Placebo (n=203), Paroxetine 20 mg/Day (n=212).
Completed Maintenance study	

Study 12	International (128 centers in Asia, Australia, Europe, and North America), multicenter, double-blind, parallel-group, placebo-controlled, randomized withdrawal with open label run-in and stabilization periods; Evaluate the efficacy of QTP XR compared to placebo in decreasing the risk of recurrence of anxiety symptoms in patients with GAD (DSM-IV-TR); 4-8 weeks of open-label run-in treatment with QTP XR; 12-18 weeks of open label stabilization treatment with QTP XR; up to 52 weeks of double-blind treatment with QTP XR or placebo with N = 216 patients each group; Flexible dosing of QTP XR 50 mg/Day, 150 mg/Day, 300 mg/Day, or Placebo.
Four month safety update studies	
Study 15	11-week clinical studies of QTP XR in the treatment of elderly patients with GAD "A Multicenter, Double-blind, Randomized, Parallel Group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release as Mono-therapy in the Treatment of Elderly Patients with GAD".
Study 16	An adjunct therapy study entitled "A Multicenter, Randomized, Double-blind, Parallel-group, Placebo controlled Study of t Efficacy and Safety of QTP XR Compared with Placebo as an Adjunct to Treatment in Patients with GAD who Demonstra or No Response to a SSRI or S-NRI SNRI Alone or in Combination with a Benzodiazepine".

7.2.1.2 Demographics

Demography of the patients from studies 9, 10, 11 and 12 are discussed in section 6.1.3.

Table 57: Safety analysis set derivation (pooled Studies 9, 10, 11; all randomized patients)

	PLA		ALL QTP XR		QTP XR 50		QTP XR 150		QTP XR 300	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total randomized	667	100.0	1581	100.0	455	100.0	678	100.0	448	100.0
Excluded from safety analysis set[a]	2	0.3	12	0.8	3	0.7	5	0.7	4	0.9
Safety analysis set	665	99.7	1569	99.2	452	99.3	673	99.3	444	99.1
TDSS analysis set[b]	416	62.4	873	55.2	263	57.8	385	56.8	225	50.2

Information obtained from Sponsor Table S 5 in Clinical Study Report.

Demography of study 15 shows that out of 448 patients included, 316 (70.5%) were women and 132 (29.5%) were men. All patients in the study were Caucasian and all sites were either European or North American (accounting for 80.4% and 19.6% of patients, respectively). Patient ages ranged from 65 to 87 years (1 patient was 65 [E5808507], despite the inclusion criteria's minimum age of 66), with a mean of 70.4 years. The treatment groups were similar with respect to mean age, and the majority of patients (87.1%) in the study were 75 years of age or younger, while 12.9% of patients were older than 75.

Study 16 was conducted in patients 18 to 65 years of age in the US. Demographic characteristics, no further details were available.

7.2.1.3 Extent of exposure (Dose/Duration)

Short term pooled studies (studies 09, 10, and 11)

The mean exposure (as determined by days on randomized treatment) in the QTP XR 300 mg group was slightly lower than in the QTP XR 50 mg and 150 mg and placebo groups. Median exposure times were the same across all groups. The total number of mean/median days on randomized treatment (does not include withdrawal period) is as follows.

- All QTP XR (N=1569): 44.0 /56
- QTP XR 300 mg (N=444): 40.3 / 55
- QTP XR 150 mg (N=673): 45.2 / 56
- QTP XR 50 mg (N=452): 46.0 / 56
- Placebo (N=665): 48.2 / 56

The total number of patient exposure years (PEY's) (includes withdrawal period) for each treatment is as follows.

- All QTP XR = 196.7 patient-years.
- QTP XR 300 mg= 51.7 patient-years.
- QTP XR 150 mg = 86.0 patient-years.
- QTP XR 50 mg= 59.9 patient-years.
- Placebo = 90.9 patient-years.

Note that total exposure to study drug was higher in the QTP XR 150 mg treatment group than in the 50 mg and 300 mg groups due to the inclusion of this dose in a greater number of studies.

Maintenance study (study 12)

The data showed total exposure to QTP XR during the combined open-label treatment and randomized treatment phases was 349 patient-years. Among the 216 patients in the QTP XR randomized safety analysis set, 107 (49.5%) were exposed to QTP XR for > 12 to ≤ 16 weeks after randomization and 34 (15.7%) were exposed to QTP XR for >28 to ≤32 weeks after randomization.

In study 12, 1224 patients with GAD received study drug during the open-label phase with a flexible dose of 50 mg, 150 mg, or 300 mg/day of QTP XR (mean duration of exposure, 85.5 days; mean of individual patients' median doses, 143 mg/day). There was minimal change in the distributions of QTP XR dose at the end of open-label run-in treatment and the end of the stabilization phase. The mean period of stability was 14.7 weeks for patients subsequently randomized to the QTP XR group and 15.9 weeks for patients subsequently randomized to in the placebo group.

Of the 433 patients assigned to randomized treatment groups, all received randomized

treatment with the exception of 1 patient in the placebo group. For patients randomized to the QTP XR treatment group, the distribution of doses at the end of the open-label treatment Phase was 26.4% for the 50 mg dose group, 49.1% for the 150 mg dose group, and 24.5% for the 300 mg dose group. The distribution of doses from the last open-label dose to the last randomized dose was similar, and nearly all patients (93%) finished on their starting dose of QTP XR after a mean duration of 15 weeks of randomized treatment.

Table 58: Summary of treatment exposure in study 12 Open-label safety analysis set

			ACTUAL TREATMENT GROUP			
	Treatment phase	Statistic	PLA (N=216)	QTP XR (N=216)	ONLY OL QTP XR (N=792)	Total (N=1224)
DAILY DOSE AT END OF PHASE (mg)	Open-label run-in phase	N	216	216	792	1224
		Mean(SD)	164.4(102.9)	160.2(84.2)	139.8(93.4)	147.7(94.1)
		Median	150	150	150	150
		Min to max	50 to 900	50 to 300	0 to 900	0 to 900
		Total	35500	34600	110725	180825
	Open-label stability phase	N	216	216	415	847
		Mean(SD)	162.7(95.9)	160.4(89.9)	153.7(105.8)	157.7(99.4)
		Median	150	150	150	150
		Min to max	50 to 300	50 to 300	0 to 1250	0 to 1250
		Total	35150	34650	63775	133575
	Entire open-label phase	N	216	216	792	1224
		Mean(SD)	162.7(95.9)	160.4(89.9)	138.3(100.0)	146.5(98.2)
		Median	150	150	150	150
		Min to max	50 to 300	50 to 300	0 to 1250	0 to 1250
		Total	35150	34650	109550	179350
	Randomized phase	N	216	216		432
		Mean(SD)	169.2(96.9)	160.2(89.1)		164.7(93.1)
		Median	150	150		150
		Min to max	50 to 300	50 to 300		50 to 300
		Total	36550	34600		71150
	Entire study	N	216	216	792	1224
		Mean(SD)	169.2(96.9)	160.2(89.1)	138.3(100.0)	147.6(98.4)
		Median	150	150	150	150
		Min to max	50 to 300	50 to 300	0 to 1250	0 to 1250
		Total	36550	34600	109550	180700
MEAN DAILY DOSE (mg)	Open-label run-in phase	N	216	216	792	1224
		Mean(SD)	149.8(72.4)	144.9(63.0)	128.8(67.2)	135.3(68.0)
		Median	143	143	136	143
		Min to max	50 to 531	50 to 286	20 to 330	20 to 531
		Total	32352	31298	102004	165654

Table extracted from Sponsor Table 11.3.1.1 in Clinical Study Report

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other Studies

There were no other known studies conducted with QTP XR.

7.2.2.2 Literature

The Sponsor included a literature review that contained the title, authors and abstract of published articles that mentioned QTP XR. The Sponsor did not provide any discussion of how the articles were identified or if, upon review, any new safety signal was identified for QTP XR.

7.2.3 Adequacy of Overall Clinical Experience

In my opinion, the submitted safety and efficacy data are sufficient to render a judgement regarding the approvability of this application.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was deemed necessary for this product.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing conducted in the development program for QTP XR is felt to be adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new pharmacokinetic data or interaction studies were conducted to support this application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor's evaluation for potential adverse events in this submission is inadequate for long-term risks for use of QTP XR for this new indication in terms of metabolic profile and TD.

7.2.8 Assessment of Quality and Completeness of Data

I conducted two formal audits as follows:

1. Examination of the accuracy and completeness of adverse event information in narrative summaries and case report tabulations relative to information contained in the corresponding Case Report Forms (CRF's).
2. Evaluation of the acceptability of the adverse coding from verbatim (investigator) terms to MedDRA preferred terms

The CRF audit compared the adverse event information in CRF's, narratives, and case report tabulations (.xpt files) for about 2.5% of 649 patients for whom CRF's were submitted with the original application

Table 59: Adverse Event audit list

Study/Center/Patient ID	CRF AE's	Narrative Summary	JMP AE Listing
Study 09/1004/e1004711	AM sedation, increased appetite, vivid dreams, irritability, diffuse paraesthesia, tingling, akathisia	OK	OK
Study 09/1033/e1033709	Sedation	OK	OK
Study 09/1074/e1074715	Dry mouth, dizziness, fatigue, somnolence, headache, blurry vision, loss of consciousness, drowsiness	OK	OK
Study 10/1024/e1024813	Sedation, dry mouth, headache, irritability	OK	OK
Study 10/1043/e1043803	Light headedness, irritable, sedation	OK	OK
Study 10/1057/e1057820	Insomnia, nausea	OK	OK
Study 11/3405/e3405720	Dry mouth , common cold, suicide attempt	OK	OK
Study 11/3720/e3720705	Diarrhea, tinnitus, panic attack, vomiting, dizziness	OK	OK
Study 11/5111/e5111712	Fatigue, Cold Feet, Paraesthesia	OK	OK
Study 12/1018/e1018602	Dizziness, daytime sedation, constipation	OK	OK
Study 12/1032/e1032604	Daytime drowsiness, sebaceous cyst in breast	OK	OK
Study 12/1075/e1075624	Dry mouth, constipation, nasal congestion	OK	OK
Study 12/1210/e1210619	Suicide attempt, dry mouth, increased appetite, somnolence, weight gain, severe depression, intentional drug overdose	OK	OK
Study 12/3006/e3006607	Lethargy, sedation, somnolence	OK	OK
Study 12/2002/e2002601	Worsening of headache, nasal congestion, somnolence	OK	OK

This audit revealed no inconsistency of adverse event information across these four sources of adverse event data.

The acceptability of the adverse event coding, which was performed by the sponsor, was assessed by comparing each verbatim term to the corresponding preferred term (and vice-versa) for the three acute studies (09, 10 and 11) and one maintenance study (12), utilizing the adverse event line listing (.xpt file) for each study. This audit did not reveal any significant deficiencies.

7.2.9 Additional Submissions, Including Safety Update

Safety analyses from the sponsor of studies 15 and 16 were submitted as part of the Four-Month Safety Update on 9-4-08. Findings with respect to deaths, and non-fatal serious adverse event, have been incorporated into section 7 of this review.

7.2 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and conclusions

The clinical review of the safety database for the QTP XR development program revealed no findings which were attributable to quetiapine treatment and inconsistent with the previously observed safety profile for quetiapine.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled Data vs. Individual Study Data

The primary source of safety data (safety analyses, deaths and other serious adverse events) was the review of the three pooled placebo-controlled studies (09, 10, and 11). All three studies were eight-week, randomized, double-blind, fixed dose comparisons of the safety and efficacy of QTP XR and placebo in patients with GAD. Studies 10 and 11 had employed active controls of ecitalopram 10 mg in study 10 and paroxetine in study 11.

7.1.1.2 Combining Data

For analysis of the CSFQ data, the GAD (short term studies 9, 10 and 11) and MDD (Short-term monotherapy Studies D1448C00001, D1448C00002, D1448C00003, and D1448C00004) were combined and reviewed collectively. The dose range used for both indications above has been 50 to 300 mg/Day of QTP XR.

7.4.1.3 Explorations for Predictive Factors

7.4.2 Explorations for Dose Dependency for Adverse Findings

Dose-Dependency of Adverse Events of the patients of studies 9, 10, and 11 are discussed in section (7.1.5.6.1).

7.4.2.1 Explorations for Time Dependency for Adverse Findings

Time-Dependency of Adverse Events was not systematically evaluated.

7.4.2.2 Explorations for Drug-Demographic Interactions

Drug-demographic interactions with Adverse Events of patients in studies 9, 10, 11 and 12 are discussed in section 7.1.5.6.4.

7.4.2.3 Explorations for Drug-Disease Interactions

Drug-disease interactions were not specifically studied in the QTP XR trials.

7.4.2.4 Explorations for Drug-Drug Interactions

No drug-drug interaction studies were conducted.

7.4.3 Causality Determination

Causality of common adverse events in this safety database was judged based on a comparison with the corresponding placebo incidence: an incidence among drug-treated patients at least twice the placebo incidence is the generally accepted criterion for a causal relationship.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimens are consistent with the pivotal trials supporting efficacy.

8.2 Drug-Drug Interactions

No drug interaction data was included in this submission.

8.3 Special Populations

Dosing in elderly patients and patients with hepatic impairment require lower starting doses of QTP XR as stated in the approved label. In this submission, no new special population studies (other than 4MSU data) were included.

8.4 Pediatrics

The Sponsor has asked for a waiver to study children under 12 years of age and a deferral for adolescents 12-18 years of age.

A Pediatric Review Committee (PeRC) meeting will be scheduled to review the pediatric deferrals, waivers and plans for clinical trials for pediatric GAD populations with QTP XR. Currently, no written requests have been initiated for pediatric trials in GAD populations for QTP XR.

Although the Sponsor has previously expressed their intention to propose a clinical trial with QTP XR to study GAD in adolescent patients, the Sponsor has not submitted any protocols at this time.

8.5 Advisory Committee Meeting

The Division has decided to discuss this set of NDA supplements for GAD along with data submitted in the NDA for MDD. Further discussion of safety risks (metabolic changes and TD) associated with longer-term use of QTP XR in non-psychotic patient population will be taken place at the Psychiatric Drug Advisory Committee meeting scheduled in April 2009.

8.6 Literature Review

The Sponsor included a literature review that contained the title, authors and abstract of published articles that mentioned QTP XR. The Sponsor did not provide any discussion of how the articles were identified or if, upon review, any new safety signal (primarily safety) was identified for QTP XR.

8.7 Postmarketing Risk Management Plan

No risk management plan was submitted.

9 LABELING REVIEW

Comments regarding GAD labeling changes are being made to the Sponsor's proposed labeling via track changes and forwarded as a separate document to the Team Leader for further editing. A summary of my recommendations is provided below.

Highlights / Indications and Usage / Generalized Anxiety Disorder

- Sponsor's proposal should be modified as treatment of generalized anxiety disorder without the statement "including maintenance of antianxiety effect".
- Sponsor should reorder indications in accordance to date of approval.

Highlights / Dosage and Administration / Generalized Anxiety Disorder

- Sponsor's proposed initial dosing is acceptable.
- Sponsor's proposed dosing range should be changed to 50 to 150 mg/Day.

INDICATIONS AND USAGE (1) / Generalized Anxiety Disorder (1.1)

- Sponsor should reorder GAD indication in accordance to date of approval.
- Sponsor's proposal to include "up to 52 weeks" in the long-term treatment paragraph should be deleted.

- *DOSAGE AND ADMINISTRATION (2) / Generalized Anxiety Disorder (2.2)*

- Proposed dosing range should be changed to 50 to 150 mg/Day.
- Add a statement that no additional benefits were conferred in the 300 mg dose.

WARNINGS AND PRECAUTIONS (5) / Orthostatic Hypotension (5.5) / Seizures (5.9) / Hypothyroidism (5.10) / Cholesterol and Triglycerides Elevations (5.11) / Transaminase Elevations (5.13) / Potential for Cognitive and Motor Impairment (5.14) / Suicide (5.18)

- Sponsor's proposed updated numbers in these sections with regards to short-term placebo controlled GAD trials are acceptable.
- Delete data derived from maintenance study.

ADVERSE REACTION (6) / Clinical Studies Experience (6.1) / Adverse Reactions Associated With Discontinuations of Treatment in Short-Term, Placebo-controlled Trails (6.1) / Adverse Reactions Occurring at an Incidence of 5% or More Among Seroquel XR Treated Patients in Long-Term, Placebo Controlled Trial (6.1) / Extrapyramidal Symptoms (6.1) / Weight Gain (6.2) / ECG changes (6.2)

- Sponsor's proposed updated numbers with regards to total number of patients exposed to QTP XR and the number of patient's years rates are acceptable.
- Sponsor's proposed updated numbers with regards to incidence of EPS, weight gain, and ECG changes in GAD trials are acceptable.
- Sponsor's proposal to include CSFQ data related to sexual dysfunction should be deleted as there is no evidence of assay sensitivity.
- Sponsor's proposal to include data related to long-term maintenance study should be deleted.

CLINICAL STUDIES (14) / Generalized Anxiety Disorder (14.1) / Short-Term Monotherapy (14.1) / Maintenance (14.1)

- Sponsor's proposal to include content related to time of onset, QLES-Q, MADRS should be deleted.
- Sponsor's proposal to include "up to 52 weeks" in the maintenance treatment paragraph should be deleted.
- In the clinical study description, add a statement that although the 300 mg dose was found to be efficacious, no additional benefit was conferred at this higher dose.
- Should modify language to include the mean stabilization duration of 15.3 weeks during the open label stabilization phase.

10 COMMENTS TO THE SPONSOR

This supplemental new drug application (NDA) is intended to support claims for efficacy and safety for GAD.

The following issues should be conveyed to the sponsor in our complete response letter:

1. Inadequate Information Regarding Longer-Term Risks for the Treatment of GAD

Although clinical efficacy has been demonstrated for QTP XR in the treatment of GAD, the sponsor should address the longer term safety risks of using this atypical antipsychotic drug in the GAD population. Specifically, metabolic risks (hyperglycemia/diabetes, hyperlipidemia, and weight gain) and any risk for tardive dyskinesia should be addressed.

Since there are multiple effective therapies approved for the treatment of GAD that do not have the same longer term safety risks, the sponsor should provide any data to support the use of QTP XR for the treatment of GAD addressing these longer-term risks (data from observational databases, post-marketing data, and literature data elucidating these longer-term metabolic effects and any risk of Tardive Dyskinesia associated with QTP XR treatment).

2. Labeling

Draft labeling that incorporates revisions in the proposed labeling should be attached.

3. Safety Update

The sponsor should include a safety update including data from all nonclinical and clinical Studies/trials of QTP XR regardless of indication, dosage form, or dose level. They should describe in detail any significant changes or findings in the safety profile in non-psychotic patient population.

11 APPENDIX

11.1 Other Secondary Efficacy Variable Results

11.1.1 Study 09

1. HAM-A total score at Week 1

HAM-A total scores at Week 1 for QTP XR 50 mg/Day, 150 mg/Day, and 300 mg/Day were statistically superior compared with Placebo.

Appendix Table 1: HAM-A total score change from randomization to Week 1 in Study 09 - LOCF, MITT analysis

		Baseline	Endpoint	LS Mean Change*	LS Mean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	212	25.1(4.1)	19.6(6.2)	-5.94	-	-
QTP XR 50 mg/Day	207	24.5(3.8)	17.7(6.1)	-7.47	-1.53	0.001
QTP XR 150 mg/Day	218	24.5(3.3)	17.0(5.7)	-8.19	-2.25	<0.001
QTP XR 300 mg/Day	207	24.4(3.3)	18.1(5.9)	-7.23	-1.29	0.006

Information obtained from Sponsor Table 22 in Clinical Study Report

* = LS mean change from randomization

2. CGI-S (Severity) total score

QTP XR 150 mg/Day (but not 50 mg/Day or 300 mg/Day) reached statistical significance
compared with placebo for the change in the CGI-S score at endpoint.

Appendix Table 2: CGI-S total score at endpoint in Study 09 - LOCF, MITT

		Baseline	Endpoint	LSMean Change *	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean (SD)			
Placebo	225	4.3(0.5)	2.9(1.3)	-1.44	-	-
QTP XR 50 mg/Day	219	4.3(0.5)	2.7(1.2)	-1.62	-0.18	0.105
QTP XR 150 mg/Day	226	4.4(0.6)	2.6(1.1)	-1.70	-0.26	0.016
QTP XR 300 mg/Day	224	4.4(0.6)	2.9(1.2)	-1.45	-0.01	0.956

Information obtained from Sponsor Table 27 in Clinical Study Report

* = LS mean change from randomization

3. CGI-I (improved) total score

QTP XR doses of 50 mg/Day and 150 mg/Day (but not 300 mg/Day) were significantly superior to placebo for the proportion of patients with a CGI-I score of “Much/very much improved” at endpoint.

Appendix Table 3: Percentage of patients with CGI-I "much/very much improved" total score at endpoint

	N	(%) with "much/very much improved" score	LSMean Change*	P-value vs. Placebo
Placebo	128	56.89%	56.9	-
QTP XR 50 mg/Day	145	66.21%	66.2	0.045
QTP XR 150 mg/Day	152	67.26%	67.3	0.023
QTP XR 300 mg/Day	130	58.04%	58.0	0.791

Information obtained from Sponsor Table 28 in Clinical Study Report
* = LS mean change from randomization

4. PSQI

QTP XR 50 mg/Day, 150 mg/Day, and 300 mg/Day experienced statistically significant improvements in sleep symptoms, as assessed by the change in the PSQI global score from randomization to endpoint, compared with patients treated with Placebo.

Appendix Table 4: PSQI at endpoint in Study 09 - LOCF, MITT

		Baseline	Endpoint	LSMean Change*	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	199	11.2 (3.6)	7.6 (3.7)	-3.31	-	-
QTP XR 50 mg/Day	201	10.2 (3.7)	6.5 (3.5)	-4.07	-0.76	p=0.024
QTP XR 150 mg/Day	205	11.2 (3.9)	6.5 (3.5)	-4.38	-1.06	p=0.001
QTP XR 300 mg/Day	200	10.9 (3..7)	6.8 (3.5)	-3.97	-0.66	p=0.048

Information obtained from Sponsor Table 33 in Clinical Study Report
* = LS mean change from randomization

5. MADRS total score

QTP XR doses of 50 mg/Day and 150 mg/Day (but not 300 mg/Day) experienced significantly greater reductions in the level of depressive symptoms, as assessed by the change in the MADRS total score from randomization to endpoint, compared with patients treated with Placebo.

11.1.2 Study 10

1. HAM-A Total Score at Day 4

QTP XR 150 mg/Day and 300 mg/Day groups showed significantly better results than placebo patients, as demonstrated by the mean change from randomization to Day 4 in HAM-A total score (QTP XR 150 mg/Day and 300 mg/day Vs. placebo: $p \leq 0.050$). Escitalopram 10 mg/Day was not significantly better than placebo at Day 4.

Appendix Table 5: HAM-A total score change from randomization to Day 4 in Study 10 - LOCF, MITT analysis

		Baseline	Endpoint	LSMean Change*	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	176	25.3 (4.3)	20.6 (6.6)	-4.5	-	-
QTP XR 150 mg/Day	170	25.0 (4.3)	18.3 (6.7)	-6.7	-2.21	<0.001
QTP XR 300 mg/Day	159	25.2 (3.9)	18.9 (6.0)	-6.3	-1.85	<0.001
ESC 10 mg/Day	164	24.6 (4.0)	20.2 (5.8)	-4.5	-0.08	0.889

Information obtained from Sponsor Table 21 in Clinical Study Report
* = LS mean change from randomization

2. CGI-S (Severity) total score

QTP XR 150 mg/Day (but not 300 mg/Day) was significantly better than placebo, as demonstrated by change from randomization to endpoint in CGI-S (QTP XR 150 mg/Day versus placebo: p≤0.050). The difference between escitalopram 10 mg/Day and placebo at Week 8 was statistically significant.

Appendix Table 6: CGI-S total score at endpoint in Study 10 - LOCF, MITT

		Baseline	Endpoint	LSMean Change *	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	211	4.4 (0.6)	3.1 (1.2)	-1.3	-	-
QTP XR 150 mg/Day	212	4.3 (0.5)	2.6 (1.2)	-1.8	-0.47	<0.001
QTP XR 300 mg/Day	201	4.4 (0.5)	2.9 (1.2)	-1.5	-0.16	0.174
ESC 10 mg/Day	203	4.3 (0.5)	2.8 (1.3)	-1.5	-0.23	0.047

Information obtained from Sponsor Table 26 in Clinical Study Report
* = LS mean change from randomization

3. CGI-I (improved) total score

The odds of being rated “much/very much improved” at endpoint were significantly greater for the QTP XR dose of 150 mg/Day, but not 300 mg/Day, than for placebo (QTP XR 150 mg/Day versus placebo: p≤0.050). There was no significant difference between escitalopram 10 mg/Day and placebo in the likelihood of patients being rated “much/very much improved”. There was also no significant difference between QTP XR

150 mg/Day or 300 mg/Day and escitalopram 10 mg/Day in the likelihood of patients being rated “much/very much improved”.

Appendix Table 7: Percentage of patients with CGI-I “much/very much improved” total score at endpoint

	N	(%) with “much/very much improved” score	P-value vs. Placebo
Placebo	211	108 (51.18)	-
QTP XR 150 mg/Day	212	138 (65.09)	0.004
QTP XR 300 mg/Day	201	115 (57.21)	0.221
ESC 10 mg/Day	203	123 (60.59)	0.059

Information obtained from Sponsor Table 27 in Clinical Study Report

4. PSQI

QTP XR 150 mg/day group, but not the 300 mg/Day group, showed significantly better results than placebo patients with regard to change from randomization to endpoint in PSQI score (QTP XR 150 mg/Day versus placebo: p≤0.050). Escitalopram 10 mg/Day was not significantly better than placebo.

Appendix Table 8: PSQI at endpoint in Study 10- LOCF, MITT

		Baseline	Endpoint	LSMean Change*	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	195	10.9 (3.7)	7.8 (3.8)	-3.1	-	-
QTP XR 150 mg/Day	194	10.8 (3.5)	5.8 (3.5)	-5.0	-1.94	<0.001
QTP XR 300 mg/Day	185	11.2 (3.5)	7.3 (3.8)	-3.8	-0.57	0.108
ESC 10 mg/Day	186	11.0 (3.4)	7.8 (3.9)	-3.0	0.08	0.810

Information obtained from Sponsor Table 32 in Clinical Study Report
* = LS mean change from randomization

11.1.3 Study 11

1. HAM-A Total Score at Day 4

QTP XR 150 mg/Day and 300 mg/Day groups showed significantly better results than placebo patients, as demonstrated by the mean change from randomization to Day 4 in HAM-A total score (QTP XR 150 mg/Day and 300 mg/day Vs. placebo: p ≤0.050). Escitalopram 10 mg/Day was not significantly better than placebo at Day 4.

Appendix Table 9: HAM-A total score change from randomization to Day 4 in Study 11 - LOCF, MITT analysis

		Baseline	Endpoint	LSMean Change*	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	176	25.3 (4.3)	20.6 (6.6)	-4.5	-	-
QTP XR 150 mg/Day	170	25.0 (4.3)	18.3 (6.7)	-6.7	-2.21	<0.001
QTP XR 300 mg/Day	159	25.2 (3.9)	18.9 (6.0)	-6.3	-1.85	<0.001
ESC 10 mg/Day	164	24.6 (4.0)	20.2 (5.8)	-4.5	-0.08	0.889

Information obtained from Sponsor Table 21 in Clinical Study Report

* = LS mean change from randomization

2. CGI-S (Severity) total score

QTP XR 50 mg/Day and 150 mg/Day were significantly better than placebo, as demonstrated by change from randomization to endpoint in CGI-S (QTP XR 150 mg/Day versus placebo p≤0.050). Paroxetine was significantly better than placebo under these conditions.

Appendix Table 10: CGI-S total score at endpoint in Study 11 - LOCF, MITT

		Baseline	Endpoint	LSMean	LSMean	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)	Change *	Difference	
Placebo	217	4.8 (0.7)	3.2 (1.4)	-1.6	-	-
QTP XR 50 mg/Day	219	4.8 (0.7)	2.9 (1.3)	-1.9	-0.32	0.008
QTP XR 150 mg/Day	206	4.8 (0.7)	2.6 (1.3)	-2.1	-0.57	<0.001
PAR 20 mg/Day	214	4.8 (0.7)	2.8 (1.4)	-2.0	-0.42	<0.001

Information obtained from Sponsor Table 26 in Clinical Study Report

* = LS mean change from randomization

3. CGI-I (improved) total score

The odds of being rated “much/very much improved” at endpoint were significantly greater for

the QTP XR dose of 150 mg/Day, but not 50 mg/Day, than for placebo (QTP XR 150 mg/Day versus placebo: p≤0.050). There was a significant difference between paroxetine 20 mg/Day and placebo in the likelihood of patients being rated “much/very much improved”. There was also no significant difference between QTP XR 50 mg/Day or 150 mg/Day and paroxetine 20 mg/Day in the likelihood of patients being rated “much/very much improved”.

Appendix Table 11: Percentage of patients with CGI-I “much/very much improved” total score at endpoint

	N	(%) with “much/very much improved” score	P-value vs. Placebo
Placebo	217	121 (55.76)	-
QTP XR 50 mg/Day	219	140 (63.93)	0.082
QTP XR 150 mg/Day	206	154 (71.30)	0.001
PAR 20 mg/Day	214	140 (65.42)	0.041

Information obtained from Sponsor Table 27 in Clinical Study Report

4. PSQI

QTP XR 150 mg/day group, but not the 300 mg/Day group, showed significantly better results than placebo patients with regard to change from randomization to endpoint in

PSQI score (QTP XR 150 mg/Day versus placebo: p≤0.050). Escitalopram 10 mg/Day was not significantly better than placebo.

Appendix Table 12: PSQI at endpoint in Study 11- LOCF, MITT

		Baseline	Endpoint	LSMean Change*	LSMean Difference	P-value vs. Placebo
	N	Mean(SD)	Mean(SD)			
Placebo	195	10.9 (3.7)	7.8 (3.8)	-3.1	-	-
QTP XR 150 mg/Day	194	10.8 (3.5)	5.8 (3.5)	-5.0	-1.94	<0.001
QTP XR 300 mg/Day	185	11.2 (3.5)	7.3 (3.8)	-3.8	-0.57	0.108
ESC 10 mg/Day	186	11.0 (3.4)	7.8 (3.9)	-3.0	0.08	0.810

Information obtained from Sponsor Table 32 in Clinical Study Report

* = LS mean change from randomization

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/s/

Kavneet-Ripi Kohli-Chhabra
1/28/2009 06:41:42 PM
MEDICAL OFFICER

Ni Aye Khin
1/30/2009 11:57:18 AM
MEDICAL OFFICER
I concur that the Division should issue a Complete Response letter for this set of NDA supplements (S-014 & 015); See memo to file for addiitonal comments.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-047/S-014 S-015
Drug Name:	Seroquel XR (quetiapine fumarate)
Indication(s):	Treatment of generalized anxiety disorder, including maintenance of anti-anxiety effect
Applicant:	AstraZeneca
Date(s):	May 6, 2008
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD-710)
Statistical Reviewer:	John Lawrence
Concurring Reviewers:	Peiling Yang
	Jim Hung
Medical Division:	Division of Psychiatry Products (HFD-130)
Clinical Team:	Kavneet-Ripi Kohli-Chhabra, Medical Reviewer
	Ni Aye Khin, Clinical Team Leader
Project Manager:	Janet Cliatt

Keywords: meta analysis, non-inferiority, active control, foreign clinical data

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Three doses studied significantly improved the HAM-A score in at least two studies. The results were not as convincing for the key secondary endpoint, change in Q-LES-Q%. For the long term study, there was a significant difference in the time to an anxiety event after the randomized withdrawal (the primary endpoint). I conclude the doses studied are effective for improving the HAM-A score and the improving the time to an anxiety event. The sponsor claims that non-inferiority to placebo is demonstrated for a safety endpoint, sexual dysfunction. I recommend that, if approved, the label not use the words "non-inferior" or "similar" to placebo since in both studies in GAD that had an active treatment arm (10 and 11) and in the two studies in MDD that had an active treatment arm (02 and 04) and when the ESC groups from studies 04 and 10 are combined, the active treatment group's CSFQ was not significantly different from placebo, suggesting that either both active controls are similar to placebo for this endpoint or that there was no assay sensitivity to compare arms within any study or when studies 04 and 10 are combined for this endpoint using this analysis. Instead, the results for sexual dysfunction should be described for all arms in the individual studies. No language in the label or advertising describing an advantage over other marketed drugs should be allowed.

1.2 Brief Overview of Clinical Studies

This clinical program included 4 completed safety and efficacy studies. Three of these (Study 9, Study 10, and Study 11) were designed to evaluate the efficacy and safety of quetiapine XR as monotherapy in the short-term treatment of generalized anxiety disorder (GAD). These 3 studies were similar and used a multicenter, double-blind, randomized, parallel-group, placebo-controlled design to compare the effects of each dose of quetiapine XR (50 mg, 150 mg, and 300 mg once daily in Study 9; 150 mg and 300 mg once daily in Study 10; and 50 mg and 150 mg once daily in Study 11) to placebo for 8 weeks in outpatients with GAD. Active controls were utilized in Study 10 (escitalopram 10 mg daily) and Study 11 (paroxetine 20 mg daily). Use of other psychotropic agents was confined to restricted use of sleep medications. Study 9 and Study 10 were conducted in the US, while Study 11 was conducted in Europe, North America, South Africa, and South America. Prior to randomization in these 3 short-term studies, there was a period of up to 28 days for washout of all psychotropic medications. After randomization, the efficacy of the study treatments with respect to symptoms of GAD was assessed at the end of Weeks 1, 2, 3, 4, 6, and 8, with an additional visit at Day 4 in Studies 10 and 11. The longer-term study, Study 12, comprised 4 periods: an enrollment/washout period of up to 28 days, an open-label run-in treatment period of 4 to 8 weeks, an open-label stabilization treatment period of 12 to 18 weeks, and a randomized withdrawal treatment period of up to 52 weeks. The quetiapine XR dose was flexible—50 mg, 150 mg, or 300 mg once daily, with 150 mg once daily suggested as the target dose. Study 12 was conducted in Asia, Australia, Europe, and North America.

1.3 Statistical Issues and Findings

For the endpoint change in the HAM-A (the primary endpoint in the three short term studies), the 50 mg/day dose was better than placebo in two studies, the 150 mg/day dose was better than placebo in three studies, and the 300 mg/day dose was better than placebo in one study. For the endpoint change in the Q-LES-Q% (the key secondary endpoint in the three short term studies), the 50 mg/day dose was not better than placebo in any study, the 150 mg/day dose was better than placebo in two out of three studies, and the 300 mg/day dose was not better than placebo in any study. The short term studies correctly handled all the multiplicity issues related to multiple doses and multiple endpoints. For the long term study, there was a significant difference in the time to an anxiety event after the randomized withdrawal (the primary endpoint).

The sponsor claims that non-inferiority to placebo is demonstrated since the lower limit of the confidence interval when pooling studies 09 + 10 + 11, i.e. $0.07 - 1.96 \times 0.31 = -0.53$, is larger than -0.75. In both studies in GAD that had an active treatment arm (10 and 11) and in the two studies in MDD that had an active treatment arm (02 and 04) and when the ESC groups from studies 04 and 10 are combined, the active treatment group's CSFQ was not significantly different from placebo, suggesting that either both active controls are similar to placebo for this endpoint or that there was no assay sensitivity to compare arms within any study or when studies 04 and 10 are combined for this endpoint using this analysis.

2. INTRODUCTION

2.1 Overview

2.1.1 Study D1448C00009

This was a 10-week, multicenter, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, Phase III study of the efficacy and safety of extended-release quetiapine fumarate (SEROQUEL XR) 50 mg/day, 150 mg/day, and 300 mg/day compared with placebo in the treatment of generalized anxiety disorder. 951 subjects were randomized in equal proportion to the four groups. 894 subjects are included in the modified intent-to-treat population (took at least 1 dose of study drug and had a randomization HAM-A assessment and at least 1 valid HAM-A assessment after randomization).

The baseline demographics of the patients studied are in Table 1. There do not appear to be any significant differences between the groups with respect to these variables. The mean age is about 40, the majority are Caucasian and female.

Table 1 Summary of demographics and other baseline data.

Demographic or baseline characteristic		PLA N=225	QTP XR 50 N=219	QTP XR 150 N=226	QTP XR 300 N=224
Demographic characteristics					
Sex: n (%)	Male	77 (34)	94 (43)	84 (37)	88 (39)
	Female	148 (66)	125 (57)	142 (63)	136 (61)
Age (years)	Mean (SD)	39.2 (11.6)	39.0 (11.7)	40.7 (11.7)	41.0 (11.9)
	Min to max	18 to 65	18 to 65	18 to 65	18 to 65
Age category (years): n (%)	18 to 39	111 (49)	118 (54)	103 (46)	100 (45)
	40 to 65	114 (51)	101 (46)	123 (54)	124 (55)
Race: n (%)	Caucasian	181 (80)	176 (80)	189 (84)	182 (81)
	Black	37 (16)	36 (16)	28 (12)	31 (14)
	Oriental	0	0	1 (0.4)	4 (1.8)
	Other	7 (3.1)	7 (3.2)	8 (3.5)	7 (3.1)
Baseline characteristics					
Weight (kg)	Mean (SD)	80.7 (18.5)	81.0 (19.7)	80.0 (19.9)	81.0 (20.3)
	Min to max	43 to 148	46 to 146	48 to 200	46 to 153
BMI (kg/m^2): n (%)	<18.5	5 (2.2)	2 (0.9)	3 (1.3)	3 (1.3)
	18.5 to <25	62 (28)	83 (38)	74 (33)	77 (34)
	25 to <30	78 (35)	62 (28)	78 (35)	68 (30)
	30 to <40	66 (29)	59 (27)	61 (27)	59 (26)
	≥40	14 (6.2)	13 (5.9)	10 (4.4)	17 (7.6)

BMI Body mass index. MITT Modified intention-to-treat. N Total number of patients in treatment group. n Number of patients in category. PLA Placebo. QTP Quetiapine. SD Standard deviation. XR Extended release.

Source: p 85 of Study Report.

The primary endpoint is the change in the HAM-A from baseline to Week 8. An important secondary variable is the change in Q-LES-Q% maximum total score from randomization to Week 8. For all efficacy measurements, the last observed value was carried forward in case of missing data. For the primary endpoint, the Bonferroni-Holm procedure was used. For the key secondary endpoint (change from baseline in Q-LES-Q % maximum total score) a fixed sequence testing procedure was used within each dose starting with the primary efficacy variable. This procedure has been demonstrated to control the overall familywise Type I error at level α.

2.1.2 Study D1448C00010

This was a 10-week, multicenter, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, Phase III study of the efficacy and safety of extended-release quetiapine fumarate (SEROQUEL XR) 150 mg/day and 300 mg/day compared with placebo and an active control (escitalopram oxalate 10 mg/day) in the treatment of generalized anxiety disorder. 854 subjects were randomized in equal proportion to the four groups. 828 subjects are included in the modified intent-to-treat population (took at

least 1 dose of study drug and had a randomization HAM-A assessment and at least 1 valid HAM-A assessment after randomization).

The baseline demographics of the patients studied are in Table 2. There do not appear to be any significant differences between the groups with respect to these variables. The mean age is about 40, the majority are Caucasian and female.

Table 2 Summary of demographics and other baseline data (MITT population).

Demographic or baseline characteristic		**PLA N=212**	**QTP XR 150 N=212**	**QTP XR 300 N=201**	**ESC 10 N=203**
Demographic characteristics					
Sex: n (%)	Male	77 (36)	69 (33)	58 (29)	70 (35)
	Female	135 (64)	143 (68)	143 (71)	133 (66)
Age (years)	Mean (SD)	36.6 (12.3)	38.2 (11.5)	39.0 (12.6)	40.4 (11.6)
	Min to max	18 to 65	19 to 64	18 to 66	20 to 64
Age category (years): n (%)	18 to 39	135 (64)	121 (57)	103 (51)	89 (44)
	40 to 65	77 (36)	91 (43)	97 (48)	114 (56)
	>65	0	0	1 (0.5)	0
Race: n (%)	Caucasian	173 (82)	172 (81)	161 (80)	160 (79)
	Black	23 (11)	27 (13)	21 (10)	30 (15)
	Oriental	2 (0.9)	1 (0.5)	4 (2.0)	1 (0.5)
	Other	14 (6.6)	12 (5.7)	15 (7.5)	12 (5.9)

Source: Table 13 of Study Report.

The primary endpoint is the change in the HAM-A from baseline to Week 8. An important secondary variable is the change in Q-LES-Q% maximum total score from randomization to Week 8. For all efficacy measurements, the last observed value was carried forward in case of missing data. For the primary endpoint, the Bonferroni-Holm procedure was used to compare each dose of the test drug to placebo. For the key secondary endpoint (change from baseline in Q-LES-Q % maximum total score) a fixed sequence testing procedure was used within each dose starting with the primary efficacy variable. This procedure has been demonstrated to control the overall familywise Type I error at level α.

2.1.3 Study D1448C00011

This was a 10-week, multicenter, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, Phase III study of the efficacy and safety of extended-release quetiapine fumarate (SEROQUEL XR) 50 mg/day and 150 mg/day compared with placebo and the active control paroxetine 20 mg/day in the treatment of generalized anxiety disorder. 873 subjects were randomized in equal proportion to the four groups. 866 subjects are included in the modified intent-to-treat population (took at least 1 dose of study drug and had a randomization HAM-A assessment and at least 1 valid HAM-A assessment after randomization).

The baseline demographics of the patients studied are in Table 3. There do not appear to be any significant differences between the groups with respect to these variables. The mean age is about 40, the majority are Caucasian and female.

Table 3 Summary of demographics and other baseline data (MITT population).

Demographic or baseline characteristic		**PLA N=217**	**QTP XR 50 N=219**	**QTP XR 150 N=216**	**PAR 20 N=214**
Demographic characteristics					
Sex: n (%)	Male	82 (38)	70 (32)	72 (33)	76 (36)
	Female	135 (62)	149 (68)	144 (67)	138 (64)
Age (years)	Mean (SD)	41.2 (12.8)	40.7 (11.6)	42.3 (12.4)	41.6 (11.8)
	Min to max	18 to 65	18 to 65	18 to 65	19 to 64
Age category (years): n (%)	18 to 39	99 (46)	102 (47)	90 (42)	99 (46)
	40 to 65	118 (54)	117 (53)	126 (58)	115 (54)
Race: n (%)	Caucasian	204 (94)	202 (93)	206 (95)	205 (96)
	Black	10 (4.6)	9 (4.1)	9 (4.2)	9 (4.2)
	Oriental	0	1 (0.5)	0	0
	Other	3 (1.4)	7 (3.2)	1 (0.5)	0
Region: n (%)	Europe	159 (73)	153 (70)	153 (71)	156 (73)
	North America	26 (12)	33 (15)	31 (14)	28 (13)
	South Africa	17 (7.8)	15 (6.8)	18 (8.3)	18 (8.4)
	South America	15 (6.9)	18 (8.2)	14 (6.5)	12 (5.6)

Source: p 83 of Study Report.

The primary endpoint is the change in the HAM-A from baseline to Week 8. An important secondary variable is the change in Q-LES-Q% maximum total score from randomization to Week 8. For all efficacy measurements, the last observed value was carried forward in case of missing data. For the primary endpoint, the Bonferroni-Holm procedure was used. For the key secondary endpoint (change from baseline in Q-LES-Q % maximum total score) a fixed sequence testing procedure was used within each dose starting with the primary efficacy variable. This procedure has been demonstrated to control the overall familywise Type I error at level α.

2.1.4 Study D1448C00012

This multicenter study had a randomized-withdrawal, parallel-group, double-blind, placebo-controlled period following open-label run-in and stabilization periods. During the open-label run-in patients received quetiapine XR 50 mg/day on Days 1 and 2, and then the dose increased to 150 mg/day on Days 3 and 4. The dose of quetiapine SR could be increased to 300 mg/day on Day 5 or thereafter, based on the clinical judgment of the investigator. Dose adjustment was permitted at any time based on the clinical judgment of the investigator. Patients with a HAM-A $\leq$12 and CGI-S score $\leq$3 after 4 weeks or 8 weeks were entered into the open-label stabilization treatment period (OLST). OLST continued for at least 12 weeks and up to 18 weeks prior to randomization. Patients meeting randomization criteria (i.e., patients who remained stable for at least 12 weeks) were allocated to a double-blind treatment to continue with blinded quetiapine XR or switch to matching placebo at the same dose as taken at the last visit of the OLST.

The baseline demographics of the patients studied are in Table 4. There do not appear to be any significant differences between the groups with respect to these variables except age (the subjects in the placebo group tended to be younger). The mean age is about 40, the majority are Caucasian and female.

Table 4 Summary of demographics and other baseline data (ITT population).

Demographic or baseline characteristic		ITT PLA (N=216)	ITT QTP XR (N=216)
Sex, n (%)	Male	79 (36.6)	71 (32.9)
	Female	137 (63.4)	145 (67.1)
Age in years[a]	Mean (SD)	41.65 (12.15)	44.78 (10.99)
	Median	42.0	46.0
	Min to max	18 to 64	21 to 65
Age distribution, n (%)[a]	18-39	95 (44.0)	68 (31.5)
	40-65	121 (56.0)	148 (68.5)
Race, n (%)	Caucasian	177 (81.9)	183 (84.7)
	Black	14 (6.5)	13 (6.0)
	Oriental	20 (9.3)	16 (7.4)
	Other	5 (2.3)	4 (1.9)
Region, n (%)	US	111 (51.4)	110 (50.9)
	North America	128 (59.3)	131 (60.6)
	Australia	12 (5.6)	5 (2.3)
	Asia	18 (8.3)	16 (7.4)
	Europe	58 (26.9)	64 (29.6)

[a] At enrollment; based on actual treatment groups for OL-only subgroup.

Source: p 94 and 95 of Study Report.

The main analysis of the time to an anxiety event was performed with a Cox proportional hazards model comparing quetiapine XR to placebo with a hazard ratio (HR) and associated 95% CI. A 2-sided Wald test of the null hypothesis of equivalent hazards was performed. If a patient discontinued from, or completed the study, without meeting the criteria for an anxiety event, the time of censoring was the date of the patient's final assessment. For the primary efficacy analysis, region was included as a stratification variable. All secondary analyses were exploratory.

2.2 Data Sources

Electronic study reports and data sets (\\cdsesub1\EVSPROD\NDA022047\0010\) and sponsor-provided tables (\\cdsesub1\EVSPROD\NDA022047\0050\)

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study D1448C00009

The primary endpoint is the change in the HAM-A from baseline to Week 8. An important secondary variable is the change in Q-LES-Q% maximum total score from randomization to Week 8. For all efficacy measurements, the last observed value was carried forward in case of missing data. Changes in HAM-A total score from randomization were analyzed with analysis of covariance (ANCOVA), with the baseline HAM-A score as covariate and including treatment as a fixed effect and center as a random effect in the model. For the primary endpoint, the Bonferroni-Holm procedure was used. For the key secondary endpoint (change from baseline in Q-LES-Q % maximum total score) a fixed sequence testing procedure was used within each dose starting with the primary efficacy variable. This procedure has been demonstrated to control the overall familywise Type I error at level α. Analysis of change from baseline to Week 8 (LOCF) in Q-LES-Q % maximum total scores tested the superiority of each dose level of quetiapine using an ANCOVA with the baseline Q-LES-Q as the covariate and including treatment as a fixed effect and center as a random effect in the model.

For the primary endpoint (change from randomization to Week 8 in the HAM-A total score), quetiapine XR 50 mg/day and 150 mg/day were statistically significantly better than placebo after adjustment for multiplicity. Quetiapine XR 300 mg/day did not show statistical significance compared to placebo after adjustment for multiplicity. For Q-LES-Q % maximum total score, none of the quetiapine XR dose groups showed a statistically significant improvement compared to placebo after adjustment for multiplicity. These results appear in Table 5.

Table 5 Analysis of primary and key secondary endpoint (D1448C00009).

Primary endpoint (change from randomization to Week 8 in the HAM-A total score)

		PLA N=225	QTP XR 50 N=219	QTP XR 150 N=226	QTP XR 300 N=224
Randomization	Mean (SD)	24.9 (4.0)	24.6 (3.8)	24.5 (3.4)	24.5 (3.4)
Week 8	Mean (SD)	13.7 (8.1)	11.3 (7.0)	11.1 (6.5)	12.7 (7.5)
Change	Mean (SD)	-11.2 (7.3)	-13.3 (7.6)	-13.5 (6.9)	-11.7 (7.2)
ANCOVA results	LS mean	-11.10	-13.31	-13.54	-11.87
	95% CI	-12.12 to -10.08	-14.34 to -12.28	-14.55 to -12.52	-12.89 to -10.85
Difference vs PLA	Est. difference		-2.21	-2.44	-0.77
	95% CI		-3.50 to -0.92	-3.72 to -1.16	-2.05 to 0.51
	p-value		<0.001	<0.001	0.240

Key Secondary Endpoint (change in Q-LES-Q % maximum total score)

Randomization	Mean (SD)	51.76 (16.14)	52.20 (14.23)	53.30 (14.89)	52.71 (15.29)
Week 8	N[a]	204	207	212	206
	Mean (SD)	63.60 (15.74)	63.10 (15.76)	64.37 (16.01)	62.29 (16.48)
Change	N[b]	204	207	212	206
	Mean (SD)	11.55 (15.49)	10.84 (15.83)	11.13 (16.28)	9.46 (16.79)
ANCOVA results	LS mean	10.96	10.36	11.11	9.27
	95% CI	8.83 to 13.10	8.25 to 12.47	9.02 to 13.21	7.16 to 11.39
Difference vs PLA	Est. difference		-0.60	0.15	-1.69
	95% CI		-3.30 to 2.10	-2.53 to 2.83	-4.39 to 1.01
	p-value		0.661	0.913	0.220

[a] Number of patients with an LOCF value at Week 8.
[b] Number of patients with a value at randomization and an LOCF value at Week 8.
Source: Study Report, Tables 18 and 19 and CI and p-values confirmed by the FDA reviewer.

Table 6 shows that in the placebo and low dose groups, about 30% of the subjects dropped out before the end of 8 weeks. 36% and 42% dropped out early in the middle and high dose groups respectively. The most common reason for dropout in the treatment groups was adverse event. "Completed study" in the last row means completed the treatment discontinuation signs and symptoms period.

Table 6 Patient disposition (D1448C00009).

	PLA	QTP XR 50	QTP XR 150	QTP XR 300
Randomized[a]	**235**	**234**	**241**	**241**
Not treated[b]	1	2	3	3
Received drug	**234 (99.6%)**	**232 (99.1%)**	**238 (98.8%)**	**238 (98.8%)**
Discontinued 8-week randomized period	70 (29.8%)	72 (30.8)	87 (36.1%)	102 (42.3%)
Adverse event	15 (6.4%)	36 (15.4%)	41 (17.0%)	58 (24.1%)
Condition under investigation worsened	1 (0.4%)	0	1 (0.4%)	0
Development of study-specific discontinuation criteria	3 (1.3%)	2 (0.9%)	2 (0.8%)	1 (0.4%)
Eligibility criteria not fulfilled	2 (0.9%)	0	1 (0.4%)	1 (0.4%)
Severe non-compliance to the CSP	6 (2.6%)	1 (0.4%)	4 (1.7%)	1 (0.4%)
Patient lost to follow-up	21 (8.9%)	16 (6.8%)	18 (7.5%)	18 (7.5%)
Patient not willing to continue study	21 (8.9%)	16 (6.8%)	19 (7.9%)	22 (9.1%)
Other	1 (0.4)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Completed 8-week randomized treatment period	**165 (70.2%)**	**162(69.2%)**	**154 (63.9%)**	**139 (57.7%)**
Completed study[c]	**128 (54.5%)**	**119 (50.9%)**	**117 (48.5%)**	**104 (43.2%)**

[a] One patient (Patient 613, E1032705) was randomized into the placebo group from MDD study D1448C00001. This patient was included in the safety analysis set but excluded from the MITT, PP, and TDSS analysis sets.

[b] Patients not treated are also counted as discontinued from the 8-week randomized treatment period.

[c] Including TDSS period.

Source: Figure 2 of Study report..

3.1.2 Study D1448C00010

The primary endpoint is the change in the HAM-A from baseline to Week 8. An important secondary variable is the change in Q-LES-Q% maximum total score from randomization to Week 8. For all efficacy measurements, the last observed value was carried forward in case of missing data. Changes in HAM-A total score from randomization were analyzed with analysis of covariance (ANCOVA), with the baseline HAM-A score as covariate and including treatment as a fixed effect and center as a random effect in the model. For the primary endpoint, the Bonferroni-Holm procedure was used. For the key secondary endpoint (change from baseline in Q-LES-Q % maximum total score) a fixed sequence testing procedure was used within each dose starting with the primary efficacy variable. This procedure has been demonstrated to control the overall familywise Type I error at level α. Analysis of change from baseline to Week 8 (LOCF) in Q-LES-Q % maximum total scores tested the superiority of each

dose level of quetiapine using an ANCOVA with the baseline Q-LES-Q as the covariate and including treatment as a fixed effect and center as a random effect in the model.

Table 7 Analysis of primary and key secondary endpoint (D1448C00010).

Primary endpoint (change from randomization to Week 8 in the HAM-A total score)

		PLA N=212	QTP XR 150 N=212	QTP XR 300 N=201	ESC 10 N=203
Randomization	Mean (SD)	25.3 (4.3)	25.0 (4.3)	25.2 (3.9)	24.6 (4.0)
Week 8	Mean (SD)	14.2 (8.3)	11.0 (7.5)	12.6 (7.2)	12.4 (7.7)
Change	Mean (SD)	-11.0 (8.4)	-14.0 (8.1)	-12.6 (7.4)	-12.2 (8.0)
ANCOVA results	LS mean	-10.72	-13.92	-12.32	-12.27
	95% CI	-11.89 to -9.55	-15.08 to -12.76	-13.51 to -11.13	-13.46 to -11.08
Difference vs PLA	Est. difference		-3.20	-1.60	-1.55
	95% CI		-4.58 to -1.82	-3.00 to -0.20	-2.95 to -0.15
	p-value		<0.001	0.025	0.030
	Level for significance[a]		0.025	0.050	
Difference vs ESC	Est. difference		-1.64	-0.05	
	95% CI		-3.04 to -0.25	-1.47 to 1.37	
	p-value		0.021	0.948	

Key Secondary Endpoint (change in Q-LES-Q % maximum total score)

		PLA N=212	QTP XR 150 N=212	QTP XR 300 N=201	ESC 10 N=203
Randomization	N[a]	212	212	201	203
	Mean (SD)	52.46 (13.89)	52.87 (13.80)	54.61 (13.46)	54.05 (15.07)
Week 8	N[b]	200	198	190	191
	Mean (SD)	61.48 (15.17)	65.29 (16.37)	61.58 (16.49)	65.61 (15.15)
Change	N[b]	200	198	190	191
	Mean (SD)	9.14 (16.21)	12.25 (15.80)	7.11 (15.89)	11.35 (16.10)
ANCOVA results	LS mean	8.36	11.83	7.41	11.50
	95% CI	6.13 to 10.58	9.61 to 14.06	5.13 to 9.69	9.22 to 13.77
Difference vs PLA	Est. difference		3.48	-0.94	3.14
	95% CI		0.76 to 6.20	-3.70 to 1.81	0.39 to 5.89
	p-value		0.012	0.502	0.025
	Level for significance[c]		0.025	0.050	

[a] Number of patients with a value at randomization.
[b] Number of patients with a value at randomization and at least 1 post-randomization value.
[c] Level for significance using the pre-defined multiple comparisons procedure
Source: Study Report, Tables 17 and 18 and CI and p-values confirmed by the FDA reviewer.

For the primary endpoint (change from randomization to Week 8 in the HAM-A total score), quetiapine XR 150 mg/day and 300 mg/day were statistically significantly better than placebo after adjustment for multiplicity. The difference between quetiapine XR 150 mg/day and escitalopram oxalate 10 mg/day trended in favor of quetiapine- the unadjusted 95% confidence interval excludes 0, but this should not be considered statistically significant since it is an exploratory analysis. For Q-LES-Q % maximum total score, the quetiapine XR 150 mg/day dose group showed a statistically significant improvement compared to placebo after adjustment for multiplicity, but the 300 mg/day dose did not. These results appear in Table 7.

Table 8 shows that in the placebo group, about 22% of the subjects dropped out before the end of 8 weeks. 29% and 39% dropped out early in the test drug groups. The most common reason for dropout in the treatment groups was adverse event. "Completed study" in the last row means completed the treatment discontinuation signs and symptoms period.

Table 8 Patient disposition (D1448C00010).

	PLA	QTP XR 150	QTP XR 300	ESC 10
Randomized	**215**	**219**	**207**	**213**
Not treated[a]	1	2	1	4
Received drug	**214 (99.5%)**	**217 (99.1%)**	**206 (99.5%)**	**209 (98.1%)**
Discontinued 8-week randomized treatment				
Adverse event	13 (6.0%)	38 (17.4%)	51 (24.6%)	19 (8.9%)
Condition under investigation worsened	1 (0.5%)	1 (0.5%)	0	1 (0.5%)
Development of study-specific discontinuation criteria	1 (0.5%)	3 (1.4%)	2 (1.0%)	3 (1.4%)
Eligibility criteria not fulfilled	0	1 (0.5%)	4 (1.9%)	1 (0.5%)
Other	2 (0.9%)	0	2 (1.0%)	1 (0.5%)
Severe non-compliance	2 (0.9%)	0	0	1 (0.5%)
Subject did not complete ≥50 days of study treatment	0	0	1 (0.5%)	0
Lost to follow-up	8 (3.7%)	12 (5.5%)	10 (4.8%)	18 (8.5%)
Not willing to continue	19 (8.8%)	8 (3.7%)	11 (5.3%)	15 (7.0%)
Completed 8-week randomized treatment period	**169 (78.6%)**	**156 (71.2%)**	**126 (60.9%)**	**154 (72.3%)**
Completed study[b]	**132 (61.4%)**	**121 (55.3%)**	**101 (48.8%)**	**124 (58.2%)**

[a] Patients that were not treated are also included as discontinuing 8-week randomized treatment.
[b] Including TDSS period.
Source: Figure 2 of Study report..

3.1.3 Study D1448C00011

The primary endpoint is the change in the HAM-A from baseline to Week 8. An important secondary variable is the change in Q-LES-Q% maximum total score from randomization to Week 8. For all efficacy measurements, the last observed value was carried forward in case of missing data. Changes in HAM-A total score from randomization were analyzed with analysis of covariance (ANCOVA), with the baseline HAM-A score as covariate and including treatment as a fixed effect and center as a random effect in the model. For the primary endpoint, the Bonferroni-Holm procedure was used. For the key secondary endpoint (change from baseline in Q-LES-Q % maximum total score) a fixed sequence testing procedure was used within each dose starting with the primary efficacy variable. This procedure has been demonstrated to control the overall familywise Type I error at level α. Analysis of change from baseline to Week 8 (LOCF) in Q-LES-Q % maximum total scores tested the superiority of each dose level of quetiapine using an ANCOVA with the baseline Q-LES-Q as the covariate and including treatment as a fixed effect and center as a random effect in the model.

For the primary endpoint (change from randomization to Week 8 in the HAM-A total score), quetiapine XR 50 mg/day and 150 mg/day were statistically significantly better than placebo after adjustment for multiplicity. The difference between quetiapine XR 150 mg/day and paroxetine 20 mg/day trended in favor of quetiapine- the unadjusted 95% confidence interval excludes 0, but this should not be considered statistically significant since it is an exploratory analysis. For Q-LES-Q % maximum total score, only the 150 mg/day quetiapine XR dose group showed a statistically significant improvement compared to placebo after adjustment for multiplicity. These results appear in Table 9.

Table 9 Analysis of primary and key secondary endpoint (D1448C00011).

Primary endpoint (change from randomization to Week 8 in the HAM-A total score)

		PLA N=217	QTP XR 50 N=219	QTP XR 150 N=216	PAR 20 N=214
Randomization	Mean (SD)	27.3 (4.4)	26.9 (4.2)	26.6 (4.2)	27.1 (4.0)
Week 8	Mean (SD)	14.8 (9.5)	12.8 (8.6)	10.6 (7.8)	12.4 (9.3)
Change	Mean (SD)	-12.5 (9.1)	-14.1 (8.8)	-16.0 (7.9)	-14.7 (9.2)
ANCOVA results	LS mean	-12.30	-13.95	-15.96	-14.45
	95% CI	-13.58 to -11.02	-15.22 to -12.68	-17.24 to -14.68	-15.74 to -13.16
Difference vs PLA	Est. difference		-1.65	-3.66	-2.15
	95% CI		-3.12 to -0.18	-5.13 to -2.19	-3.63 to -0.68
	p-value		0.027	<0.001	0.004
	Level of significance[a]		0.050	0.025	
Difference vs PAR	Est. difference		0.50	-1.51	
	95% CI		-0.97 to 1.98	-2.99 to -0.03	

Key Secondary Endpoint (change in Q-LES-Q % maximum total score)

		PLA N=217	QTP XR 50 N=218	QTP XR 150 N=216	PAR N=214
Randomization	N[a]	215	218	216	214
	Mean (SD)	48.91 (15.71)	48.00 (13.53)	46.88 (14.76)	46.36 (14.93)
Week 8	N[b]	209	207	203	204
	Mean (SD)	55.56 (17.04)	57.05 (16.18)	60.08 (15.61)	57.53 (18.17)
Change	N[c]	207	207	203	204
	Mean (SD)	6.48 (17.11)	9.08 (15.38)	13.58 (15.71)	11.35 (18.27)
ANCOVA results	LS mean	7.44	9.27	13.19	10.85
	95% CI	5.26 to 9.63	7.10 to 11.45	11.00 to 15.39	8.65 to 13.05
Difference vs PLA	Est. difference		1.83	5.75	3.4
	95% CI		-0.96 to 4.62	2.94 to 8.56	0.60 to 6.21
	p-value		0.198	<0.001	0.017
	level of significance[d]		0.050	0.025	

[a] Number of patients with a value at randomization and at least 1 post-randomization value.
[b] Number of patients with an LOCF value at Week 8.
[c] Number of patients with a value at randomization and an LOCF value at Week 8.
[d] Levels of significance were determined using the MTP

Source: Study Report, Tables 18 and 19 and CI and p-values confirmed by the FDA reviewer.

Table 10 shows that in the placebo group, about 19% of the subjects dropped out before the end of 8 weeks. About 25% dropped out early in the quetiapine groups. The most common reason for dropout in the treatment groups was adverse event. "Completed study" in the last row means completed the treatment discontinuation signs and symptoms period.

Table 10 Patient disposition (D1448C00011).

	PLA	QTP XR 50	QTP XR 150	PAR 20
Randomized	**217**	**221**	**218**	**217**
Not treated[a]	0	1 (0.5%)	0	2 (0.9%)
Received drug	**217 (100.0%)**	**220 (99.5%)**	**218 (100.0%)**	**215 (99.1%)**
Discontinued 8-week randomized period	**41 (18.9%)**	**57 (25.8%)**	**55 (25.2%)**	**44 (20.3%)**
Lost to follow-up	1 (0.5%)	2 (0.9%)	3 (1.4%)	3 (1.4%)
Adverse event	8 (3.7%)	25 (11.3%)	32 (14.7%)	16 (7.4%)
Development of study-specific discontinuation criteria	0	1 (0.5%)	0	1 (0.5%)
Patient not willing to continue	14 (6.5%)	13 (5.9%)	8 (3.7%)	15 (6.9%)
Lack of therapeutic response	13 (6.0%)	9 (4.1%)	1 (0.5%)	4 (1.8%)
Eligibility criteria not fulfilled	0	1 (0.5%)	1 (0.5%)	1 (0.5%)
Other	0	0	1 (0.5%)	2 (0.9%)
Severe noncompliance	3 (1.4%)	5 (2.3%)	7 (3.2%)	2 (0.9%)
<50 days of study treatment	2 (0.9%)	1 (0.5%)	2 (0.9%)	0
Completed 8-week randomized treatment period	**176 (81.1%)**	**164 (74.2%)**	**163 (74.8%)**	**173 (79.7%)**
Completed study[b]	**126 (58.1%)**	**115 (52.0%)**	**113 (51.8%)**	**119 (54.8%)**

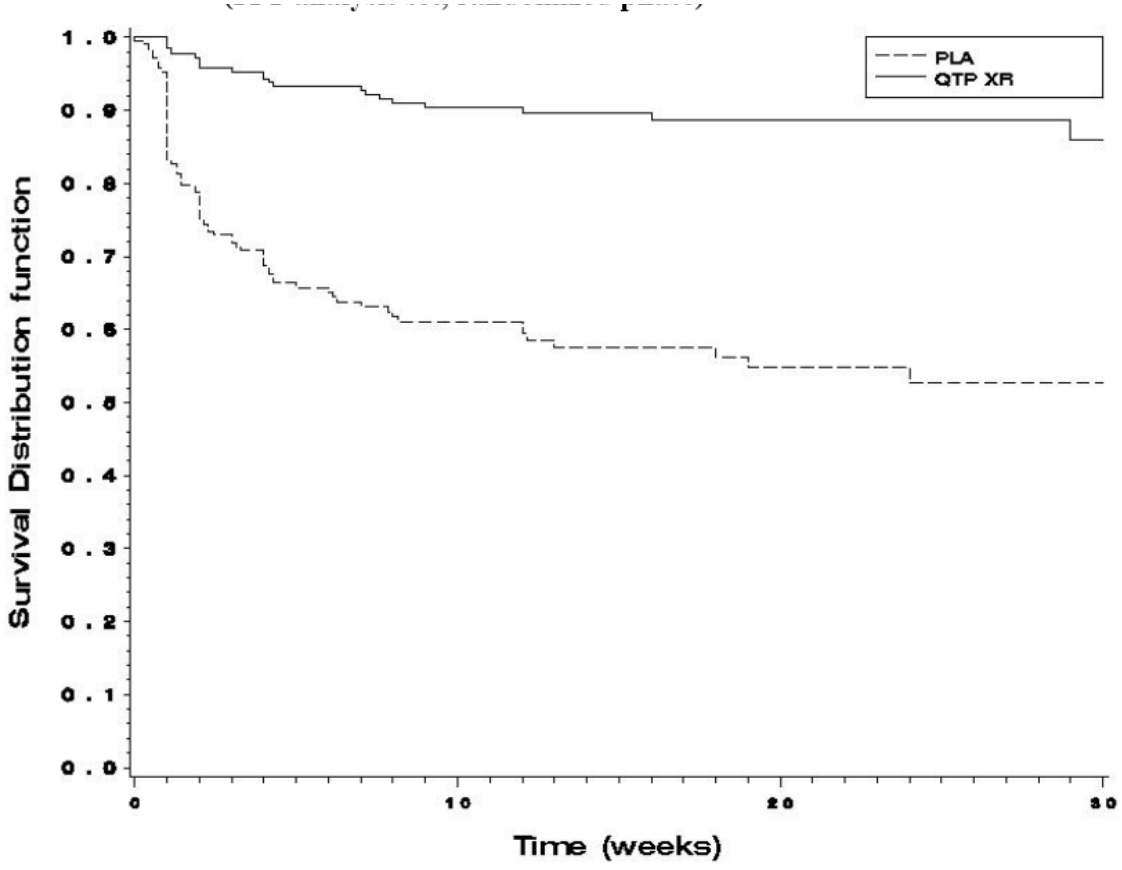
[a] Patients not treated are also counted as discontinued from the 8-week randomized treatment period.
Source: Figure 2 of Study report..

3.1.4 Study D1448C00012

The primary endpoint is the time to anxiety event. The main analysis of the time to an anxiety event was performed with a Cox proportional hazards model comparing quetiapine XR to placebo with a hazard ratio (HR) and associated 95% CI. A 2-sided Wald test of the null hypothesis of equivalent hazards was performed. If a patient discontinued from, or completed the study, without meeting the criteria for an anxiety event, the time of censoring was the date of the patient's final assessment. For the primary efficacy analysis, region was included as a stratification variable. All secondary analyses were exploratory.

For the primary endpoint (time to anxiety event), quetiapine XR was statistically significantly better than placebo. The estimated hazard ratio was 0.19 with a 95% CI of (0.12, 0.31) and the p-value was smaller than 0.0001 (from Study Report and confirmed by FDA). The Kaplan-Meier estimates of the event-free survival curves (not stratified by region) are shown in Figure 1.

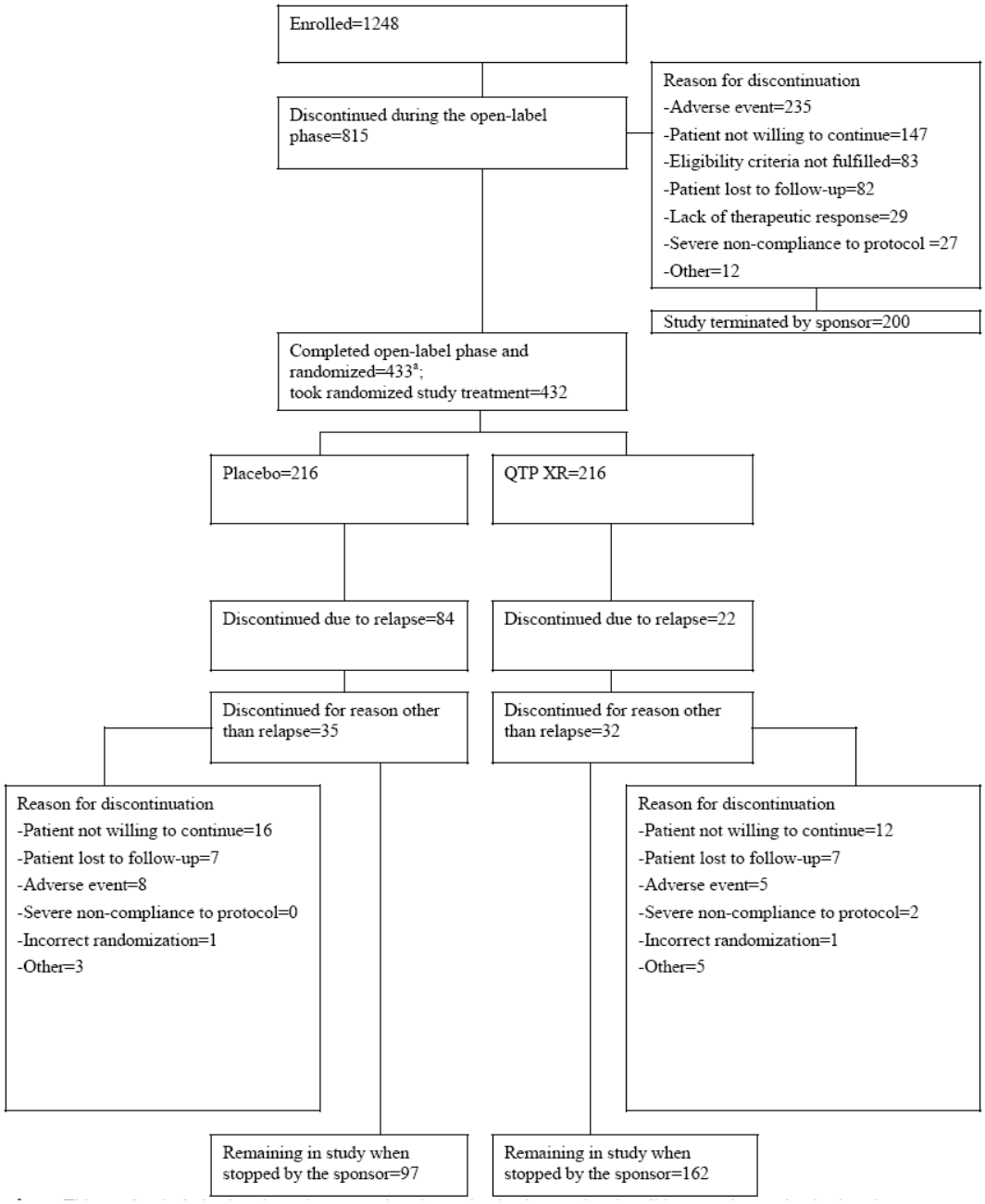
Figure 1 Kaplan-Meier estimates of anxiety-event free survival curves.



Source: Study Report, Figure 6.

Figure 2 shows that approximately the same number of the subjects dropped out early in the withdrawal period for reasons other than relapse in both the quetiapine and placebo groups (35 vs. 32 subjects). The most common reason for dropout in the treatment groups was "patient not willing to continue".

Figure 2 Patient disposition (D1448C00011).



Source: Figure 2 of Study report.

3.2 Evaluation of Safety

3.2.1 Study D1448C00009

According to the Study Report, the overall incidence of AEs was highest in the quetiapine XR treatment arms, with a higher incidence in the quetiapine XR 150 mg/day group compared with the other treatment groups. Most AEs were mild to moderate in severity. There were no deaths in this study. The incidence of SAEs in the quetiapine XR treatment groups was low (0.8% in the 150 mg/day group and 2.1% in the 300 mg/day group). Both the quetiapine XR 50 mg/day and placebo groups had no SAEs. The number of patients with AEs considered by the investigator to be possibly related to study treatment was higher in the quetiapine XR groups than in the placebo group. The number of patients withdrawing from the study due to an AE was higher in the quetiapine XR groups compared to placebo and was highest in the quetiapine XR 300 mg/day group. The most common AEs in the quetiapine XR groups (AEs experienced by at least twice as many patients in any quetiapine XR group as in the placebo group and in ≥2% of patients in any treatment group) were dry mouth, somnolence, sedation, and constipation.

3.2.2 Study D1448C00010

According to the Study Report, the overall incidence of AEs was highest in the quetiapine XR treatment arms, with a similar incidence in both dose groups. Most AEs were mild to moderate in severity. There were no deaths in this study. The incidence of SAEs in the quetiapine XR treatment groups was low (at most 1%). The number of patients with AEs considered by the investigator to be possibly related to study treatment was higher in the quetiapine XR groups than in either the placebo group or the escitalopram group. The number of patients withdrawing from the study due to an AE was higher in the quetiapine XR groups compared to placebo or the escitalopram group. The most common AEs in the quetiapine XR groups were dry mouth, somnolence, sedation, constipation, dyspepsia, vomiting, and irritability.

3.2.3 Study D1448C00011

According to the Study Report, the overall incidence of AEs was highest in the quetiapine XR 150 mg/day treatment arm, followed by the paroxetine and quetiapine 50 mg/day groups. Most AEs were mild to moderate in severity. There were no deaths in this study, but 1 death occurred prior to randomization. The incidence of SAEs in the quetiapine XR treatment groups was low (less than 1.5%). The number of patients with AEs considered by the investigator to be possibly related to study treatment was higher in the quetiapine XR groups than in the placebo group and highest in the highest dose group. The number of patients withdrawing from the study due to an AE was higher in

the quetiapine XR groups compared to placebo and was highest in the quetiapine XR 150 mg/day group. The most common AEs in the quetiapine XR groups were dry mouth, somnolence, fatigue, dizziness, and sedation, which occurred at a higher incidence compared to placebo.

3.2.4 Study D1448C00012

According to the Study Report, Quetiapine XR was generally well tolerated in the maintenance treatment of GAD across the dose range 50 mg/day to 300 mg/day.

3.2.5 Analysis of sexual dysfunction from GAD and MDD studies

In order to compare the combined quetiapine group versus placebo, the change from randomization in Change in Sexual Functioning Questionnaire (CSFQ) total score to End of treatment (Week 6 or 8 LOCF) was analyzed by the sponsor using an ANCOVA model. The randomization CSFQ total score was used as the covariate, while treatment, gender, and study was used as fixed effects and centre as a random effect nested within study. Analyses were done within individual studies as well as across pooled studies. The results appear in Table 11. The sponsor claims that non-inferiority to placebo is demonstrated since the lower limit of the confidence interval when pooling studies 09 + 10 + 11, i.e. –0.54, [Note: the lower limit reported in the study report is -0.53, the difference is due to rounding] is larger than –0.75. In both studies in GAD that had an active treatment arm (10 and 11) and in the two studies in MDD that had an active treatment arm (02 and 04) and when the ESC groups from studies 04 and 10 are combined, the active treatment group's CSFQ was not significantly different from placebo [i.e. not statistically significant at two-sided level α=0.05], suggesting that either both active controls are similar to placebo for this endpoint or that there was no assay sensitivity to compare arms within any study or when studies 04 and 10 are combined for this endpoint using this analysis.

Table 11 Sponsor's analysis of CSFQ data (studies referenced by last two digits D1448C000xx; note: 01, 02, 03, and 04 are MDD, studies 09, 10, and 11 are GAD).

Study or Studies	Treatment group	N (Trt)	N (Pbo)	LS Mean†	SE	95% CI LS Mean ± SE
02	QTP XR 150	152	157	–0.58[a]	0.79[a]	(–2.13, 0.97)
02	QTP XR 300	152	157	0.18[a]	0.79[a]	(–1.37, 1.73)
02	DUL 60	149	157	0.18[a]	0.80[a]	(–1.39, 1.75)
04	QTP XR	157	155	0.96[a]	0.99[a]	(–0.98, 2.90)
04	ESC	156	155	0.16[a]	0.98[a]	(–1.76, 2.08)
10	QTP XR 150	217	214	0.24[a]	0.67[a]	(–1.07, 1.55)
10	QTP XR 300	206	214	–0.03[a]	0.68[a]	(–1.36, 1.30)
10	ESC 10	209	214	–0.62[a]	0.67[a]	(–1.93, 0.69)
11	QTP XR 50	220	217	0.21[a]	0.64[a]	(–1.04, 1.46)
11	QTP XR 150	218	217	0.84[a]	0.64[a]	(–0.41, 2.09)
11	PAR 20	215	217	–0.36[a]	0.64[a]	(–1.61, 0.89)
04+10	ALL QTP XR	580	369	0.63[a]	0.51[a]	(–0.37, 1.63)
04+10	ESC	365	369	–0.3[a]	0.56[a]	(–1.40, 0.80)
09+10+11	ALL QTP XR	1462	633	0.07[b]	0.31[b]	(–0.54, 0.68)
01+02+03+04 +09+10+11	ALL QTP XR	2482	1208	0.12[c]	0.24[c]	(–0.35, 0.59)

† Estimated placebo-subtracted LS Mean Change. Negative values suggest worsening of sexual dysfunction compared to placebo.

[a] Source: sponsors tables in \\Cdsesub1\evsprod\NDA022047\0050\m5\53-clin-stud-rep\535-rep-effic-safety-stud\generalized-anxiety-disorder\5353-rep-analys-data-more-one-stud\response-to-query-csfq-total-score-by-gender

[b] Source: Sponsors table S 44 in \\Cdsesub1\evsprod\NDA022047\0010\m2\27-clin-sum\summary-of-clinical-safety.pdf

[c] Source: Sponsors table S 46 in \\Cdsesub1\evsprod\NDA022047\0010\m2\27-clin-sum\summary-of-clinical-safety.pdf

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study D1448C00009

For age <40, the unadjusted 95% CIs for the primary endpoint for the three doses are

(-4.25, -0.50), (-4.98, -1.1), and (-3.95, -0.04). For age 40 or older, the unadjusted 95% CIs for the primary endpoint for the three doses are (-4.04, -0.44), (-3.77, -0.34), and (-1.52, 1.91). [from FDA analysis]

For Caucasian race, the unadjusted 95% CIs for the primary endpoint for the three doses are (-3.57, -0.72), (-3.54, -0.74), and (-2.1, 0.72). For Black race, the unadjusted 95% CIs for the primary endpoint for the three doses are (-4.45, 2.16), (-6.2, 0.88), and (-4.51, 2.48). [from FDA analysis]

For Males, the unadjusted 95% CIs for the primary endpoint for the three doses are (-4.56, -0.53), (-3.9, 0.21), and (-4.03, 0.03). For females, the unadjusted 95% CIs for the primary endpoint for the three doses are (-3.79, -0.38), (-4.51, -1.21), and (-1.64, 1.7). [from FDA analysis]

4.1.2 Study D1448C00010

For age <40, the unadjusted 95% CIs for the primary endpoint for the two doses are (-4.8, -1.17) and (-2.1, 1.72). For age 40 or older, the unadjusted 95% CIs for the primary endpoint for the two doses are (-5.63, -1.18) and (-5.44, -1.06). [from FDA analysis]

For Caucasian race, the unadjusted 95% CIs for the primary endpoint for the two doses are (-5.04, -1.95) and (-3.12, 0.03). For Black race, the unadjusted 95% CIs for the primary endpoint for the two doses are (-6.38, 2.11) and (-6.21, 2.8). [from FDA analysis]

For Males, the unadjusted 95% CIs for the primary endpoint for the two doses are (-5.06, -0.29) and (-3.3, 1.72). For females, the unadjusted 95% CIs for the primary endpoint for the two doses are (-5.21, -1.79) and (-3.69, -0.26). [from FDA analysis]

4.1.3 Study D1448C00009

For age <40, the unadjusted 95% CIs for the primary endpoint for the two doses are (-1.45, 2.84) and (-3.74, 0.71). For age 40 or older, the unadjusted 95% CIs for the primary endpoint for the two doses are (-5.37, -1.29) and (-7.22, -3.21). [from FDA analysis]

For Caucasian race, the unadjusted 95% CIs for the primary endpoint for the two doses are (-3.45, -0.37) and (-5.4, -2.34). For Black race, the unadjusted 95% CIs for the primary endpoint for the two doses are (-1.61, 5.17) and (-1.72, 4.93). [from FDA analysis]

For Males, the unadjusted 95% CIs for the primary endpoint for the two doses are (-4.57, 0.37) and (-5.88, -1.03). For females, the unadjusted 95% CIs for the primary endpoint for the two doses are (-3.45, 0.32) and (-5.55, -1.75). [from FDA analysis]

4.1.4 Study D1448C00012

For age <40, the unadjusted 95% CIs for the hazard ratio for the primary endpoint is (0.04, 0.3). For age 40 or older, the unadjusted 95% CI is (0.14, 0.42). [from Table 11.2.1.3 of Study Report]

For Caucasian race, the unadjusted 95% CIs for the hazard ratio for the primary endpoint is (0.1, 0.3). For Black race, the unadjusted 95% CI is (0.08, 3.02). [from Table 11.2.1.3 of Study Report]

For Males, the unadjusted 95% CIs for the hazard ratio for the primary endpoint is (0.03, 0.35). For Females, the unadjusted 95% CI is (0.13, 0.37). [from Table 11.2.1.3 of Study Report]

4.1.5 Pooled analysis of sexual dysfunction from three short-term studies

The results for the pooled analysis of CSFQ by gender appear in Table 12 (for more details of the analysis, see *3.2.5 Analysis of sexual dysfunction from GAD and MDD studies*). For men, neither the lower limit nor the point estimate are larger than –0.75, but for women the lower limit of the CI is larger than –0.75.

Table 12 Sponsor's analysis of CSFQ data for all short term GAD studies by gender

Sex	Visit	Statistic	PLA (N=665)	ALL QTP XR (N=1569)
MALE	Randomization	n	236	564
		Mean (SD)	51.0 (8.0)	50.0 (8.0)
		Median	52.0	51.0
		Min-Max	27 to 69	22 to 70
	End of Treatment	n	227	517
		Mean (SD)	52.0 (8.0)	51.0 (9.0)
		Median	53.0	51.0
		Min-Max	27 to 67	22 to 70
		LS Mean	2.99	2.13
		SE	0.46	0.33
		95% CI	2.08, 3.90	1.48, 2.78
		LS Mean vs PLA		-0.86
		SE		0.52
		95% CI		-1.88, 0.16
FEMALE	Randomization	n	420	982
		Mean (SD)	40.0 (10.0)	40.0 (9.0)
		Median	40.0	40.0
		Min-Max	14 to 68	18 to 67
	End of Treatment	n	406	945
		Mean	42.0 (10.0)	42.0 (10.0)
		Median	42.0	43.0
		Min-Max	18 to 68	18 to 68
		LS Mean	0.72	1.30
		SE	0.35	0.25
		95% CI	0.04, 1.40	0.81, 1.79
		LS Mean vs PLA		0.58
		SE		0.38
		95% CI		-0.17, 1.34

Source: Table S 45 of Integrated Summary of Safety.

4.2 Other Special/Subgroup Populations

In the long term withdrawal study, the 95% CI for the hazard ratios for the primary endpoint in the US and Non-US regions were (0.07, 0.29) and (0.4, 0.5) respectively [from Table 11.2.1.3 of Study Report].

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For the endpoint change in the HAM-A (the primary endpoint in the three short term studies), the 50 mg/day dose was better than placebo in two studies, the 150 mg/day dose was better than placebo in three studies, and the 300 mg/day dose was better than placebo in one study. For the endpoint change in the Q-LES-Q% (the key secondary endpoint in the three short term studies), the 50 mg/day dose was not better than placebo in any study, the 150 mg/day dose was better than placebo in two out of three studies, and the 300 mg/day dose was not better than placebo in any study. The short term studies correctly handled all the multiplicity issues related to multiple doses and multiple endpoints. For the long term study, there was a significant difference in the time to an anxiety event after the randomized withdrawal (the primary endpoint). The sponsor claims that non-inferiority to placebo is demonstrated since the lower limit of the confidence interval for CSFQ from their analysis of the three short term studies pooled together, i.e. -0.53, is larger than -0.75.

The sponsor claims that non-inferiority to placebo is demonstrated for a safety endpoint, sexual dysfunction. But, in both studies in GAD that had an active treatment arm (10 and 11) and in the two studies in MDD that had an active treatment arm (02 and 04) and when the ESC groups from studies 04 and 10 are combined, the active treatment group's CSFQ was not significantly different from placebo, suggesting that either both active controls are similar to placebo for this endpoint or that there was no assay sensitivity to compare arms within any study or when studies 04 and 10 are combined for this endpoint using this analysis.

5.2 Conclusions and Recommendations

Three doses studied significantly improved the HAM-A score in at least two studies. The results were not as convincing for the key secondary endpoint, change in Q-LES-Q%. For the long term study, there was a significant difference in the time to an anxiety event after the randomized withdrawal (the primary endpoint). I conclude the doses studied are effective for improving the HAM-A score and the improving the time to an anxiety event. The sponsor claims that non-inferiority to placebo is demonstrated for a safety endpoint, sexual dysfunction. I recommend that, if approved, the label not use the words "non-inferior" or "similar" to placebo since in both studies in GAD that had an active treatment

arm (10 and 11) and in the two studies in MDD that had an active treatment arm (02 and 04) and when the ESC groups from studies 04 and 10 are combined, the active treatment group's CSFQ was not significantly different from placebo, suggesting that either both active controls are similar to placebo for this endpoint or that there was no assay sensitivity to compare arms within any study or when studies 04 and 10 are combined for this endpoint using this analysis. Instead, the results for sexual dysfunction should be described for all arms in the individual studies. No language in the label or advertising describing an advantage over other marketed drugs should be allowed.

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