CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results of the multi-center, randomized, double blind, parallel group, and placebo-controlled study suggested 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.

1.2 Brief Overview of Clinical Studies

The sponsor submitted one phase III study to support the use of quetiapine SR in maintenance therapy for patients with schizophrenia. Study D1444C00004 was a multi-center, randomized, double blind, parallel-group, placebo-controlled trial conducted in Bulgaria, Poland, Russia, Ukraine, and India. The study included two phases: A total of 327 patients started the open label stabilization treatment period; 197 patients completed the stabilization period and were randomized to either quetiapine SR or placebo in the double-blind phase. The sponsor planned two interim analyses. The first interim analysis included 171 randomized patients.

All patients were Caucasian with an average age of 35 years. The male-female ratio was about 3 to 2. Doses investigated were flexible and ranged from 400 mg/day to 800 mg/day for the planned duration of one year. The primary endpoint was time to schizophrenic relapse. The primary analysis was based on the Cox proportional hazard model utilizing the Score test.

1.3 Statistical Issues and Findings

The objective of the study was to demonstrate that long-term use of quetiapine SR prevented schizophrenic relapse in patients who were stable in their psychotic symptoms. The randomization period was planned to be one year. However, at the first interim analysis after 45 relapses, upon the recommendations from the DSMB, the sponsor terminated the trial prematurely for efficacy. The interim statistical analysis utilized the O'Brien-Flemming boundary.

This reviewer confirmed the sponsor's findings that quetiapine SR was superior to placebo in the prevention of schizophrenic relapse as measured by the time to schizophrenic relapse. The primary findings were consistent for secondary supportive analyses. For schizophrenic patients, it is unethical to conduct maintenance study in the United States. Therefore, this study was conducted entirely in foreign countries. Because no data was collected in the United States, from a statistical perspective, care must be taken to generalize the results to the U.S. population. The secondary claim on the number of relapses was not pre-specified. The secondary claim on the rate of relapse, though pre-specified, it was not clear if this endpoint was concurred by the Division. In addition, because there was not any replication, the secondary endpoints on the rate of relapse and the number of relapses cannot be used for label claims.

2. INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of quetiapine fumarate SR in the relapse prevention of schizophrenia.

According to the sponsor, schizophrenia is a chronic and disabling idiopathic psychotic disorder with an estimated worldwide prevalence of approximately one percent. The costs of schizophrenia in terms of care, lost productivity, and homelessness place a high social and financial burden on the patient, family, and community. In patients with schizophrenia, compliance with a treatment program is often problematic. It is estimated that as many as fifty percent of patients with schizophrenia may fail to adhere to the treatment regimens which leads to treatment failure, relapse, hospitalization, or suicide. There are many reasons for the noncompliance. Among them, a treatment complexity is an important factor.

The Food and Drug Administration (FDA) approved quetiapine fumarate in 1997 in an immediate release (IR) form for the treatment of schizophrenia. Subsequently, the FDA approved quetiapine fumarate for the treatment of acute mania associated with bipolar disorder in 2003. In 2007, the FDA approved quetiapine fumarate in an extended release (XR) form for the acute treatment of schizophrenia. This formulation was also known as a sustained release (SR) formulation. This new presentation will permit quetiapine to be administered once daily instead of two or three times a day with the IR formulation. This treatment simplification will, hopefully, increase the compliance and decrease the treatment failure.

In addition to short-term treatment, long-term maintenance of efficacy of quetiapine is necessary to reduce or delay the risk of relapse. Clinical practice has documented the evidence of efficacy of quetiapine in long-term maintenance. However, there is not any study to compare directly quetiapine SR versus placebo in maintenance therapy. In this application, the sponsor submitted one long-term efficacy study with the intention to demonstrate that quetiapine SR is more efficacious to placebo in the prevention of relapse of schizophrenia (Study D1444C00004).

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\n20639\S_029\2007-01-22\crt\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Objectives

Primary: To demonstrate the efficacy in long-term use of quetiapine fumarate SR versus placebo in preventing relapse in schizophrenic patients.
Secondary:
- To demonstrate that quetiapine SR is superior to placebo by evaluating the risk of relapse (defined as proportion of relapses per treatment group).
- To document that quetiapine SR is superior to placebo in treating positive and negative symptoms of schizophrenia by evaluating the Positive and Negative Syndrome Scale (PANSS) total score and PANSS sub scores.
- To document the continuing stability of negative symptoms with quetiapine SR by evaluating the change in PANSS-Negative score from baseline to last visit before relapse.
- To document the effect of quetiapine SR on global clinical status as measured by the Clinical Global Impression-Severity of Illness (CGI-S), change from baseline to last visit.
- To document the effect of quetiapine SR on global clinical status as measured by the Clinical Global Impression-Improvement (CGI-I) at last visit.
- To show that quetiapine SR was safe and well tolerated in long-term use.

3.1.2 Study Design

This was a multi-center, randomized, double blind, parallel group, and placebo-controlled study. Prior to randomization, subjects were on treatment for 16 weeks to ensure that patients were clinically stable and receiving a stable dose of quetiapine. Patients were judged stable if they had:

- a CGI-S score $\leq$ 4 and a PANSS score $\leq$ 60 at baseline with no change $\geq$ 10 points in PANSS total score from enrollment to baseline visit or from enrollment to the visit 8 weeks before randomization, and
- a stable dose of quetiapine SR in the dose range 400 to 800 mg/day.

In this stabilization period, quetiapine was initiated according to a cross-titration schedule given in Table 1. Ongoing antipsychotic medication was tapered off to minimize possible adverse events associated with its discontinuation. The investigators could adjust the dose within the range of 400 mg/day to 800 mg/day according to each patient's tolerability.

Table 1. Cross-titration Schedule during the Stabilization Period

	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

(Source: Clinical Study Report: Study D1444C00004; Table 5, page 74)

The double-blind period started at randomization. Subjects were assigned to either quetiapine group or placebo group according to the cross-titration schedule given in Table 2.

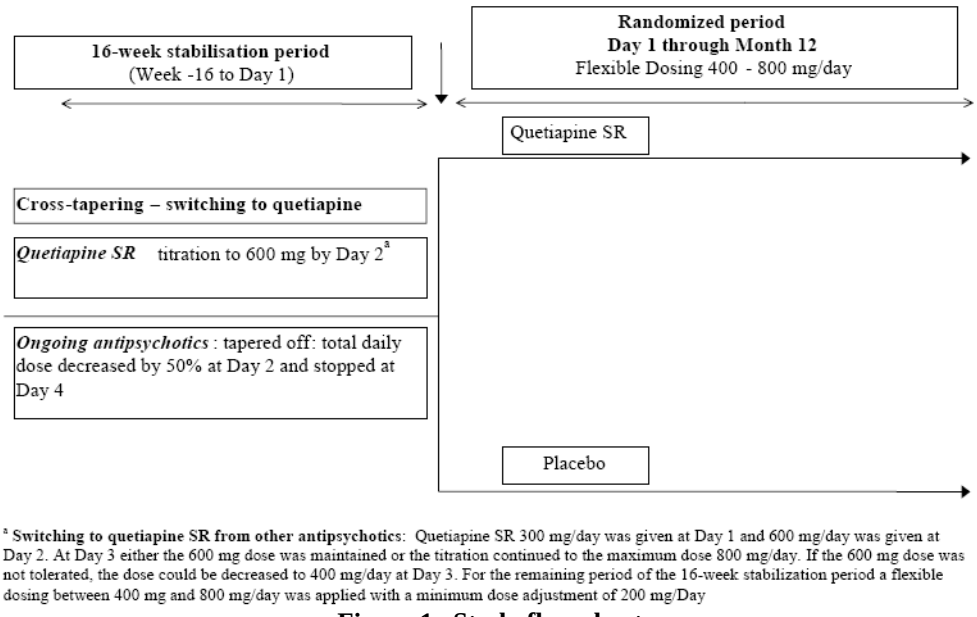
Table 2. Cross-titration Schedule during the Randomization Period

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

Tablets of 50 mg and 200 mg will be available
[a] Remaining dose

(Source: Clinical Study Report: Study D1444C00004; Table 6, page 74)

The sponsor planned to treat patients for one year or until relapse. There were two planned interim analyses. One was planned after 45 observed relapses and the second was planned after 60 relapses. The final analysis would be performed after 90 relapses. Upon the recommendation from the Data Safety and Monitoring Board (DSMB), the sponsor decided to stop the trial early for efficacy after the first interim analysis. Figure 1 shows the design of the study.



[a] **Switching to quetiapine SR from other antipsychotics**: Quetiapine SR 300 mg/day was given at Day 1 and 600 mg/day was given at Day 2. At Day 3 either the 600 mg dose was maintained or the titration continued to the maximum dose 800 mg/day. If the 600 mg dose was not tolerated, the dose could be decreased to 400 mg/day at Day 3. For the remaining period of the 16-week stabilization period a flexible dosing between 400 mg and 800 mg/day was applied with a minimum dose adjustment of 200 mg/Day

Figure 1. Study flow chart

(Source: Clinical Study Report: Study D1444C00004; Figure 1, page 61)

The study enrolled subjects from Bulgaria, Poland, Russia, Ukraine, and India from March 2005 to April 2006. Subjects included male and female between the age of 18 and 65, who were clinically stable before entering the stabilization period, and who had a PANSS score of ≤ 60 at enrollment and baseline.

The sponsor determined that 90 documented schizophrenic relapses were sufficient for a 90% power to detect a hazard ratio of 0.50 with a two-tailed test at a significant level 0.05. To adjust the significant level to account for interim analyses, the sponsor utilized the O'Brien-Flemming's method.

3.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint is the time to first schizophrenic relapse. The time to first schizophrenic relapse is the time between randomization and first relapse, measured in days. The Cox proportional hazard model with treatment as the only factor is used to estimate the hazard ratio of relapse rate between treatment groups. A score test is used to test the null hypothesis that the hazard ratio is equal to unity. Table 3 presents the O'Brien-Flemming's boundary for the significant levels used at interim analyses and the final analysis.

Table 3. Boundary Significant Levels

	Number of observed relapses	O'Brien-Flemming boundary significant levels
Interim analysis I	45	0.0045
Interim analysis II	60	0.0138
Final analysis	90	0.0443

(Source: Clinical Study Report: Study D1444C00004; Table 14, page 109)

The primary analysis is based on the Interim Intent-to-Treat (IITT) population. The IITT population includes all Intent-to-Treat (ITT) patients and all assessments available at the time of the interim analysis.

Selected Secondary endpoints and analyses:

- Risk of relapse: the risk of relapse is defined as the proportion of patients having a schizophrenia relapse at six months in each treatment group. The Cox proportional hazard model as above is used to estimate the risk of relapse. In the Cox model, one minus the estimation of the survivor function at six months provides the estimation for this proportion.
- CGI-S: proportion of patients with a CGI-S ≤ 4 at the last assessment is computed.
- CGI-I: a two-sided t-test is used to test the mean CGI-I scores to be equal for both treatment groups at the last visit.

The Total Intent-to-Treat (Total ITT) population is used for these secondary analyses. The total ITT population includes all ITT patients including visits

occurring after the interim analysis as well as additional patients entering between the interim analysis and the stop of the study.

3.1.4 Efficacy Results

3.1.4.1 Study Population

Subjects participating in the study came from Bulgaria, Poland, Russia, Ukraine, and India. A total of 327 patients started the open label stabilization treatment period and 197 patients completed this period. The interim analysis included 171 randomized patients. The patient disposition is presented in Figure 2.

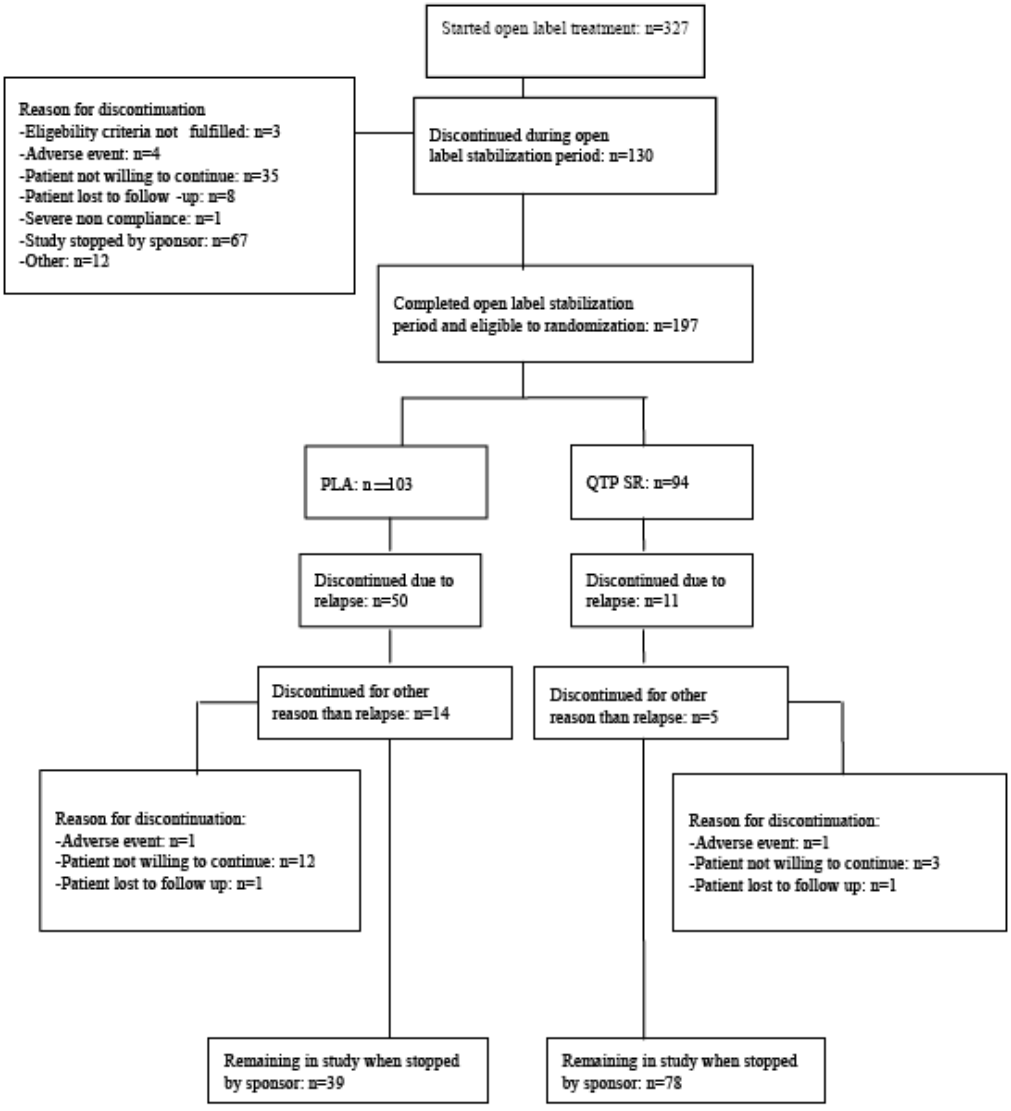


Figure 2. Patient disposition of the total ITT population
(Source: Clinical Study Report: Study D1444C00004; Figure 2, page 117)

Table 4 summarizes key demographic and baseline disease characteristics of the interim intent-to-treat sample. Female subjects accounted for about 40% of the total sample. Subjects were between the ages of 18 to 63 with the average age of 35. All subjects were Caucasian. Patients in this study, on average, had a total PANSS

score of 49 at randomization and a CGI-S of 2.7. In general, the demographic and baseline disease characteristics appeared balanced between the two arms of the study.

Table 4. Demographic and Baseline Disease Characteristics in the Interim Intent-to-Treat Sample

	Placebo	QTP SR	Total
Sex: n (%)			
Male	54 (62.1%)	49 (58.3%)	103 (30.2%)
Female	33 (37.9%)	35 (41.7%)	68 (39.8%)
Age at enrollment (years)			
n	87	84	171
Mean (SD)	33.2 (9.6)	36.6 (10.6)	34.9 (10.2)
Min. – Max.	18 - 56	18 - 63	18 - 63
Race: n (%)			
Caucasian	87 (100%)	84 (100%)	171 (100%)
Others	0	0	0
PANSS total score at enrollment			
n	87	84	171
Mean (SD)	52.5 (7.3)	52.8 (7.3)	52.7 (7.3)
Min. – Max.	33 – 60	31 – 60	31 – 60
PANSS total score at randomization			
n	86	84	170
Mean (SD)	48.3 (7.5)	48.3 (7.9)	48.3 (7.7)
Min. – Max.	30 - 59	31 - 60	30 - 60
CGI severity of illness at enrollment			
n	87	84	171
Mean (SD)	3.0 (0.7)	3.0 (0.7)	3.0 (0.7)
Min. – Max.	1.0 – 4.0	1.0 – 4.0	1.0 – 4.0
CGI severity of illness at randomization			
n	86	84	170
Mean (SD)	2.7 (0.8)	2.7 (0.7)	2.7 (0.7)
Min. – Max.	1.0 - 4.0	1.0 - 4.0	1.0 - 4.0

(Source: Clinical Study Report: Study D1444C00004; Tables 20, 21, pages 120, 122 and reviewer's results)

3.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary endpoint was the time to schizophrenic 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:

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

The primary endpoint was analyzed by the Cox proportional hazards model using treatment as the only factor in the interim ITT population. The comparison between

quetiapine SR and placebo was done via score test. The primary analysis result is presented in Table 5.

Table 5. Sponsor's Primary Efficacy Analysis: Time to Schizophrenic Relapse (Interim ITT Population). Score's test, comparison of QTP SR versus Placebo with Cox Regression

	Placebo (N=87)	QTP SR (N=84)
Numbers of relapses (%)	36 (41.4)	9 (10.7)
Comparison between treatment groups		
Hazard ratio	0.16	
95% confidence interval	(0.08, 0.34)	
p-value	< .0001	

(Source: Clinical Study Report: Study D1444C00004; Table 27, page 131)

Figure 3 presents the Kaplan-Meier estimate of the survival distribution function. The Kaplan-Meier shows consistency with the Cox proportional hazard analysis that quetiapine group separated from placebo.

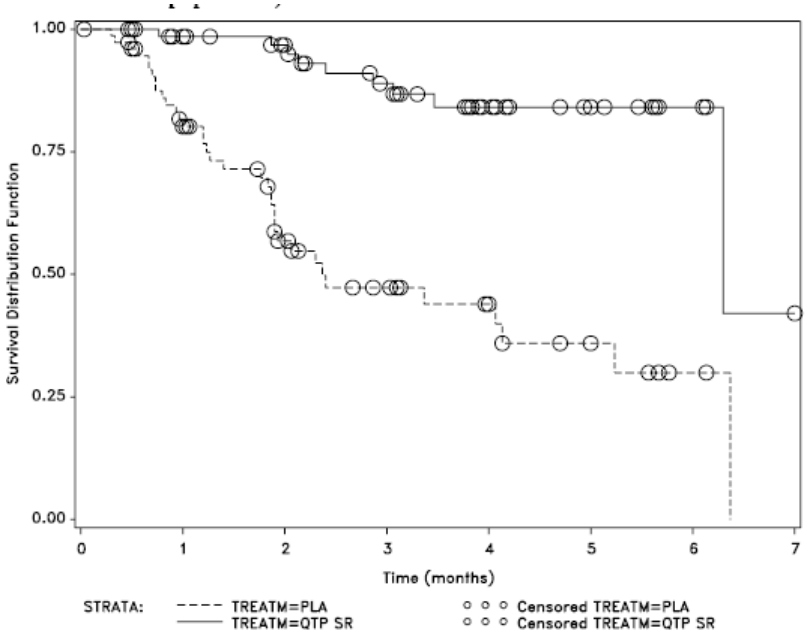


Figure 3. Time to schizophrenic relapse, Kaplan-Meier curves (Interim ITT Population)
(Source: Clinical Study Report: Study D1444C00004; Figure 3, page 132)

3.1.4.3 Sponsor's Efficacy Results for Selected Secondary Endpoints

Time to relapse in total ITT population: The total ITT population included all ITT patients including visits occurring after the interim analysis as well as additional patients entering between the interim analysis and the stop of the study. The time to relapse in the total ITT population is presented in Table 6 and is similar to the primary analysis.

Risk of schizophrenic relapse at 6 months: The risk of relapse at 6 months was defined as the proportion of patients having a schizophrenic relapse at 6 months and was estimated by one minus the survivor function at 6 months. The survivor function was estimated using the Cox model as above. The two-sided test of the

null hypothesis that the proportions of patients with relapse were equal between two treatment arms was performed. The results are presented in Table 6.

CGI-S: The proportion of patients with a CGI-S $\leq$ 4 at last assessment was calculated for each treatment group. An estimated odd ratio and 95% confidence interval comparing quetiapine SR and placebo were computed and presented in Table 6.

CGI-I: The mean value of the CGI-I score for each treatment at last assessment was estimated and presented for each treatment group. A two-sided t-test of the hypothesis that the mean CGI-I scores were equal between two treatment arms was performed. The results are presented in Table 6.

Secondary analyses on these endpoints suggested that patients receiving quetiapine SR separated from the placebo group.

Table 6. Sponsor's Efficacy Results on Selected Secondary Analyses (Total ITT Population)

Outcome Variable		Placebo	QTP SR	Estimated Difference/ Hazard ratio/ Odds ratio (95% CI)	p-value
Time to schizophrenic relapse	Sample size (N)	103	94		
	Number of relapse (%)	50 (48.5)	11 (11.7)	HR: 0.13 (0.07, 0.25)	<.0001
Risk to schizophrenic relapse at 6 months	Sample size (N)	103	94		
	Proportion of patients	68.2	14.3	Diff: -54.0 (-65.4, -42.5)	<.0001
CGI-S	Sample size (N)	100	93		
	Patient with CGI-S ≤ 4 at last visit: n (%)	84 (84.0%)	87 (93.6%)	OR: 2.76 (1.03, 7.40)	0.0375
CGI-I	Sample size (N)	100	93		
	Mean score at last visit	4.5	3.7	Diff: -0.83 (-1.24, -0.42)	<.0001

(Source: Reproduced from Clinical Study Report: Study D1444C00004; Table 25, page 129)

3.1.4.4 Statistical Reviewer's Results and Comments

This reviewer confirmed the sponsor's findings on the primary endpoint as presented above.

Permutation test to examine the robustness of the Score test

When the Statistical Analysis Plan for this study was submitted, the Agency had a concern that the asymptotic p-value for the Score test obtained from the SAS system may not be reliable because the number of events required for analysis was small. Instead, the Agency recommended the exact p-value. This reviewer conducted the permutation test. The p-value from the permutation test was similar to the asymptotic p-value reported from the SAS system.

Analysis excluding patients who were not clinically stable

According to the sponsor, 27 subjects were randomized despite not being considered clinically stable. They are summarized in Table 7.

Table 7. Randomized patients who were not clinically stable

	Placebo	QTP SR
Total ITT population	14	13
Interim ITT population	11	12
Patients with relapses in the interim ITT population	6	3

(Source: Sponsor's communication by email and reviewer's results)

Table 8 presents the interim primary analysis excluding patients with these violations. The results are similar to the sponsor's primary results. However, in this analysis, there are only 36 relapses (compared to the planned 45 relapses). Therefore, the amount of information, and thus, the O'Brien-Flemming boundary need to be adjusted accordingly. The p-value in Table 5 should be compared to a significant level of 0.0008 (East software version 4 © Cytel Software Corporation, 2005).

Table 8. Primary Efficacy Analysis: Time to Schizophrenic Relapse (Interim ITT Population). Score's test, comparison of QTP SR versus Placebo with Cox Regression (excluding patients who were not stable)

	Placebo (N=76)	QTP SR (N=72)
Numbers of relapses (%)	30 (39.5)	6 (8.3)
Comparison between treatment groups		
Hazard ratio	0.14	
95% confidence interval	(0.06, 0.34)	
p-value	< .0001	

(Source: Sponsor's results communicated by email)

Patients with relapses before the interim analysis date and were not included in the interim ITT analysis

According to the sponsor, on February 15, 2006, the 45th relapse event was recorded. On February 20, 2006, the data was transferred to the DSMB for the interim analysis. Due to a delay in recording, three patients (E1101004, E1401007, and E1404007) had relapses before February 15, but were not included in the interim analysis. All three patients were in the placebo arm. Consequently, the interim primary results would not change.

Patients with missing data at the interim analysis performed by the DSMB

According to the sponsor, seven subjects (three in placebo and four in QTP) with missing data at the interim analysis performed by the DSMB were included in the analysis performed by AstraZeneca as the correct values were inserted during the clean file process. Two additional subjects (one in placebo and one in QTP) with randomization date after the last visit date. None of these patients had relapses. Consequently, the interim primary results would not change.

Infrequent visits after Day 30

Efficacy assessments occurred every 30 days after Month 1. Thirty-one out of 45 relapses occurred after Day 30. Sixteen out of 45 relapses occurred after Day 60. Thus, for these relapses, the time to relapse would be less accurate.

Analysis on risk of schizophrenic relapse

The secondary analysis on risk of schizophrenic relapse performed by this reviewer revealed a slight difference from the sponsor's results. Table 9 presents the reviewer's results.

Table 9. Reviewer's Efficacy Results on Selected Secondary Analyses (Total ITT Population)

Outcome Variable		Placebo	QTP SR	Estimated Difference (95% CI)	p-value
Risk to schizophrenic	Sample size (N)	103	94	Diff: -56.0	<.0001
relapse at 6 months	Proportion of patients	70.7	14.7	(-67.3, -44.7)	

(Source: Reviewer's results)

3.2 Evaluation of Safety

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 Gender

There were more male than female patients in this study. The analysis of time to schizophrenic relapse stratified by gender appeared consistent with the primary result.

Table 10. Reviewer's Primary Efficacy Analysis: Time to Schizophrenic Relapse by Gender (Interim ITT Population). Score's test, comparison of QTP SR versus Placebo with Cox Regression

	Placebo	QTP SR
Male	N = 54	N = 49
Numbers of relapses (%)	23 (42.6)	7 (14.3)
Comparison between treatment groups		
Hazard ratio (95% CI)	0.21 (0.09, 0.49)	
Female	N = 33	N = 35
Number of relapses (%)	13 (39.4)	2 (5.7)
Comparison between treatment groups		
Hazard ratio (95% CI)	0.09 (0.02, 0.41)	

(Source: Reviewer's results)

4.1.2 Race

Because all patients were classified as Caucasians, this reviewer omitted the analysis stratified by race.

4.1.3 Age

Since subjects in this study were between the age of 18 and 63, this reviewer omitted the analysis stratified by age.

4.2 Other Subgroups

4.2.1 Geographical Regions

This reviewer performed an analysis stratified by geographical regions (India, Poland/Bulgaria, and Russia/Ukraine). Due to a small number of relapses in the Poland/Bulgaria and India groups, the results should be interpreted with caution. Numerical results appeared consistent with the primary analysis in the Russia/Ukraine subgroup.

Table 11. Reviewer's Primary Efficacy Analysis: Time to Schizophrenic Relapse by Geographical Regions (Interim ITT Population). Score's test, comparison of QTP SR versus Placebo with Cox Regression

	Placebo	QTP SR
India	N = 16	N = 17
Numbers of relapses (%)	6 (37.5)	1 (5.9)
Comparison between treatment groups		
Hazard ratio (95% CI)	0.12 (0.01, 0.97)	
Russia/Ukraine	N = 64	N = 59
Number of relapses (%)	29 (45.3)	7 (11.9)
Comparison between treatment groups		
Hazard ratio (95% CI)	0.16 (0.07, 0.37)	
Poland/Bulgaria	N = 7	N = 8
Number of relapses (%)	1 (14.3)	1 (12.5)
Comparison between treatment groups		
Hazard ratio (95% CI)	0.63 (0.04, 10.88)	

(Source: Reviewer's results)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The objective of the study was to demonstrate that long-term use of quetiapine SR prevented schizophrenic relapse in patients who were stable in their psychotic symptoms. The randomization period was planned to be one year. However, at the first interim analysis after 45 relapses, upon the recommendations from the DSMB, the sponsor terminated the trial prematurely for efficacy. The interim statistical analysis utilized the O'Brien-Flemming boundary.

This reviewer confirmed the sponsor's findings that quetiapine SR was superior to placebo in the prevention of schizophrenic relapse as measured by the time to schizophrenic relapse. The primary findings were consistent for secondary supportive analyses. For schizophrenic patients, it is unethical to conduct maintenance study in the United States. Therefore, this study was conducted entirely in foreign countries. Because no data was collected in the United States, from a statistical perspective, care must be taken to generalize the results to the U.S. population. The secondary claim on the number of relapses was not pre-specified. The secondary claim on the rate of relapse, though pre-specified, it was not clear if this endpoint was concurred by the Division. In addition, because there was not any replication, the secondary endpoints on the rate of relapse and the number of relapses cannot be used for label claims.

5.2 Conclusions and Recommendations

The results of the multi-center, randomized, double blind, parallel group, and placebo-controlled study suggested 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.

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/s/

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