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RESEARCH**

APPLICATION NUMBER:
22-172s000

MEDICAL REVIEW(S)

**Review and Evaluation of Clinical Data
NDA #22-172**

Sponsor: AstraZeneca UK Limited
Drug: Quetiapine Fumarate Sustained-Release Tablets
Indication: Schizophrenia
Material Submitted: Responses to FDA Requests for Additional Information
Correspondence Dates: September 7, 2007; September 21, 2007; September 24, 2007; September 26, 2007
Dates Received: September 7, 2007; September 21, 2007; September 24, 2007; September 26, 2007

I. Background

On 1/22/07, the sponsor submitted this NDA for the approval of quetiapine fumarate sustained-release tablets (QTP SR) for [REDACTED] ^{(b)(4)} adult patients with schizophrenia.

On 8/31/07, the clinical and statistical review team emailed the sponsor the following request:

Please provide a primary efficacy analysis excluding patients who a) did not have change of < 10 points in the PANNS total score from enrollment to baseline, b) did not meet inclusion criteria at enrollment (including the patients described on page 120 of 3494 of the Clinical Study Report), and c) did not meet inclusion criteria at randomization (including the patients described on page 120 of 3494 of the Clinical Study Report). In addition, please provide the subject numbers for these patients.

On 9/14/07, the clinical review team emailed the sponsor the following:

1. Please provide information concerning overdose experience for Seroquel XR, it was missing from the submission.

2. Please provide information on withdrawal of your product in other countries, if any, and submission of marketing authorization applications to foreign regulatory agencies.
3. Your submission does not describe how the inclusion criterion of a "stable dose of quetiapine SR" was determined. Please provide this information.
4. Please provide demographic analyses for efficacy (e.g., subset analyses to evaluate the effect of age and gender on treatment response as measured by primary efficacy variable) for the interim ITT population.
5. In the submission, you state that there were no serious adverse events leading to death during the open label stabilization period and that there was one fatal SAE during the randomized treatment period. Please state whether or not there were any deaths during or immediately following both the open label stabilization period and randomized treatment period.
6. Regarding the inclusion criteria of a PANSS score \leq 60 at the enrollment and baseline visits, please verify whether this refers to a PANSS total score.
7. Regarding the relapse definition of an increase on PANSS score of 30% from baseline, please clarify whether this refers to a PANSS total score.

These submissions contain their responses to the above.

II. Clinical Data

A. Modified Primary Efficacy Analysis

The following table is extracted from the sponsor's submission:

Table 1 Time to schizophrenic relapse (interim ITT population) excluding patients that did not meet inclusion/exclusion criteria at enrolment/randomization. Score test, comparison of quetiapine SR versus placebo with Cox regression

	PLA N=76	QTP SR N=72
No. of relapses (%)	30 (39.5)	6 (8.3)
Comparison between treatment groups		
Hazard ratio	0.14	
95% CI	0.06, 0.34	
p-value	0.0000005237	

CI Confidence interval. ITT Intention-to-treat. PLA Placebo. QTP Quetiapine. SR Sustained-release. N Number of patients in treatment group.

Note: Score test used in Cox regression analysis

Note: Due to the low rate of relapse in the quetiapine SR group it is not possible to calculate a reliable median time to relapse. The number of relapses is presented for information. The p value relates to the analysis of time to schizophrenic relapse.

Seroquel SR Submission. Source document: PRINCESS_TABLE_IITT.SAS. Generated: 16:01:24 04Sep2007 DB version prod: 12.

B. Overdose Experience

All cases of overdose were by definition doses in excess of 800 mg/day.

Using an AstraZeneca global safety database (Clintrace) search for all overdose cases, 31 overdose reports with QTP SR were identified, all of which were accidental. No adverse events were reported for 30 of these overdoses.

One overdose (Case ID #2005UW07057, Patient ID #1420 in Study 133) was associated with a non-serious adverse event of vomiting. The day after the patient was withdrawn from the study, the patient expressed strong thoughts of suicide but did not have a specific plan. The patient was hospitalized for safety and stabilization and was discharged two days later when the event was considered resolved. Of note, no narrative was provided in either the sponsor's 9/24/07 submission or in the CSR for Study 133.

In study 146, there were 12 additional reports of overdoses which were not clearly coded in the Clintrace database with respect to the formulation of the drug. None of these 12 was associated with AEs.

In study 004, there were 4 additional patients who took overdoses. The sponsor did not state whether these overdoses were associated with AEs.

In study 041, there was one additional non-serious AE report of "overdose". The sponsor did not state whether this overdose was associated with AEs.

C. Foreign Regulatory Information

Seroquel or Seroquel XR has not been withdrawn in any country for any reason.

Seroquel XR is approved in Hungary, Slovakia and The Netherlands. Marketing authorization applications for

Seroquel XR have also been submitted to the following countries: Canada, Australia, New Zealand, United Kingdom, Italy, Switzerland, Czech Republic, Slovenia, Estonia, Romania, Lithuania, Turkey, Bulgaria, Latvia, Austria, Belgium, Finland, Sweden, Denmark, Ireland, Luxembourg, Germany, Spain, Portugal, Greece, Norway, Iceland, Poland, Cyprus, Malta, México, Brazil, South Africa, South Korea and the Philippines.

D. Stable dose of QTP SR Definition

The sponsor states that the definition of a stable dose was based on the investigator's judgment.

E. Demographic Analyses for Efficacy for the Interim ITT Population

The sponsor performed subset analyses to evaluate the effect of the following variables on treatment response for study 004 using the interim ITT population.

- Age (18-39 vs. 40-65 years old)
- Gender

Based on the interim ITT population, age and gender did not appear to significantly affect time to schizophrenic relapse with Cox regression. Appendices 1 and 2 present data based on these subgroups. The sponsor did not perform a subset analysis to evaluate the effect of race, since all patients were Caucasian.

F. Deaths

There were no deaths during or immediately following the open label stabilization period and one SAE leading to death in the randomized treatment period. Immediately following the randomized treatment period there were no deaths.

G. Inclusion Criteria PANSS Score

The sponsor clarified that PANSS score referred to the PANSS total score.

H. Relapse Definition PANSS Score

The sponsor clarified that PANSS score referred to the PANSS total score.

III. Conclusions and Recommendations

This submission is a full and adequate response to most of the clinical issues raised in our emails. There is no clinical information in this submission that would change our previous conclusions about the approvability of QTP SR (b)(4) in adult patients with schizophrenia.

However, the following should be communicated to the sponsor:

1. Please submit a narrative for the overdose report that was associated with vomiting and suicidal thoughts (Case ID #2005UW07057, Patient ID #1420 in Study 133) described in your 9/24/07 submission.
2. Please submit associated adverse event data and narratives, if appropriate, for the 4 overdose reports in Study 004 and the one overdose report in Study 041 described in your 9/24/07 submission.

From a clinical perspective, this application may be approved when agreement is reached on product labeling.

Michelle M. Chuen, M.D.
October 23, 2007

cc: NDA #22-172
HFD-130 (Div. File)
HFD-130/MChuen
/TLaughren
/MMathis
/NKhin
/KUpdegraff

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/s/

Michelle Chuen
10/23/2007 03:45:45 PM
MEDICAL OFFICER

Ni Aye Khin
10/24/2007 04:53:31 PM
MEDICAL OFFICER

CLINICAL REVIEW

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Reviewer(s) Name(s) Michelle M. Chuen, M.D.
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Established Name Quetiapine Fumarate Sustained-
Release Tablets
Trade Name Seroquel XR
Therapeutic Class Antipsychotic
Applicant AstraZeneca UK Limited

Priority Designation S

Formulation 50, 200, 300, and 400 mg Tablets
Dosing Regimen 400-800 mg/day
Indication Schizophrenia
Intended Population Adults with Schizophrenia

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this application be granted approvable status. There is a request¹ to which the sponsor has not yet responded. This response will be reviewed in an addendum. It is also recommended that further information be requested (see section 9.2). Final approval is contingent on satisfactory responses to the concerns conveyed in this request and in the approvable letter, satisfactory statistical and CMC reviews, and mutual agreement on labeling (see section 9.4).

1.1.1 Risk Management Activity

There are no recommendations for risk management beyond those already in the sponsor's proposed labeling and in the undersigned reviewer's comments on the sponsor's proposed labeling. Please see Section 9.4 for further details.

1.1.2 Required Phase 4 Commitments

There are no additional recommendations.

1.1.3 Other Phase 4 Requests

There are no additional recommendations.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

The safety and efficacy of QTP SR in the treatment of relapse prevention in adult patients with schizophrenia is based on study 004, which consisted of a 16-week open-label period (flexible dosing with 400, 600, or 800 mg/day) followed by up to a 12-month double-blind flexible-dose period (400, 600, or 800 mg/day). The study was stopped after a pre-planned interim analysis after 45 relapses, and the maximum double-blind period was 9 months. Safety was evaluated in 327 patients.

¹ Primary efficacy analysis excluding patients who a) did not have change of < 10 points in the PANNS total score from enrollment to baseline, b) did not meet inclusion criteria at enrollment (including the patients described on page 120 of 3494 of the Clinical Study Report), and c) did not meet inclusion criteria at randomization (including the patients described on page 120 of 3494 of the Clinical Study Report).

1.2.2 Efficacy

Study 004 demonstrated that patients remaining clinically stable on QTP SR randomized to flexible-dose QTP SR experienced a significantly longer time to relapse than patients randomized to placebo.

1.2.3 Safety

A total of 327 patients received QTP SR and had safety data in Study 004. Review of the safety database revealed no findings which were attributable to QTP SR treatment and inconsistent with the previously observed safety profile for quetiapine.

1.2.4 Dosing Regimen and Administration

Dosing in study 004 was flexible (400, 600, or 800 mg) both during open-label treatment and during double-blind therapy. Since patients did not receive fixed doses in this trial, no assessment of dose-response for delaying relapse of schizophrenia was possible.

1.2.5 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

1.2.6 Special Populations

Age and gender did not appear to significantly affect treatment response as measured by time to schizophrenic relapse. Please see Section 6.1.4 for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Quetiapine fumarate (SEROQUEL) has been approved for treatment of bipolar disorder (depression and mania) and schizophrenia. Quetiapine fumarate sustained-release (SEROQUEL XR) is a marketed antipsychotic which has been approved for the treatment of schizophrenia.

(b) (4)

2.2 Currently Available Treatment for Indications

The 23 moieties approved in the U.S. for the treatment of schizophrenia are: chlorpromazine, promazine, prochlorperazine, perphenazine, trifluoperazine, thioridazine, acetophenazine, propiomazine, fluphenazine, piperacetazine, haloperidol, chlorprothixine, thiothixine, mesoridazine, molindone, loxapine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone.

2.3 Availability of Proposed Active Ingredient in the United States

Quetiapine fumarate (SEROQUEL, quetiapine) is a marketed drug which was first approved on September 26, 1997. The extended-release capsule was approved on May 17, 2007. It has 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, hyperglycemia and diabetes mellitus.

2.4 Important Issues with Pharmacologically Related Products

There are no other important issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

On 9/26/97, the NDA approval letter for SEROQUEL informed the sponsor of a Phase 4 commitment to conduct a relapse prevention study to evaluate the safety and effectiveness of SEROQUEL in long-term use for schizophrenia.

On 11/29/01, the sponsor submitted a draft clinical trial protocol intended to fulfill two of the Phase 4 commitments (cataract evaluation and relapse prevention). On 8/29/02, the Division indicated that an active controlled, non-inferiority study was not adequate for assessing relapse prevention. On 11/11/03 indicated the initiation of protocol D1441C00131, and on 2/25/04 the Division indicated that a longer stability period (4 to 6 months before randomization to placebo or active treatment) was required.

On 2/28/04 the sponsor submitted the protocol for study D1444C00004 to NDA 20-639 which replaced study D1441C00131. The sponsor asked the Agency for concurrence to use SR formulation. On 1/14/05, FDA informed the sponsor that SEROQUEL SR was an acceptable formulation for the relapse prevention Phase 4 Commitment.

On 2/16/06, the sponsor submitted the interim statistical analysis plan for Study D1444C00004 and informed the Division that the study had reached target enrollment. On 3/2/06, the sponsor emailed the Division and requested confirmation that the termination of study D1444C00004 at

the interim analyses would fulfill the relapse prevention study Phase 4 post marketing commitment for NDA 20-639.

On 3/28/06, the sponsor informed the Division that the planned initial interim analysis for Study D1444C00004 revealed a significant difference in time to relapse between the two treatment groups (SEROQUEL SR vs. placebo) and that the sponsor ended the study at the DSMB's recommendation and in accordance with good medical practice. On 4/11/06, the Division emailed the sponsor comments from the statistical reviewer which indicated that if termination of the study D1444C00004 occurred according to the statistical analysis plan it would fulfill the Phase 4 commitment for a relapse prevention study.² On 4/20/06, the Division emailed the sponsor and agreed that the sponsor's approach for submitting the results from study D144C00004 would satisfy the post marketing study agreement for NDA 20-639.

A 4-Month Safety Update to the NDA was submitted on November 16, 2006.

On 12/11/06, the sponsor submitted a letter to NDA 20-639 informing the Division of their plans to submit a sNDA to fulfill the Phase 4 commitment to conduct a relapse prevention study, with the intention to describe the study's outcome in the label for NDA 22-047.

This NDA was submitted to the Agency on 1/22/07. The Filing Meeting was held on 3/22/07, and it was concluded that this supplement was fileable. The User Fee due date is 11/22/07.

2.6 Other Relevant Background Information

The sponsor states that the relapse prevention indication for SEROQUEL is not approved in any market. However, undersigned reviewer was unable to locate any information on withdrawal of SEROQUEL XR in other countries, or on submission of marketing authorization applications to foreign regulatory agencies.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

An Environmental Assessment was requested since approval of this supplement will likely increase the use of Seroquel XR. This assessment was completed by Raanan A. Bloom, Ph.D., Senior Environmental Officer, Center for Drug Evaluation and Research, on August 20, 2007. It was concluded that no further testing is required and no adverse effects are expected from the

² According to an 8/22/07 email from statistical reviewer, Dr. Phillip Dinh, the sponsor prespecified the criteria for stopping for efficacy based on the O'Brien-Flemming boundary, and they met those criteria.

introduction of quetiapine fumarate into the environment due to the use of Seroquel XR. A Finding of No Significant Impact (FONSI) was recommended.

According to an 8/29/07 email from Tom Oliver, Ph.D., Chemistry Team Leader, there are no outstanding CMC issues or concerns. At the time of completion of this review, neither the final review or a draft of the CMC review by Chemistry reviewer, Prafull Shiromani, Ph.D. was available.

3.2 Animal Pharmacology/Toxicology

There is no new animal pharmacology/toxicology data in this submission.

3.3 Statistical Review and Evaluation

Philip Dinh, Ph.D. is the statistical reviewer for this NDA. His final review is pending at the time of completion of this review. Based on a draft of his review, he has indicated that study 004 suggests that quetiapine SR (flexible dose ranging from 400mg to 800mg daily) was superior to placebo in the prevention of relapse of schizophrenia as indicated by the longer time to schizophrenic relapse.

3.4 DSI Clinical Site Inspections

At the time of completion of this review, the Clinical Inspection Summary is still pending.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The safety and efficacy of QTP SR in the treatment of relapse prevention in adult patients with schizophrenia is based on study 004, which consisted of a 16-week open-label flexible-dose period which was followed by up to a 12-month double-blind flexible-dose period. The study was stopped after a pre-planned interim analysis after 45 relapses, and the maximum double-blind period was 9 months.

4.2 Tables of Clinical Studies

Study 004 was an international, multicenter, randomized, double blind, parallel-group, placebo-controlled Phase III study to evaluate prevention of relapse in patients with schizophrenia in stable condition receiving QTP SR or placebo over a period of up to 1 year. The study was

stopped after a pre-planned interim analysis after 45 relapses, and the maximum double-blind period was 9 months.

4.3 Review Strategy

A listing of the items examined during the course of this review is provided in Table 4.3.1.

Submission Date	Items Reviewed
November 16, 2006	4-Month Safety Update Integrated Summary Case Report Forms
January 22, 2007	Clinical Study Report: Study 004 Proposed Labeling Financial Disclosure Certification Application Summary Case Report Tabulations (.xpt files)
April 26, 2007	Response to FDA Request
July 11, 2007	Proposed Labeling

4.4 Data Quality and Integrity

The efficacy data was examined by the statistical reviewer, Phillip Dinh, Ph.D., and there were no outliers or sites identified that were felt to be driving the efficacy results. Two (2) sites in Ukraine were chosen for Division of Scientific Investigations (DSI) inspection: Dr. Natalia Maruta and Dr. Vladislav Demchenko. This was based on the number of enrollments. Results of the DSI inspections are described in section 3.4.

I conducted an audit of adverse event safety data by comparing Case Report Forms (CRF's) and adverse event line listings for consistency of adverse event information across these two documents in a random sample of 2 patients. Narrative Summaries were provided only for deaths, serious adverse events, and discontinuations due to adverse events. Results are described in section 7.2.7 of this review.

4.5 Compliance with Good Clinical Practices

Study 004 was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

4.6 Financial Disclosures

For purposes of this NDA, study 004 is considered “covered clinical stud[ies]” in accordance with 21 CFR 54.2 (e).

Among the clinical investigators in these studies, none were identified by the sponsor as having financial arrangements that require disclosure.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new pharmacokinetic data are presented in this sNDA.

5.2 Pharmacodynamics

No new pharmacodynamic data are presented in this sNDA.

5.3 Exposure-Response Relationships

Since this was a flexible dose study, exposure-response relationships were not explored.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This supplemental application seeks to establish the safety and efficacy of QTP SR for (b) (4) adult patients with schizophrenia.

6.1.1 Methods

The sponsor has conducted one multicenter study to evaluate the efficacy of QTP SR for relapse prevention in adult patients with schizophrenia.

6.1.2 General Discussion of Endpoints

There were no meetings held to specifically discuss endpoints for this NDA.

6.1.3 Study Design

Study 004, consisted of 2 phases in a relapse prevention design:

- 1) a 16-week open-label treatment phase using flexible doses of QTP SR (400 to 800 mg/day)
- 2) randomization of stable patients to flexible-dose QTP SR or placebo for up to 1 year of double-blind study treatment

The study was stopped after a pre-planned interim analysis after 45 relapses, and the maximum double-blind period was 9 months.

This study will be reviewed in detail in Section 10.1.

6.1.4 Efficacy Findings

Predictors of Response

The sponsor performed subset analyses to evaluate the effect of the following variables on treatment response for study 004 using the total ITT population. Of note, the sponsor did not provide analyses using the interim ITT population.

- Age (18-39 vs. 40-65 years old)
- Gender

Based on the total ITT population, age and gender did not appear to significantly affect time to schizophrenic relapse with Cox regression. The appendices in Section 10.4 present data based on these subgroups. The sponsor did not perform a subset analysis to evaluate the effect of race, since all patients were Caucasian.

Size of Treatment Effect

Please see “Efficacy Results” in Section 10.1.

Duration of Treatment

No study addressing the long-term efficacy of QTP SR in schizophrenia has been completed. Study 004 examined the efficacy of QTP SR in a double-blind extension in which patients remaining clinically stable on QTP SR for 16 weeks were randomized to flexible-dose QTP SR (400 to 800 mg/day) or placebo. Patients randomized to QTP SR were significantly less likely to relapse than patients randomized to placebo (relapse rates of 12% vs. 48%, respectively; $p < 0.0001$).

6.1.5 Clinical Microbiology

Since QTP SR is a solid oral formulation, this section is not applicable.

6.1.6 Efficacy Conclusions

In summary, Study 004 demonstrated that patients remaining clinically stable on QTP SR randomized to flexible-dose QTP SR experienced a significantly longer time to relapse than patients randomized to placebo.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This evaluation of the safety of QTP SR for relapse prevention in adult patients with schizophrenia is based on one completed study (004).

Serious adverse events, common adverse events, laboratory data, vital sign changes, and ECG findings were evaluated.

7.1.1 Deaths

According to the sponsor, no patient had an SAE leading to death during the open label stabilization period.

During the randomized treatment period, one (1) patient had a fatal SAE: Patient E1206004 was a 25-year old man who took QTP SR 800 mg/day during the open label stabilization period and placebo during the randomized treatment period. On Day 173 of randomized treatment, the patient committed suicide by jumping out of a window. The event was not witnessed and the patient died on the day of the event. The total score of the PANSS scale was 50 on Day 90, 53 on Day 119, and 50 on Day 152 of randomized treatment. Before starting the study, the patient was taking haloperidol 20 mg for schizophrenia, amitriptyline 75 mg for depression, and trihexyphenidyl 12 mg for extrapyramidal symptoms, all of which were discontinued by Day 4 of the stabilization period.

7.1.2 Other Serious Adverse Events

A serious adverse event was defined by the sponsor as an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product (including comparator or placebo) that fulfilled one or more of the following criteria:

- resulted in death
- was immediately life-threatening
- required in-patient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability or incapacity
- was a congenital abnormality or birth defect
- was an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

There were no serious adverse events reported during the open label stabilization period. One (1) patient had a serious adverse event during the randomized treatment period: Patient E1208003 was a 36-year old man who had a peritonsillar abscess on Day 15 of randomized treatment with placebo. The patient was consequently hospitalized and given intravenous

ceftriaxone 2000 mg. The patient withdrew consent and discontinued from the study, and the adverse event resolved the following day. Before starting the study, the patient was taking trifluoperazine 10 mg until the day before Day 1 of the stabilization period. QTP SR 800 mg/day was taken during the open label stabilization period. Of note, I reviewed this patient's lab data, and there was no evidence of leukopenia or neutropenia.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, the comparison of dropout rates between placebo- and QTP SR-treated patients is difficult to interpret and will not be discussed in this review.

7.1.3.2 Adverse events associated with dropouts

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, the comparison of dropout incidence due to adverse events between placebo- and QTP SR-treated patients is difficult to interpret and will not be discussed in this review.

Tabulations of treatment-emergent adverse events that led to dropout in study 004 were examined.³ There were no adverse events leading to dropout that have not been previously observed in association with QTP. There were two dropouts due to neutrophil count decreased.

The DPP safety team was consulted regarding the issue of neutropenia associated with quetiapine, and, according to a 7/24/07 review by DPP Safety Reviewer, Lourdes Villalba, labeling negotiations are ongoing, including the addition of a section under Precautions for "Leukopenia, Neutropenia and Agranulocytosis". The findings of 2 dropouts due to neutrophil count decreased in this study further support Dr. Villalba's labeling recommendations as detailed in her 7/24/07 review.

7.1.3.3 Other significant adverse events

No other clinically significant adverse events were reported.

7.1.4 Other Search Strategies

The sponsor submitted searches for adverse events associated with EPS, QT prolongation, diabetes mellitus, neutropenia and agranulocytosis, and suicidality. However, because the double-blind period of study 004 followed a QTP SR open-label treatment period, the

³ Tables 11.3.5.2-1 and 11.3.5.2-2 of the Study Report for study 004

comparison of these subsets of adverse events between placebo- and QTP SR-treated patients is difficult to interpret and will not be discussed in this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Information about AEs was collected from time Informed Consent was obtained, during the stabilization and the randomized treatment periods, and reported on the appropriate sections of the pCRF, whether or not considered related to the investigational product. This included AEs spontaneously reported by the patient and/or observed by the investigators or center staff. At each visit except the enrollment visit, the patient was asked a non-specific open question “Have you had any health problems since the previous Visit?” The patients were also instructed to volunteer AEs noted at any time during the study. For each AE the following were recorded on the pCRF:

- description of the event
- start and stop date
- whether it constituted an SAE or not
- action taken with regard to investigational product
- if the AE caused the patient to discontinue the study
- intensity
- causality to investigational product
- outcome

The latest version of the adverse event dictionary, Medical Dictionary for Regulatory Activities (MedDRA), was used for the classification and analysis of AEs entered in the study database. For regulatory reporting, SAEs were processed in the Global Drug Safety Database Clintrace and coded using MedDRA.

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

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor provided a thesaurus for the coding of all adverse events in the safety database. This listing was examined to assess the adequacy of coding. No important deficiencies were found.

7.1.5.3 Incidence of common adverse events

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, the comparison of incidence of treatment-emergent adverse events between placebo- and QTP SR-treated patients is difficult to interpret and will not be discussed in this review.

7.1.5.4 Common adverse event tables

Please see Section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, the common and drug-related adverse events were difficult to identify and will not be discussed in this review.

7.1.5.6 Additional analyses and explorations

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, additional analyses and explorations such as demographic effects on adverse event incidence and dose relatedness were difficult to interpret and will not be discussed in this review.

7.1.6 Less Common Adverse Events

I reviewed the table of all adverse events in study 004⁴ and, other than a case of neutrophil count decrease already described in the adverse events leading to dropouts section above, did not find any adverse events that were considered serious adverse events but not already classified as serious.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine hematology, chemistry, and urinalysis testing were done at the time points indicated in the following table extracted from the sponsor's submission:

⁴ AELOG.xpt

Event	-16 wks	-12 wks	-8 wks	-4 wks	Day 1	Month 2-6 (every 30d)	Month 9	Month 12 or Relapse
Visit	1a	1c	1e	1g	2	5-9	12	15/Final visit
	Stabilization period				Randomized Period			
Hematology	√	√	√	√	√	Month 3 and 6	√	√
Clinical chemistry, P- glucose, S-Insulin, HbA _{1c}	√		√		√	Month 3 and 6	√	√
Thyroids	√		√		√	Month 3 and 6		√
Lipids	√		√		√	Month 6		√
Urinalysis	√				√	Month 6		√
Urine drug screen and serum pregnancy test [women]	√							

7.1.7.2 Standard analyses and explorations of laboratory data

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, analyses and explorations of laboratory data such as analyses focused on measures central tendency, analyses focused on outliers or shifts from normal to abnormal, and marked outliers and dropouts for laboratory abnormalities were difficult to interpret and will not be discussed in this review.

7.1.7.3 Additional analyses and explorations

No additional analyses or explorations which would substantially impact on the safety profile of this drug were conducted.

7.1.7.4 Special assessments

No special assessments which would significantly impact on the safety profile of this drug were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Pulse rate and blood pressure, were performed at the enrollment, then monthly during the stabilization period and up to one month after randomization, then quarterly. Supine and standing blood pressure and pulse rate were measured. Body weight was measured at enrollment, monthly during the stabilization period and up to one month after randomization,

then quarterly. Height was measured at enrollment. Waist circumference was measured (in centimeters) at enrollment, at randomization and at last visit in the morning before breakfast.

7.1.8.2 Standard analyses and explorations of vital signs data

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, analyses and explorations of vital signs data such as analyses focused on measures of central tendency, analyses focused on outliers or shifts from normal to abnormal, and marked outliers and dropouts for vital signs abnormalities were difficult to interpret and will not be discussed in this review.

7.1.8.3 Additional analyses and explorations

There are no other analyses which would impact the safety profile of quetiapine SR.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

A 12-lead ECG was performed at enrollment, at randomization, month 6 and month 12.

7.1.9.2 Standard analyses and explorations of ECG data

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, analyses and explorations of ECG data such as analyses focused on measures central tendency, analyses focused on outliers or shifts from normal to abnormal, and marked outliers and dropouts for ECG abnormalities were difficult to interpret and will not be discussed in this review.

7.1.9.3 Additional analyses and explorations

No additional analyses or explorations of ECG data were conducted.

7.1.10 Human Reproduction and Pregnancy Data

There were no studies in this submission designed specifically to assess safety in human reproduction and pregnancy. A review of serious adverse events revealed no pregnancies.

7.1.11 Overdose Experience

The sponsor's submission did not contain any information regarding overdose.

7.1.12 Postmarketing Experience

There is no postmarketing data in this submission.

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 004 was a multi-center, randomized, double blind, parallel-group, placebo-controlled flexible-dose study with 2 periods (16-week open-label, 12-month double-blind) in 358 adult outpatients with schizophrenia treated with QTP SR (400 to 800 mg once daily) during the open-label period and QTP SR (400 to 800 mg once daily) or placebo during the double-blind period. Safety population consisted of 327 patients.

7.2.1.2 Demographics

TABLE 7.2.1.2.1 : STUDY 004 BASELINE DEMOGRAPHICS, SAFETY POPULATION								
TX (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Hispanic	Other
QTP SR (327)	35.7	18-64	59	41	100	0	0	0

7.2.1.3 Extent of exposure (dose/duration)

The duration of exposure by mean daily dose during the stabilization period is displayed in the Table 7.2.1.3.1 below. The overall mean daily dose was 646 mg.

TABLE 7.2.1.3.1: MEAN DAILY DOSE OF QTP SR FOR PATIENTS BY TIME INTERVAL, OPEN-LABEL SAFETY POPULATION, STABILIZATION PERIOD

Mean dose (mg/day)	Day 1 - Day 14	Total
	QTP SR N=327 n(%)	QTP SR N=327 n(%)
<400 mg	6(1.8)	1(0.3)
400mg - ≤500mg	41(12.5)	57(17.4)
>500mg - ≤600mg	132(40.4)	102(31.2)
>600mg - ≤700mg	46(14.1)	27(8.3)
>700mg - ≤800mg	82(25.1)	140(42.8)
>800mg	0	0

N Number of patients in treatment group. n Number of patients. QTP Quetiapine. SR Sustained-release.
Study: D1444C00004 Source document: ST_DOSE_DIST_RAND415_OL.SAS. Generated: 18:24:32 31Aug2006 DB version prod: 6.

The duration of exposure by mean daily dose during randomized treatment period is displayed in the Table 7.2.1.3.2 below. The overall mean daily dose was 669 mg.

TABLE 7.2.1.3.2 DISTRIBUTION OF MEAN STUDY MEDICATION DOSE DURING THE RANDOMIZED PERIOD (RANDOMIZED SAFETY POPULATION)

Mean dose (mg/day)	Day 1 - Day 14		Day 15 - Day 30		Month 2		Month 3 - Month 4		≥ Month 5		Total	
	PLA N=103 n(%)	QTP SR N=94 n(%)	PLA N=93 n(%)	QTP SR N=92 n(%)	PLA N=76 n(%)	QTP SR N=86 n(%)	PLA N=43 n(%)	QTP SR N=69 n(%)	PLA N=15 n(%)	QTP SR N=43 n(%)	PLA N=103 n(%)	QTP SR N=94 n(%)
<400 mg	0	0	0	1(1.1)	0	0	0	0	0	0	0	0
400mg - ≤500mg	25(24.3)	13(13.8)	20(21.5)	14(15.2)	18(23.7)	13(15.1)	11(25.6)	12(17.4)	4(26.7)	8(18.6)	23(22.3)	14(14.9)
>500mg - ≤600mg	28(27.2)	34(36.2)	24(25.8)	31(33.7)	18(23.7)	28(32.6)	11(25.6)	19(27.5)	5(33.3)	14(32.6)	23(22.3)	30(31.9)
>600mg - ≤700mg	4(3.9)	0	1(1.1)	1(1.1)	1(1.3)	2(2.3)	0	2(2.9)	0	1(2.3)	4(3.9)	4(4.3)
>700mg - ≤800mg	45(43.7)	45(47.9)	48(51.6)	45(48.9)	39(51.3)	43(50.0)	21(48.8)	36(52.2)	6(40.0)	20(46.5)	52(50.5)	44(46.8)
>800mg	1(1.0)	2(2.1)	0	0	0	0	0	0	0	0	1(1.0)	2(2.1)

N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Study: D1444C00004 Source document: ST_DOSE_DIST_RAND415.SAS. Generated: 11:30:50 11Sep2006 DB version prod: 6.

During the total study period, including both stabilization and randomization periods, a total of 63 patients (19% of all 327 patients) had an exposure to QTP SR for over 6 months. Of note, the sponsor did not provide an enumeration of mean daily dose and total duration of exposure for the total study period.

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 SR.

7.2.2.2 Postmarketing experience

There is no postmarketing data in this submission.

7.2.2.3 Literature

The sponsor stated that overall conclusions regarding the safety of Seroquel SR were supported by the results of a worldwide literature search for Seroquel IR (immediate release) tablets reported in the Periodic Safety Report dated 19 September 2005, Section 7.3 Published Studies. They report that this literature search was recently repeated for the PSUR dated 20 September 2006.

The literature from 01 August 2005 through 31 July 2006 for SEROQUEL was reviewed utilizing [REDACTED] ^{(b) (4)}

[REDACTED] The search was designed to capture all relevant safety information with the use of the active ingredient, quetiapine.

The sponsor stated that in their opinion, the results of the literature searches reflect the known safety profile for Seroquel IR and do not highlight any additional issue affecting the safety of Seroquel SR.

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate.

7.2.4 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

There were no studies addressing metabolic, clearance, or interaction in this submission.

7.2.6 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

There are no recommendations for further study.

7.2.7 Assessment of Quality and Completeness of Data

The efficacy data was examined by the statistical reviewer, Phillip Dinh, Ph.D., and there were no outliers or sites identified that were felt to be driving the efficacy results. Two (2) sites in Ukraine were chosen for Division of Scientific Investigations (DSI) inspection: Dr. Natalia Maruta and Dr. Vladislav Demchenko. This was based on the number of enrollments. Results of the DSI inspections are described in section 3.4.

An audit of the Case Report Forms (CRF's), Narrative Summaries, and adverse event data listings was conducted for 2 of the 7 patients⁵ with submitted CRF's whom I randomly selected from the database for this supplement. The adverse event data listings examined were AELOG.xpt.

An examination of the adverse event information across these sources for each of the 2 patients revealed reasonable consistency and completeness.

7.2.8 Additional Submissions, Including Safety Update

There was no safety update because the study was completed at the time of submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This submission revealed only findings consistent with the previously observed safety profile of QTP SR.

⁵ This consisted of patients E1206004 and E1305001.

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 sponsor's submission contained only one study.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Please see Section 7.1.5.6

7.4.2.2 Explorations for drug-demographic interactions

Please see Section 7.1.5.6.

7.4.3 Causality Determination

Because the double-blind period of study 004 followed a QTP SR open-label treatment period, causality was difficult to interpret and was not discussed in this review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

QTP SR has been approved for doses of 400, 600, and 800 mg/day. This submission did not contain any fixed dose studies.

8.2 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

8.3 Special Populations

Please see Section 6.1.4.

8.4 Pediatrics

The sponsor's submission contains a request for a full pediatric waiver for NDA 20-639 (SEROQUEL), but does not contain information regarding pediatric issues for this NDA. Please see Section 8.4 of my April 9, 2007 review of NDA 22-047 for a discussion of the sponsor's previous pediatric plans.

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drugs Advisory Committee.

8.6 Literature Review

The sponsor stated that overall conclusions regarding the safety of Seroquel SR were supported by the results of a worldwide literature search for Seroquel IR (immediate release) tablets reported in the Periodic Safety Report dated 19 September 2005, Section 7.3 Published Studies. They report that this literature search was recently repeated for the PSUR dated 20 September 2006.

The literature from 01 August 2005 through 31 July 2006 for SEROQUEL was reviewed utilizing [REDACTED] (b) (4)

[REDACTED] The search was designed to capture all relevant safety information with the use of the active ingredient, quetiapine.

The sponsor stated that in their opinion, the results of the literature searches reflect the known safety profile for Seroquel IR and do not highlight any additional issue affecting the safety of Seroquel SR.

8.7 Postmarketing Risk Management Plan

There are no additional recommendations.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor has provided evidence from one study (study 004) that supports the claim of (b) (4) QTP SR in adult patients with schizophrenia at doses of 400 to 800 mg once daily. (b) (4)

Review of the safety database revealed no findings which were attributable to QTP SR treatment and inconsistent with the previously observed safety profile for quetiapine.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this application be granted approvable status. There is a request⁶ to which the sponsor has not yet responded. This response will be reviewed in an addendum.

In addition, it is recommended that the following be conveyed to the sponsor in the approvable letter:

1. Please provide information concerning overdose experience.
2. Please provide information on withdrawal of your product in other countries and submission of marketing authorization applications to foreign regulatory agencies.
3. You state that no patient had a serious adverse event leading to death during the open label stabilization period and that there was one fatal SAE during the randomized treatment period. Please explicitly state whether or not there were any deaths during or immediately following both the open label stabilization period and randomized treatment period.
4. Please provide demographic analyses for efficacy (e.g., subset analyses to evaluate the effect of age and gender on treatment response as measured by primary efficacy variable) for the interim ITT population.
5. Your submission does not describe how the inclusion criterion of a “stable dose of quetiapine SR” was determined. Please provide this information.
6. Regarding the inclusion criteria of a PANSS score \leq 60 at the enrollment and baseline visits, you do not specifically state whether this refers to a PANNS total score, PANSS-Positive score (PANSS-P), PANSS-Negative score (PANSS-N), or PANSS-General Psychopathology score (PANSS-G). Please clarify.

⁶ Primary efficacy analysis excluding patients who a) did not have change of < 10 points in the PANNS total score from enrollment to baseline, b) did not meet inclusion criteria at enrollment (including the patients described on page 120 of 3494 of the Clinical Study Report), and c) did not meet inclusion criteria at randomization (including the patients described on page 120 of 3494 of the Clinical Study Report).

7. Regarding the relapse definition of an increase on PANSS score of 30% from baseline, you do not specifically state whether this refers to a PANSS total score, PANSS-Positive score (PANSS-P), PANSS-Negative score (PANSS-N), or PANSS-General Psychopathology score (PANSS-G). Please clarify.

Final approval is contingent on satisfactory responses to the concerns conveyed in this request and in the approvable letter, satisfactory statistical and CMC reviews, and mutual agreement on labeling (see section 9.4).

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

9.3.1 Risk Management Activity

There are no recommendations for risk management beyond those already in the sponsor's proposed labeling and in the undersigned reviewer's comments on the sponsor's proposed labeling. Please see Section 9.4 for further details.

9.3.2 Required Phase 4 Commitments

There are no additional recommendations.

9.3.3 Other Phase 4 Requests

There are no additional recommendations.

9.4 Labeling Review

The following comments are based on a review of the clinical sections of sponsor's proposed labeling as presented in their July 11, 2007 submission.

Please see Section 9.4 of my review for NDA 22-047 for additional labeling recommendations for SEROQUEL XR. Below is my review of sections of labeling pertaining specifically to this NDA.

(b) (4)

9.5 Comments to Applicant

See section 9.2 of this review.

Michelle M. Chuen, M.D.
September 6, 2007

cc: NDA 22-172
HFD-130/Division File
HFD-130/MChuen
/NKhin
/MMathis
/TLaughren
/KUpdegraff

10 APPENDICES

10.1 Review of Individual Study Reports

Study 004⁷

Investigators/Sites

Twenty eight investigators conducted this study at 26 sites in Europe (2 in Bulgaria, 4 in Poland, 9 in Russia, and 6 in Ukraine) and Asia (5 in India). Investigators and sites are listed in Appendix 10.3.1 in Section 10.3 extracted from the sponsor's submission.

Objectives

By protocol, the objective of this trial was to demonstrate superior efficacy of quetiapine fumarate sustained-release (SR) to placebo by evaluating relapse prevention in long-term use in patients with schizophrenia as measured by the time to first psychiatric relapse up to one year (time to relapse was assessed using randomization and time to first instance of the first psychiatric relapse).

Relapse was defined as deterioration in the patient's condition despite study drug dose adjustments according to at least one of the definitions stated below:

- hospitalization due to worsening of the schizophrenia
- an increase on the Positive and Negative Syndrome Scale (PANSS) score of 30% from baseline (randomization)
- a rating of much worse or very much worse (score 6 or 7) on the Clinical Global Impression–Global Improvement (CGI-I) scale
- need for any other antipsychotic medication to treat psychosis

Patient Sample

Important inclusion criteria were:

- age 18 to 65 years, inclusive
- documented clinical diagnosis of schizophrenia for at least 2 years, as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria
- clinically stable before entering the study, i.e., a CGI-S ≤ 4 and treatment with anti-psychotic agents(s) unchanged (both compound and dose) within 4 weeks prior to entering the study
- clinically stable during the stabilization period, i.e., he/she is receiving a stable dose of quetiapine SR⁸, had a CGI-S ≤ 4 at enrollment and baseline with no change ≥ 10 points in

⁷ Note that important protocol changes are incorporated into my description of the protocol.

⁸ Of note, the sponsor does not describe how a "stable dose" was determined.

PANSS total score from enrollment to baseline visit or from enrollment to Week -8 (8 weeks before randomization)

- A PANSS score⁹ ≤ 60 at the enrollment and baseline visits

The following were relevant exclusion criteria:

- at significant risk of suicide
- diagnosis of any DSM-IV Axis I disorder other than schizophrenia, concurrent organic mental disorder, or mental retardation
- history of non-compliance
- diabetes mellitus (DM) fulfilling one of the following criteria:
 - unstable DM defined as enrollment HbA1c >8.5%
 - admitted to hospital for treatment of DM or DM related illness in past 12 weeks
 - not under care of physician responsible for patient's DM care
 - physician responsible for patient's DM care did not indicate that patient's DM is controlled
 - physician responsible for patient's DM care did not approve patient's participation in the study
 - had not been on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period was not less than 8 weeks
 - taking insulin whose daily dose on one occasion in the past 4 weeks was more than 10% above or below their mean dose in the preceding 4 weeks
- clozapine use within two months and/or valproic acid, lithium or antidepressants within the past month
- depot antipsychotic injection within 1 dosing interval (for the depot)
- known intolerance to, or lack of response to previous treatment with quetiapine
- use of any of the following potent cytochrome P450 3A4 inhibitors within 2 weeks (e.g.: ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluvoxamine, nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir)
- use of any of the following potent cytochrome P450 3A4 inducers (e.g., phenytoin, carbamazepine, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St John's wort) within 2 weeks
- female patients who were pregnant, lactating or at risk of pregnancy
- a thyroid-stimulating hormone (TSH) concentration more than 10% above the upper limit of the normal range of the laboratory used for sample analysis, whether or not the patient was being treated for hypothyroidism

⁹ Of note, the sponsor does not specifically state whether this refers to a PANNS total score, PANSS-Positive score (PANSS-P), PANSS-Negative score (PANSS-N), or PANSS-General Psychopathology score (PANSS-G).

Design

This was a one-year, multi-center, randomized, double blind, parallel group, placebo-controlled study. A 16-week stabilization period preceded randomization. During a 4-day cross-titration phase, ongoing antipsychotic treatment was phased out and quetiapine SR was phased in according to the following table extracted from the sponsor's submission:

	Day 1	Day 2	Day 3	Day 4
Ongoing antipsychotic treatment	75% ^a	50% ^a	25% ^a	0%
Quetiapine SR	300 mg	600 mg	400, 600 or 800 mg	400, 600 or 800 mg

^a Remaining dose

For the remaining period of the 16-week stabilization period a flexible dosing between 400 mg and 800 mg/day was applied with the minimum dose adjustment of 200 mg/day. If the ongoing anti-psychotic was a depot medication, the start of the stabilization period was planned to take place 5-7 days prior to the next planned depot injection. Patients were instructed to take the investigational product once daily in the evening.

Patients were judged clinically stable if they met the following criteria: CGI-S ≤ 4 and a PANSS score¹⁰ ≤ 60 at enrollment and baseline with no change ≥ 10 points in PANSS total score from enrollment to baseline visit or from enrollment to Week -8 (8 weeks before randomization) and were receiving a stable dose of quetiapine SR. Patients to be enrolled in the stabilization period were patients already receiving a stable dose of antipsychotic medication and whom the principal investigator at each site judged clinically stable.

Following randomization, a cross-titration of 4 days started where open-label quetiapine SR was phased out and blinded quetiapine SR was phased in according to the following table extracted from the sponsor's submission:

¹⁰ Of note, the sponsor does not specifically state whether this refers to a PANNS total score, PANSS-Positive score (PANSS-P), PANSS-Negative score (PANSS-N), or PANSS-General Psychopathology score (PANSS-G).

	Day 1	Day 2	Day 3	Day 4
Open-label quetiapine SR	75% ^a	50% ^a	25% ^a	0%
Doses in mg and number of tablets	300 (2x50,1x200)	200 (1x200)	100 (2x50)	0 mg
	450 (1x50,2x200)	300 (2x50,1x200)	150 (3x50)	0 mg
	600 (3x200)	400 (2x200)	200 (1x200)	0 mg
Blinded quetiapine SR or placebo				
Doses in mg and number of tablets	100 (2x50)	200 (1x200)	300 (2x50,1x200)	400 (2x200)
	150 (3x50)	300 (2x50,1x200)	450 (1x50,2x200)	600 (3x200)
	200 (1x200)	400 (2x200)	600 (3x200)	800 (4x200)

Tablets of 50 mg and 200 mg will be available

^a Remaining dose

The cross-titration was followed by a one-year treatment period (i.e., randomized period) during which dosing was flexible in 200 mg increments, i.e., the dose could be 400, 600 or 800 mg/Day. Dosage could be adjusted for therapeutic efficacy and/or tolerability reasons within the allowed dosing range at every visit or at extra visits, when needed, throughout the study.

The patients were instructed to take the investigational product once daily, in the evening. In case of deterioration of schizophrenia, the investigator was advised to make dose adjustments of the investigational product. If the symptoms were not sufficiently decreased, the investigator could discontinue the patient from the study.

Compliance was to be discussed at each study Visit. Patients judged to be non-compliant could continue in the study, but were to be counseled on the importance of taking their study medication as prescribed. Patients who were repeatedly or severely non-compliant could, at the Investigator's discretion, be discontinued.

Efficacy Assessments

The protocol-defined primary efficacy variable was time to relapse, with relapse defined as deterioration in the patient's condition despite study drug dose adjustments according to at least one of the definitions stated below:

- hospitalization due to worsening of the schizophrenia.
- an increase on PANSS score¹¹ of 30% from baseline
- a rating of "much worse" or "very much worse" on the CGI-I

¹¹ Of note, the sponsor does not specifically state whether this refers to a PANNS total score, PANSS-Positive score (PANSS-P), PANSS-Negative score (PANSS-N), or PANSS-General Psychopathology score (PANSS-G).

- need of other antipsychotic medication to treat psychosis

The PANSS was administered at baseline, Month 1, 2, 3, 4, 5, 6, 9, and 12 (or at relapse/discontinuation). The CGI was administered at Day 14, Month 1, 2, 3, 4, 5, 6, 9, and 12 (or at relapse/discontinuation). Of note, these scales were not administered at Month 7, 8, 10, or 11. According to an 8/30/07 email from Dr. Phillip Dinh, Statistical Reviewer, 43 of the 45 relapses occurred before Day 180, so this was unlikely to negatively impact the efficacy results.

No key secondary variables were identified.

Efficacy Analysis

The ITT population were those who took randomized study treatment, classified according to the treatment to which they were randomized. The interim ITT population included all ITT patients used in the interim analysis. Only the visits used in the interim analysis were included. The interim ITT population was used for the primary efficacy analysis.

The primary outcome variable was time to schizophrenic relapse. The main analysis of time to schizophrenic relapse was a Cox proportional hazards model to estimate the hazard ratio of relapse rate between treatment groups, with a 95% confidence interval. A two-sided test of the null hypothesis that the hazard ratio was equal to unity was performed. As test statistic, the score test was used.

Due to the group sequential design of the study, adjusted significance levels for the primary tests were used to ensure an overall type I error of $\alpha=0.05$. The O'Brien-Flemming boundary was used which had an adjusted significance level of 0.004455 for the test after the first interim analysis.

For patients not experiencing a relapse, the time to event was censored when a patient discontinued or completed the study without meeting any of the relapse criteria. The time of censoring was the date of the patient's final assessment.

Treatment was the only independent variable in the model; no other covariates were used.

Due to the large number of centers in relation to the number of patients, the effects of center and treatment-by-center interaction were not formally investigated in the primary analysis. No analysis was performed on individual centers or a subgroup of centers.¹²

Interim analysis was performed by a DSMB, which analyzed the primary outcome variable (relapse), only.

¹² According to an 8/27/07 email from statistical reviewer, Dr. Phillip Dinh, this was appropriate.

To account for the possibility of early closure of the study due to an observed treatment difference in the interim analysis, the sample size and the significance level were adjusted according to the O'Brien-Flemming method. At each analysis the observed p-value was compared to the boundary significance level rather than the overall significance level alpha. In this study two interim analyses were planned after 45 and 60 observed relapses. If the study would not have been stopped at one of the interim analyses, the study would have continued until 90 relapses had been observed.

The calculation in the table below was based on an adjusted critical value of 2.011 for the standardized test statistics. The value of 2.011 for analyses after 45, 60 and 90 relapses was calculated using a multidimensional integration routine. Computing known values internally validated this integration routine.

	Number of observed relapses	O'Brien-Flemming boundary significance levels
Interim analysis I	45	0.004455
Interim analysis II	60	0.013779
Final analysis	90	0.044325

At the first interim analysis (after 45 relapses) the decision to stop the study was taken after recommendation from the DSMB, since the result was significant at the 0.004455 significance level.

Baseline Demographics

The table below displays the demographic characteristics of the interim ITT patient sample by treatment group. No patient under age 18 or over age 63 participated in this study. There were no major differences between the 4 treatment groups with respect to age, gender, or race.

Treatment (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Oriental	Other
QTP SR (84)	36.6	18-63	58	42	100	0	0	0
Placebo (87)	33.2	18-56	62	38	100	0	0	0

¹³ Figures may not add up to 100% due to rounding.

Baseline Severity of Illness

For the interim ITT population, treatment groups had no major differences with respect to mean baseline PANSS total score (mean scores of 48.3 in QTP SR patients and 48.1 in placebo patients).

Patient Disposition

Three hundred twenty seven (327) patients entered the open-label phase and were dispensed study medication. A total of 130 (40%) patients discontinued treatment during the open-label treatment period, mostly due to “study stopped by sponsor” (67/327), “patient not willing to continue” (35/327), “other” (12/327), and lost to follow-up (8/327).

A total of 197 patients were randomized to double-blind (103 to placebo and 94 to quetiapine SR). Up to the interim analysis, 171 patients had been randomized (87 patients to placebo group and 84 patients to quetiapine group), which comprised the interim ITT population.

The numbers of total ITT patients in-study over time are displayed in Appendix 10.3.2. Of note, the sponsor did not provide this data for the interim ITT population. However, per an 8/30/07 conversation with Dr. Phillip Dinh, Statistical Reviewer, this data would not have any impact on our efficacy conclusions.

When the study was stopped by the sponsor, 83% (78/94) of QTP SR patients and 38% (39/103) of placebo patients remained in the study. When the study was stopped by the sponsor, for the randomized safety population, overall dropout rates were much higher in the placebo group [17% (16/94) of QTP SR patients and 62% (64/103) of placebo patients]. When the study was stopped by the sponsor, based on the randomized safety population, dropout rates due to relapse were also much higher in the placebo group [12% (11/94) of QTP SR patients and 49% (50/103) of placebo patients].

Of note, 14% (13/94) of QTP SR patients and 13% (13/103) of placebo patients were randomized despite not meeting the inclusion criteria for randomization. In addition, at enrollment, 13.2% (26/197) of randomized patients were enrolled despite not meeting inclusion criteria.

Dosing Information

Dosing information is displayed in Table 10.1.3 below.

TABLE 10.1.3: MEAN DAILY DOSE OF QTP SR FOR PATIENTS BY TIME INTERVAL, RANDOMIZED SAFETY POPULATION, RANDOMIZED PERIOD

Mean dose (mg/day)	Day 1 - Day 14		Day 15 - Day 30		Month 2		Month 3 - Month 4		≥ Month 5		Total	
	PLA N=103 n(%)	QTP SR N=94 n(%)	PLA N=93 n(%)	QTP SR N=92 n(%)	PLA N=76 n(%)	QTP SR N=86 n(%)	PLA N=43 n(%)	QTP SR N=69 n(%)	PLA N=15 n(%)	QTP SR N=43 n(%)	PLA N=103 n(%)	QTP SR N=94 n(%)
<400 mg	0	0	0	1(1.1)	0	0	0	0	0	0	0	0
400mg - ≤500mg	25(24.3)	13(13.8)	20(21.5)	14(15.2)	18(23.7)	13(15.1)	11(25.6)	12(17.4)	4(26.7)	8(18.6)	23(22.3)	14(14.9)
>500mg - ≤600mg	28(27.2)	34(36.2)	24(25.8)	31(33.7)	18(23.7)	28(32.6)	11(25.6)	19(27.5)	5(33.3)	14(32.6)	23(22.3)	30(31.9)
>600mg - ≤700mg	4(3.9)	0	1(1.1)	1(1.1)	1(1.3)	2(2.3)	0	2(2.9)	0	1(2.3)	4(3.9)	4(4.3)
>700mg - ≤800mg	45(43.7)	45(47.9)	48(51.6)	45(48.9)	39(51.3)	43(50.0)	21(48.8)	36(52.2)	6(40.0)	20(46.5)	52(50.5)	44(46.8)
>800mg	1(1.0)	2(2.1)	0	0	0	0	0	0	0	0	1(1.0)	2(2.1)

N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Study: D1444C00004 Source document: ST_DOSE_DIST_RAND415.SAS. Generated: 11:30:50 11Sep2006 DB version prod: 6.

Concomitant Medications

The table below, extracted from the sponsor’s submission, details permitted, restricted, and prohibited medications, where Visit 1a refers to the enrollment visit (prior to entering the open-label stabilization period).

Use category	Type of medication	Timelines and instructions	Reason (if applicable)
Permitted			
	Any previous, current or new medications for medical illnesses, not listed under restricted or prohibited medication Sections below.	As needed based on Investigator’s judgment and the patients medical needs.	
	Oral benztropine mesylate (up to 6 mg/Day) may be administered. If this is not locally available, the following may be used: Trihexyphenidyl up to 6 mg/Day or biperiden 6 mg/Day or procyclidine up to 30 mg/Day.	Prophylactic use of these medications is not permitted.	For the treatment of any new emerging EPS AEs.
	Lorazepam can be used at a maximum daily dose of 4 mg/Day. When lorazepam is not available in a given country oxazepam at a maximum daily dose of 60 mg/Day can be used.	Not more than 4 consecutive days in any 7-Day period.	To treat symptoms of agitation

	Agents designed to prevent pregnancy: intrauterine device in place, oral contraceptives, or injectable or implantable hormonal agents.		To avoid pregnancy during the study.
Restricted	Anticholinergic medication used prior to entry in the study	Should be discontinued by end of the first week of quetiapine SR initiation. Thereafter the drugs mentioned above may be used to treat emergent EPS adverse events but not prophylactically.	Use of anticholinergic medication is a secondary variable under study.
Restricted cont.	Patients taking medication for sleep can continue to do so provided they are only taken at bedtime for sleep. If sleep medications are initiated after enrollment, the allowed medications are: zolpidem tartrate maximum permissible dose is 10 mg/Day. chloral hydrate: maximum permissible dose is 2 g/Day zaleplon: maximum permissible dose is 20 mg/Day. zopiclone maximum permissible dose is 7.5 mg/Day.		
Prohibited	Antihypertensive medication including betablockers, thiazide diuretics, alpha-blockers, etc. Quetiapine, as medication outside the study Clozapine Antidepressants, lithium, valproic acid	Stable dosage for at least 1 month before Visit 1a and during study. During the study Within 2 months of Visit 1a and during the study Within 1 month of Visit 1a and during study	Avoid confounding factors Medication under study + avoid confounding factors Avoid confounding factors Avoid confounding factors

	Previous and concomitant antipsychotic medication other than quetiapine SR	Should be withdrawn during quetiapine SR initiation. Not allowed during the study after Day 8 of the stabilization period	Avoid confounding factors
	All benzodiazepine, anxiolytic, hypnotic and sedative medication except those listed above in "permitted" or "restricted".	During the study.	Avoid confounding factors
	Depot antipsychotics	Within 1 dosing interval prior to Visit 1a	Exclusion criteria
Prohibited cont.	All contraindicated medications, as detailed in country specific Prescribing Information for quetiapine	At enrollment and during the study.	Patient safety.
	Potent cytochrome P450 3A4 inducers (phenytoin, carbamazepine, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St John's wort)	Within 2 weeks prior to Visit 1a.	Exclusion criteria Pharmacokinetics interaction
	Potent cytochrome P450 3A4 inhibitors (including but not limited to ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluvoxamine, nefazodone, troleandomycin, inidinavir, nelfinivir, ritonavir, and saquinavir)	Within 2 weeks prior to Visit 1a.	Exclusion criteria Pharmacokinetics interaction

With respect to the percentages of interim ITT population patients using various concomitant medications during the study, there was no major difference between treatment groups (21% in placebo patients and 20% in QTP SR patients), and the most frequently used were paracetamol and benzodiazepines (diazepam, lorazepam, and zolpidem). Based on the randomized safety population, there were 8/103 (8%) patients in the placebo group and 1/94 (1%) patient in the QTP SR group identified as protocol violators because of prohibited medication use during the double-blind period.

Efficacy Results

Efficacy data displays may be found in the following figures and tables.

TABLE 10.1.4: TIME TO SCHIZOPHRENIC RELAPSE (INTERIM ITT POPULATION), SCORE TEST, COMPARISON OF QTP SR VERSUS PLACEBO WITH COX REGRESSION

	PLA N=87	QTP SR N=84
No. of relapses (%)	36 (41.4)	9 (10.7)
Comparison between treatment groups		
Hazard ratio	0.16	
95% CI	0.08, 0.34	
p-value	<.0001	

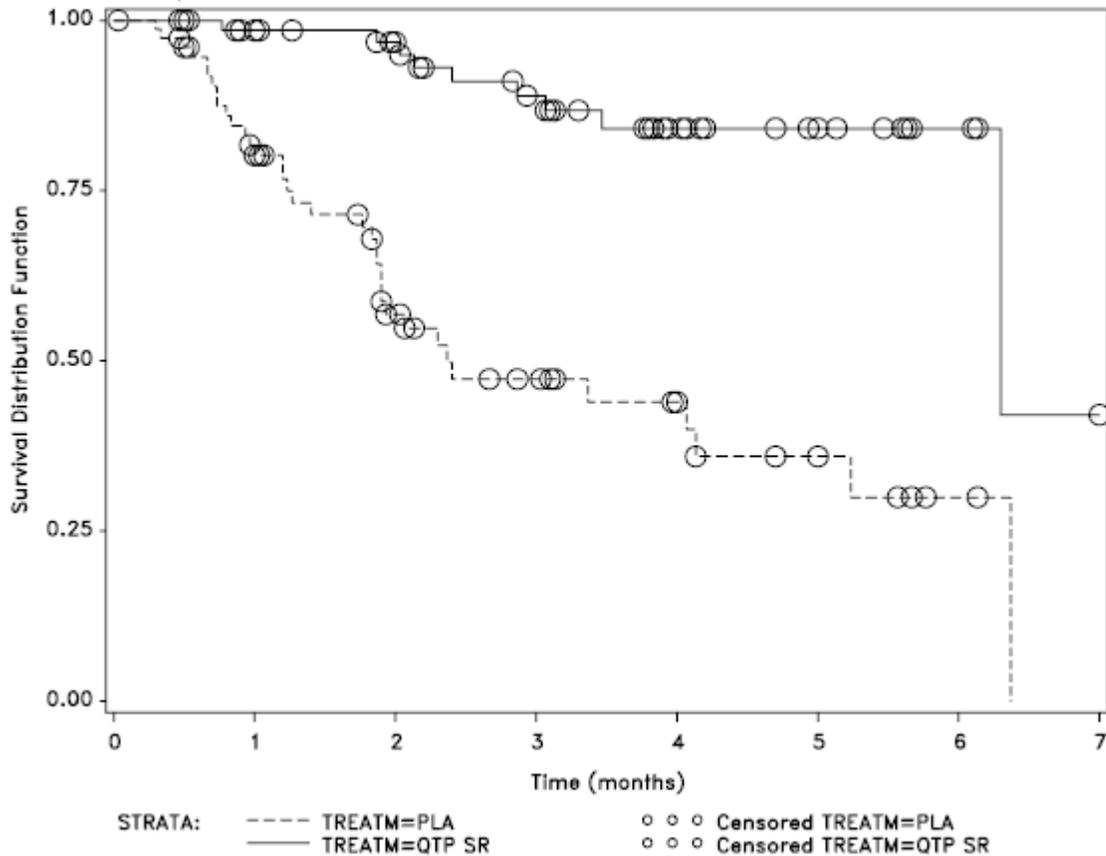
CI Confidence interval. ITT Intention-to-treat. PLA Placebo. QTP Quetiapine. SR Sustained-release. N Number of patients in treatment group.

Note: Score test used in Cox regression analysis.

Note: Due to the low rate of relapse in the quetiapine SR group it is not possible to calculate a reliable median time to relapse. The number of relapses is presented for information. The p value relates to the analysis of time to schizophrenic relapse.

Study: D1444C00004 Source document: ETI_COX_SCORE_ITT.SAS. Generated: 15:23:14 30Aug2006 DB version prod: 6.

FIGURE 10.1.1: TIME TO RELAPSE, KAPLAN-MEIER CURVES (INTERIM ITT POPULATION)



ITT Intention-to-treat. PLA Placebo. QTP Quetiapine. SR Sustained-release.

Note: The drop of the quetiapine SR Kaplan Meier curve at the end of the figure is due to a late relapse of a single patient at a time where only two quetiapine SR patients were at risk. The drop of the placebo Kaplan Meier curve at the end of the figure is due to a late relapse of a single patient at a time where no other placebo patient was at risk. The right hand parts of the Kaplan Meier curves (after 6 months exposure) depend on single events. These parts doesn't give reliable estimates of the percentage of relapse free patients.

Study: D1444C00004 Source document: ETI_KM_IITT.SAS. Generated: 15:40:11 30Aug2006 DB version prod: 6.

The primary efficacy analysis was a Cox proportional hazards model and the result was significant. The relapse rate for the placebo-treated patients was 48% (50/103), compared with a 12% (11/94) relapse rate for QTP SR-treated patients.

Per a 3/29/07 email from statistical reviewer, Phillip Dinh, Ph.D., none of the study sites adversely impacted the efficacy results.

Conclusions

197 patients with schizophrenia who were clinically stable on flexible doses of QTP SR 400 mg to 800 mg/day were randomized to either flexible doses of QTP SR (n=94) or placebo (n=103) for observation of relapse. Stabilization during the open-label phase was defined by meeting the following criteria: receiving a stable dose of quetiapine SR, a CGI-S ≤ 4 and a PANSS score ≤ 60 with no change ≥ 10 points in PANSS total score from enrollment to baseline visit or from enrollment to Week -8 (8 weeks before randomization). Relapse was defined as deterioration in the patient's condition according to at least one of the following: hospitalization due to worsening of the schizophrenia, an increase on the PANSS score of 30% from baseline, a rating of "much worse" or "very much worse" on the CGI-I, or need of other antipsychotic medication to treat psychosis. In the randomized phase, patients receiving QTP SR experienced a significantly longer time to relapse.

10.2 Line-by-Line Labeling Review

See section 9.4 for a discussion of the clinical changes to labeling based on this NDA.

10.3 Appendix to Individual Study Reports

APPENDIX 10.3.1: LIST OF INVESTIGATORS FOR STUDY 004

Country	Centre No.	Name (First name, Last name)	Centre address	Qualifications	Present position	Role in the study
Bulgaria	1001	Todor Tolev	State Psychiatric Hospital, 1, Magda Petkanova, Radnevo 6260	MD	Medical Director	Principal Investigator
Bulgaria	1002	Loris Sayan	Complex "Lazur", Park "Ezero", Bourgas 8000	MD	Manager	Principal Investigator

Quetiapine Fumarate Sustained-Release Tablets

Poland	1101	Mariusz Perucki	Regional Neuropsychiatric Hospital, Siekowo 81, Przemet 64-100	MD, MSc	Chief of Psychiatric Clinic	Principal Investigator
Poland	1102	Alexander Araszkievicz	Medical Academy in Bydgoszcz, ul.Kurpinskiego 19, Bydgoszcz 85-096	MD, PhD, Professor	Head of Department	Principal Investigator
Poland	1103	Witold Rembalski	Regional Neuropsychiatric Hospital, Pl.Paderewskiego 1a, Koscian 64-000	MD, MSc	Head of Psychiatric Ward	Principal Investigator
Poland	1104	Jaroslawn Strzelec	Inventiva Biomedical and Sport Research, 12a Tylna Str., Tuszyn 95-080	MD, PhD	Head of Outpatient Psychiatric Department	Principal Investigator
Russia	1201	Aleksander Kociubynski	Bekhterev Psychoneurological Research Institute, 3 Bekhterev str, St Petersburg 193019	MD, PhD	Director of Department	Principal Investigator
Russia	1202	Galina Panteleeva	Mental Health Research Centre of RAMS, 34 Kashiroskoye shosse, Moscow 115522	MD, PhD	Head of Clinical Department	Principal Investigator
Russia	1203	Mikhail Y Popov	Psychiatric Hospital no 3 of Skortsov-Stepanov Psychiatry, 36 Fersmskoye shosse, St. Petersburg 197341	MD, PhD	Senior Research Associate	Principal Investigator
Russia	1204	Vladimir Tochilov	Mechnikov Medical Academy, Moika Embarkment 126, St. Petersburg 190000	MD, PhD	Chief of Department of Psychiatry	Principal Investigator
Russia	1205	Aleksandr Mouzitchenko	Russian State Medical University, Psychiatric Hospital no 4, Potesnaya 3, admin.building no 1, Moscow 107076	MD, PhD	Professor	Principal Investigator
Russia	1206	Mikhail Ivanov	Bekhterev Psychoneurological Research Institute, 3, Bekhterev str, St.Petersburg 193019	MD, PhD	Head of Department	Principal Investigator
Russia	1207	Yuri V Popov	Bekhterev Psychoneurological Research Institute, 3, Bekhterev str, St.Petersburg 193019	MD, PhD	Deputy Director of Bekhterev Research Institute	Principal Investigator
Russia	1208	Mikhail Burducovsky	4 th Psychiatric Hospital, Department of Psychiatry, 128/71 Ligovsky Prospect, St.Petersburg 191119	MD, PhD	Head Doctor of Psychiatric Hospital	Principal Investigator
Russia	1209	Yuri Alexandrovsky	Serbsky National Research Centre for Social and Forensic Psychiatry, 47, Volokolamskoye shosse, Moscow 123367	MD, PhD	Professor	Principal Investigator
Ukraine	1301	Viktor Samokhvalov	Crimean State Medical University, Department of Psychiatry, R.Luxemburg Str.27, Symferopil 95006	MD, Professor	Chief of Psychiatric Department	Principal Investigator
Ukraine	1302	Valeriy Bitensky	Odesa State Medical University, Department of Psychiatry, Acad. Vorobyova Str.9, Odesa 65006	MD, PhD, Professor	Head of Psychiatric Department	Principal Investigator
Ukraine	1303	Svitlana Moroz	Dnipropetrovsk Regional Clinical Hospital, Psychosomatic Center, Oktyabrskaya Sqr.14, Dniiproptrevsk 49616	MD	Head of Psychosomatic Department	Principal Investigator
Ukraine	1304	Natalia Maruta	Institute of Neuorlogy, Psychiatry and Narcology within AMS of Ukraine, Acad. Pavlov Str.26, Kharkiv 61068	MD, PhD, Professor	Head of Department of Borderline Disorders	Principal Investigator
Ukraine	1305	Vladislav Demchenko	Kyiv Psychosomatic Hospital no 2, Department of Psychiatry, Myropilska Str.8, Kyiv 02660	MD	Head and Medical Director	Principal Investigator

Ukraine	1306	Iryna Viokh	D.Galytsky Lviv State Medical University, Department of Psychiatry, Kulparkvivska Str.95, Lviv 79021	MD, PhD, Professor	Head of Department	Principal Investigator
India	1401	Prasad Rao	Asha Hospital, Department of Psychiatry, 298, Road no.14, Banjara Hills, Hyderabad 500034	MD	Director	Principal Investigator
India	1402	Podila Sharma	Kasturba Hospital, Department of Psychiatry, Manipal, Kamataka 576104	MD, professor	Head of Psychiatric Department	Principal Investigator
India	1403	Jitendra Trivedi	King George Medical University and GM & Associated Hospital, Department of Psychiatry, Shahmina Road, Lucknow, Uttar Pradesh 226003	MD, professor	Psychiatric Department	Principal Investigator
India	1404	Nagesh Pai	K.S Hegde Medical Academy, Department of Psychiatry, Daralakette, Post Nityananda Nagar, Mangalore, Kamataka 574160	MD, professor	Head of Psychiatric Department	Principal Investigator
India	1405	Shiv Gautam	Psychiatric Centre, Department of Psychiatry, Janta Colony, Jaipur, Rajasthan 302004	MD, professor	Head of Psychiatric Department	Principal Investigator

APPENDIX 10.3.2: PANNS TOTAL SCORE, CHANGE FROM RANDOMIZATION BY VISIT (OC, TOTAL ITT POPULATION)

		PLA N=103	QTP SR N=94
Randomization			
n ^a		102	93
Randomization	Mean (SD)	47.34 (7.71)	48.01 (8.00)
Month 1			
n ^a		99	93
Randomization	Mean (SD)	47.41 (7.75)	47.92 (8.07)
Visit	Mean (SD)	55.80 (16.71)	49.02 (11.42)
Change	Mean (SD)	8.38 (14.76)	1.10 (8.58)
	Median	2.00	0.00

	Min to max	-6.0 to 66.0	-7.0 to 65.0
Month 2			
n ^a		61	78
Randomization	Mean (SD)	48.13 (7.56)	48.22 (7.92)
Visit	Mean (SD)	55.00 (14.12)	48.55 (11.65)
Change	Mean (SD)	6.87 (12.38)	0.33 (7.09)
	Median	2.00	-1.00
	Min to max	-9.0 to 47.0	-12.0 to 42.0
Month 3			
n ^a		28	62
Randomization	Mean (SD)	49.00 (6.26)	47.76 (8.01)
Visit	Mean (SD)	50.89 (10.96)	47.42 (11.31)
Change	Mean (SD)	1.89 (9.07)	-0.34 (6.69)
	Median	0.00	-1.00
	Min to max	-8.0 to 36.0	-12.0 to 25.0
Month 4			
n ^a		20	47
Randomization	Mean (SD)	48.95 (6.24)	47.83 (7.58)
Visit	Mean (SD)	52.80 (13.14)	45.17 (8.58)
Change	Mean (SD)	3.85 (11.31)	-2.66 (5.50)
	Median	2.00	-2.00
	Min to max	-9.0 to 36.0	-26.0 to 9.0
Month 5			
n ^a		13	41
Randomization	Mean (SD)	49.85 (6.08)	48.22 (7.18)
Visit	Mean (SD)	51.31 (10.14)	46.27 (7.79)
Change	Mean (SD)	1.46 (10.04)	-1.95 (5.04)
	Median	-1.00	-1.00
	Min to max	-8.0 to 29.0	-15.0 to 10.0
Month 6			
n ^a		9	31
Randomization	Mean (SD)	51.78 (5.70)	47.55 (7.75)
Visit	Mean (SD)	58.78 (18.43)	46.97 (11.59)
Change	Mean (SD)	7.00 (19.24)	-0.58 (9.94)

	Median	0.00	-3.00
	Min to max	-8.0 to 50.0	-17.0 to 35.0
Month 9			
n ^a		0	2
Randomization	Mean (SD)		48.50 (4.95)
Visit	Mean (SD)		46.00 (5.66)
Change	Mean (SD)		-2.50 (0.71)
	Median		-2.50
	Min to max		-3.0 to -2.0

^a Number of patients with assessment at randomization and at the specified visit.

PANSS Positive and Negative Syndrome Scale. ITT Intention-to-treat. N Number of patients in treatment group. OC Observed Cases.

PLA Placebo. QTP Quetiapine. SR Sustained-release. SD Standard deviation.

Study: D1444C00004, Source document: ETI_PANSS_TOT_CHA400.SAS. Generated: 13:13:47 22Aug2006 DB version prod: 6.

10.4 Appendix to Integrated Review of Efficacy (Section 6)

APPENDIX 10.4.1.1: TIME TO SCHIZOPHRENIC RELAPSE, COMPARISON OF QTP SR VERSUS PLACEBO WITH COX REGRESSION FOR STUDY 004 BY AGE GROUP (TOTAL ITT POPULATION)

AGE GROUP		PLA	QTP SR
18-39	No. of patients	74	60
	No. of relapses	36	6
	Comparison between treatment groups		
	Hazard ratio	0.12	
	95% CI	0.05, 0.30	
	p-value	<.0001	
40-65	No. of patients	29	34
	No. of relapses	14	5
	Comparison between treatment groups		
	Hazard ratio	0.13	
	95% CI	0.04, 0.39	
	p-value	<.0001	

CI Confidence interval. ITT intention to treat. PLA Placebo. QTP Quetiapine. SR Sustained release. 004 D1444C00004.

Seroquel SR Submission. Source document: S_RELAPSE_AGE.SAS. Generated: 15:07:41 06Sep2006 DB version prod: 6.

Source: Table E- 39, Clinical Summary of Efficacy Section 2.7.3, SR schizophrenia.

APPENDIX 10.4.1.2: TIME TO SCHIZOPHRENIC RELAPSE, COMPARISON OF QTP SR VERSUS PLACEBO WITH COX REGRESSION FOR STUDY 004 BY GENDER (TOTAL ITT POPULATION)

SEX		PLA	QTP SR
Female	No. of patients	38	37
	No. of relapses	17	3
	Comparison between treatment groups		
	Hazard ratio	0.10	
	95% CI	0.03, 0.34	
	p-value	<.0001	
Male	No. of patients	65	57
	No. of relapses	33	8
	Comparison between treatment groups		
	Hazard ratio	0.16	
	95% CI	0.07, 0.35	
	p-value	<.0001	

CI Confidence interval. ITT intention to treat. PLA Placebo. QTP Quetiapine. SR Sustained release. 004 D1444C00004.
 Seroquel SR Submission. Source document: S_RELAPSE_SEX.SAS. Generated: 15:07:47 06Sep2006 DB version prod: 6.
 Source: Table E- 38, EU Clinical Summary of Efficacy Section 2.7.3, SR schizophrenia.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Michelle Chuen
9/27/2007 04:12:26 PM
MEDICAL OFFICER

That EA paragraph was correct in a previous version
of my review, but didn't make it to
the final version somehow. Sorry about that. I
also checked on the CMC review, and it
was not in DFS at the time of
completion of my review, so that part's correct.Thx

Ni Aye Khin
9/28/2007 04:58:28 PM
MEDICAL OFFICER

I agree with Dr. Chuen's recommendation that this application
be granted approvable status. See memo to file
for additional comments.