CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-008

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-008 / 000
Drug Name:	Requip® (Ropinirole Hydrochloride) XL 24-Hour™ Tablets
Indication(s):	Parkinson's Disease
Applicant:	GlaxoSmithKline
Date(s):	Date of Submission: February 9, 2007
	PDUFA Date: December 7, 2007
Review Priority:	Standard Review
Biometrics Division:	Division I, Office of Biometrics
Statistical Reviewer:	Sharon Yan, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	James Hung, Ph.D., Director
Medical Division:	Division of Neuropharm
Clinical Team:	Leonard Kapcala, M.D., Medical Reviewer
	Norman Hershkowits, M.D., Acting Medical Team Leader
	Eric Bastings, M.D., Acting Medical Deputy Director
Project Manager:	Susan Daugherty

Table of Contents

1. EXECUTIVE SUMMARY

This NDA contains clinical data in support of an extended release formulation of ropinirole for treatment of the symptoms of idiopathic Parkinson's disease (PD). The demonstration of clinical efficacy for ropinirole CR tablets is principally based on the results of Study 169.

1.1 Conclusions and Recommendations

The pivotal study 169 has demonstrated that ropinirole CR is superior to placebo as adjunctive therapy to L-dopa, assessed by the primary endpoint of change from baseline in awake time spent "off".

Study— has showed some evidence that ropinirole CR may have an effect in delaying the onset of dyskinesia. The study was terminated early, and no subjects had completed the study. Data from Study 228 should be interpreted with caution. b(4)

1.2 Brief Overview of Clinical Studies

Study 169 was a randomized, double-blind, placebo-controlled, parallel group study that compared ropinirole CR tablets to placebo as adjunctive therapy to L-dopa in subjects with advanced stage PD who had demonstrated a lack of control with L-dopa therapy. The primary efficacy variable was mean absolute change from baseline in awake time "off" at week 24.

Other studies included in the application are studies 168 and 228. Study 168 was a 3-period crossover non-inferiority study of ropinirole CR and ropinirole IR monotherapy in early-stage disease of PD. Study 228 compared ropinirole CR and Sinemet (carbidopa/L-dopa) as an adjunctive therapy to L-dopa in delaying in onset of dyskinesia.

1.3 Statistical Issues and Findings

An interaction between the treatment and prior exposure to ropinirole CR was observed in the primary efficacy analysis of total awake time spent "off". A change from baseline of -2.3 hours for 12 ropinirole CR-treated subjects who had prior exposure to ropinirole CR was in line of the overall mean change for ropinirole CR group. However, it is difficult to explain the mean change of -2.5 hours for the 9 placebo-treated subjects who had prior exposure to ropinirole CR, while the overall mean change for the placebo group was -0.5 hour.

Study 228 provided some insight into the time course of development of dyskinesia. The study compared ropinirole CR with Sinemet in time to dyskinesia, a possible complication of the therapy. Rigorous comparisons to evaluate the equivalency of ropinirole CR and Sinemet in efficacy were not specified in the protocol, and no statistical inferential analyses in efficacy were presented in the submission. Data from Study 228 should be interpreted with caution since early termination of the study resulted in lower enrollment, a shorter period of observation and, as a result, a smaller number of events.

2. INTRODUCTION

Ropinirole immediately release (IR) was approved for the treatment of Parkinson's disease in July 1996. The current application is to support the use of a controlled-release formulation of ropinirole (REQUIP XL 24-HOUR Extended Release Tablets) for treatment of the symptoms of idiopathic Parkinson's disease. The demonstration of clinical efficacy for ropinirole CR tablets is principally based on the results of Study 169, which compared ropinirole CR tablets to placebo as adjunctive therapy to L-dopa in subjects with advanced stage Parkinson's disease (PD) based on change from baseline in awake time "off".

Other studies included in the application are studies 168 and 228. Study 168 was a 3-period crossover non-inferiority study of ropinirole CR and ropinirole IR monotherapy in early-stage disease of PD. Study 228 compared ropinirole CR and Sinemet (carbidopa/L-dopa) as an adjunctive therapy to L-dopa in delaying in onset of dyskinesia.

2.1 Overview

Study 169 was a randomized, double-blind, placebo-controlled, parallel group study that compared ropinirole CR tablets to placebo as adjunctive therapy to L-dopa in subjects with advanced stage PD who had demonstrated a lack of control with L-dopa therapy. The primary efficacy variable was mean absolute change from baseline in awake time "off" at week 24. The study was conducted in 67 centers in US and 7 European countries with 393 subjects enrolled.

Study 168 was a randomized, double-blind, three-period, two-treatment crossover study. It was designed to demonstrate the non-inferiority of the ropinirole CR tablet to the currently marketed ropinirole IR tablet as monotherapy in subjects with early stage PD. The crossover design consisted of an initial 12-week up-titration period followed by three 8-week flexible-dose maintenance periods. At the treatment crossovers, subjects were switched overnight between tablet formulations to the nearest equivalent dose.

Study 228 was a randomized, double blind, parallel group, active-controlled flexible dose study to assess the efficacy of up to two years of therapy with ropinirole CR (2-24mg/day) compared with that of Sinemet (carbidopa/L-dopa, 50-1000mg/day), as adjunctive therapy to L-dopa in PD subjects who were not optimally controlled on their baseline dose of L-dopa. In September 2005, Study 228 was terminated for administrative reasons after a blinded review of the dyskinesia rate indicated that the study could not achieve its goals within a reasonable timeframe. At the time of the study termination 208 of the 350 subjects originally planned were enrolled.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for documents of this NDA is listed below:

\\Cdsesub1\NONECTD\N22008\N_000

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Evaluation of Study 169

3.1.1.1 Objectives and Design of the Study

The primary objective of Study 169 was to evaluate the efficacy of ropinirole CR as adjunctive therapy to L-dopa in subjects with Parkinson's disease.

Study 169 was a multicenter, randomized, double-blind, parallel group, placebo-controlled study to compare the efficacy of 6-months therapy of ropinirole CR tablets with that of placebo as adjunctive therapy to L-dopa in subjects with advanced stage Parkinson's disease who were not optimally controlled on L-dopa.

A total of 368 subjects were planned and 393 subjects were actually randomized. The study was conducted in 67 centers in US and 7 European countries.

Following screening, eligible subjects entered a 14-day single-blind placebo run-in period. Subjects were then randomized (1:1) to double-blind treatment with either ropinirole CR tablets (2-24 mg once daily) or placebo tablets, in addition to their background L-dopa therapy, for 24 weeks. All subjects were started on a 2 mg/day dose of ropinirole CR or placebo equivalent and were progressed through the first three dose levels (2 mg, 4 mg and 6 mg) during the first three weeks of the study. Thereafter, the dose titration regimen was to be followed until an optimal therapeutic dose was achieved with minimum dose of 6 mg/day. The maximum dose for ropinirole CR was 24 mg/day.

Once an optimal therapeutic dose was achieved, the subject was maintained on that dose for the remainder of the treatment phase unless further titration was required. When subjects were titrated to a dose of 8 mg/day ropinirole CR or matching placebo, the planned reduction in L-dopa dose began. If symptom control was maintained following the first reduction in L-dopa dose, the total dose of L-dopa was reduced again when the subject was titrated to the next higher level of study medication. If loss of symptom control occurred with the reduction in the background L-dopa dose, the dose of ropinirole CR/matching placebo was to be increased to the next higher dose level with no adjustment in the dose of L-dopa. If loss of symptom control persisted, subjects were to have their ropinirole CR/matching placebo titrated up an additional dose level and could return to the clinic at weekly intervals, if necessary, for these up-titration visits. Subjects who did not experience an improvement in symptoms following upward titration of ropinirole CR/matching placebo by two dose levels were to be "rescued" with L-dopa. The dose of L-dopa was allowed to be increased to baseline levels but must not have increased above them. If it was clinically necessary to increase the dose of L-dopa above baseline levels, the subject was withdrawn from the study.

3.1.1.2 Efficacy Endpoints and Statistical Analysis Methods

3.1.1.2.1 Primary Endpoint and Statistical Analysis

The primary efficacy endpoint for the study was the mean change from baseline in awake time "off" at week 24 last observation carried forward (LOCF).

Diary cards completed by the subjects were used to assess the duration of "off" and "on" periods. Two 24-hour diary cards were completed by the subject prior to each visit. The subjects were asked to complete diary cards on the same two days of each relevant week. Each 30 minute period was marked as either "off", "on" or asleep. In addition, troublesome dyskinesia during "on" periods was recorded in the diary.

The change from baseline to study endpoint for the amount of total awake time "off" was analyzed using parametric analysis of covariance. The statistical model included terms for country, baseline absolute amount of awake time "off" and treatment group, regardless of their significance. No interaction terms were included in this primary model.

3.1.1.2.2 Secondary Efficacy Endpoints and Analyses

The secondary endpoints for the evaluation of efficacy included mean change from baseline in amount and percent of awake time spent "off", "on" with or without troublesome dyskinesias, mean change from baseline in UPDRS motor score and in UPDRS Activities of Daily Living (ADL) score, proportion of subjects with a score of much improved or very much improved on the CGI Global Improvement (CGI-I) scale, and many other variables.

Normal, linear models were to be fitted to each of the continuous efficacy variables specified above and logistic regression models were to be fitted to the binary secondary endpoint described above. Interactions were not to be investigated for these secondary endpoints.

3.1.1.3 Study Results

3.1.1.3.1 Disposition of Subjects

A total of 393 subjects were randomized to the study and received at least one dose of investigational product (ropinirole CR: 202 subjects; placebo: 191 subjects). One subject in the ropinirole CR group and one subject in the placebo group did not have at least one post-baseline assessment and were excluded from the ITT population.

A summary of subject completion and discontinuation is presented in Table 1.

Table 1 Summary of Subject Completion and Discontinuation (Source: Table 10 of sponsor's study report)

	Ropinirole CR N=202		Placebo N=191		Total N=393	
	n	(%)	n	(%)	n	(%)
Completion Status						
Completed	168	(83)	134	(70)	302	(77)
Prematurely Discontinued	34	(17)	57	(30)	91	(23)
Primary Reason for Premature Discontinuation [1]						
Lack of Efficacy	6	(3)	27	(14)	33	(8)
Subject Decided to Withdraw	9	(4)	13	(7)	22	(6)
Adverse Event	12	(6)	10	(5)	22	(6)
Other [2]	4	(2)	3	(2)	7	(2)
Protocol Violation	1	(<1)	2	(1)	3	(<1)
Non-Compliance	2	(<1)	1	(<1)	3	(<1)
Sponsor Terminated Study [3]	0		1	(<1)	1	(<1)

3.1.1.3.2 Demographic and Baseline Characteristics

Demographic characteristics for the ITT population are summarized in Table 2.

Table 2 Summary of Demographic Characteristics of ITT Patient Population (Source: Table 13 of sponsor's Study Report)

	Ropinirole CR N=201		Placebo N=190		Total N=391	
Age (years)						
Mean (SD)	66.3 (9.17)		66.0 (9.74)		66.2 (9.44)	
Median (Range)	68.0 (36 - 87)		67.0 (34 - 84)		68.0 (34 - 87)	
Age Group, n (%)						
18-64	73	(36)	78	(41)	151	(39)
65-74	93	(46)	69	(36)	162	(41)
≥75	35	(17)	43	(23)	78	(20)
Sex, n (%)						
Male	117	(58)	129	(68)	246	(63)
Female	84	(42)	61	(32)	145	(37)
Race, n (%)						
White/Caucasian	195	(97)	182	(96)	377	(96)
American Hispanic	3	(1)	2	(1)	5	(1)
East/South East Asian	2	(<1)	2	(1)	4	(1)
Black	0		3	(2)	3	(<1)
Arabic/North African	1	(<1)	0		1	(<1)
Other	0		1	(<1)	1	(<1)

In the ITT population there was a slightly higher proportion of males in the placebo group compared to the ropinirole CR group (68% versus 58%). The treatment groups were well-balanced for all other demographic characteristics.

The treatment groups were generally well-balanced for Parkinson's disease history at screening. However, there was a slightly larger proportion of subjects with stage III disease in the ropinirole CR group compared to the placebo group (44% vs 34%) and a slightly smaller proportion with stage IV disease (4% vs 13%).

A summary of subject's Parkinson's disease history at screening for the ITT population is shown in Table 3.

Table 3 Summary of Parkinson's Disease History at Screening (Source: Table 14 of Sponsor's Study Report)

	Ropinirole CR N=201		Placebo N=190		Total N=391	
Age of Onset of PD (yrs)						
N	200		188		388	
Mean (SD)	57.6 (10.53)		57.3 (10.74)		57.5 (10.62)	
Median (Range)	59.0 (29 - 82)		58.0 (29 - 82)		58.0 (29 - 82)	
Disease Duration (yrs)						
N	200		188		388	
Mean (SD)	8.55 (4.759)		8.63 (5.152)		8.59 (4.947)	
Median (Range)	7.40 (0.0 - 28.1)		8.05 (-0.6 - 25.2)		7.90 (-0.6 - 28.1)	
Duration of L-dopa (yrs)						
N	199		187		386	
Mean (SD)	6.47 (4.445)		6.60 (4.327)		6.53 (4.383)	
Median (Range)	5.40 (0.2 - 22.2)		6.00 (0.1 - 23.5)		5.60 (0.1 - 23.5)	
Hoehn & Yahr Stage, n (%)						
Stage I	0		0		0	
Stage I.5	0		0		0	
Stage II	53	(26)	60	(32)	113	(29)
Stage II.5	51	(25)	41	(22)	92	(24)
Stage III	88	(44)	65	(34)	153	(39)
Stage IV	9	(4)	24	(13)	33	(8)
Stage V	0		0		0	

3.1.1.3.3 Titration of Dose

At Week 24 LOCF the mean dose of investigational product was 18.8 mg/day (median 20 mg/day) in the ropinirole CR group and 20.0 mg/day (median 24 mg/day) of placebo equivalent in the placebo group. At Week 24, investigational product was up-titrated to the maximum dose of 24 mg/day, or placebo equivalent, for 50% (102/202) of subjects in the ropinirole CR group and for 56% (107/191) of subjects in the placebo group.

An additional category of study conduct violation was identified during a review of protocol violations on blinded data. It was noted that 11 patients (4 in ropinirole CR and 7 in placebo) never reduced their dose of L-dopa, although the protocol included a mandatory reduction once the subject reached dose level 4. Thus, subjects who reached dose level 4 of study medication but did not reduce total daily dose of L-dopa were categorized as major protocol violators and are excluded from the PP population.

3.1.1.3.4 Efficacy Results - Sponsor's Analysis

Primary Efficacy Results - Change from Baseline in Total Awake Time Spent "Off" at Week 24

The primary efficacy endpoint was mean change from baseline in total awake time spent "off" at Week 24. The sponsor used analysis method of ANCOVA model with terms of treatment and pooled center with baseline "off" time as a covariate, which was the protocol specified analysis. The grouping of centers into countries, although not precisely specified in the reporting and analysis plan (RAP), was reasonable in the reviewer's opinion based on small number of subjects in most centers. Summary statistics for this endpoint are presented in Table 4.

Table 4 Summary Statistics for Change from Baseline in Total Awake Time Spent "Off" at Week 24 LOCF (Source: Table 24 of Sponsor's Study Report)

Total Awake Time Spent "Off" (Hours)	Ropinirole CR N=201	Placebo N=190
Baseline	**n=201**	**n=190**
Mean (SD)	7.0 (2.80)	7.0 (2.58)
Median (Min, Max)	6.8 (3.0, 17.5)	6.5 (3.3, 15.8)
Week 24 LOCF	**n=201**	**n=190**
Mean (SD)	4.9 (3.54)	6.6 (3.55)
Median (Min, Max)	4.8 (0.0, 18.0)	6.9 (0.0, 16.8)
Change from Baseline to Week 24 LOCF[1]	**n=201**	**n=190**
Mean (SD)	-2.1 (3.20)	-0.4 (3.25)
Median (Min, Max)	-2.4 (-13.9, 11.5)	-0.4 (-13.4, 11.6)

At baseline the mean total awake time spent "off" was approximately 7 hours in each treatment group. At Week 24 LOCF, the total awake time spent "off" had, on average, decreased by approximately 2 hours in the ropinirole CR group and by approximately half an hour in the placebo group. The adjusted mean difference in total awake time spent "off" between ropinirole CR and placebo was -1.7 hours (95% CI: [-2.34, -1.09], $p<0.0001$) indicating a statistically significant benefit of ropinirole CR over placebo. Similar results were obtained in the observed cases (OC) analysis or per protocol analysis.

At all visits from Week 2 OC to Week 24 OC there was a statistically significant benefit of ropinirole CR over placebo in the total awake time spent "off".

One covariate by treatment interaction, prior exposure to ropinirole, was found to be statistically significant (p=0.0400). In the ITT population, 21 (5%) subjects had prior exposure to ropinirole CR (ropinirole CR: 12/201, 6%; placebo: 9/190, 5%). The primary model, adjusting for country and baseline awake time spent "off", was fitted separately for those subjects who did and did not have prior exposure to ropinirole CR.

For subjects without prior exposure to ropinirole CR, the results obtained were similar to those obtained from the analysis containing all subjects. For the subjects who had prior exposure to ropinirole CR, the adjusted mean change from baseline in awake time spent "off" was -2.3 for the 12 ropinirole CR-treated subjects and -2.5 for the 9 placebo-treated subjects.

Secondary Efficacy Results

There were over a dozen of secondary efficacy variables listed in the protocol. No multiplicity adjustment was proposed. Results of a selected number of secondary efficacy analyses are presented in the following table for descriptive purposes.

Table 5 Summary of Secondary Efficacy Results (Source: Sponsor's results summarized by the reviewer)

Variable	Ropinirole	Placebo	Nominal p-value
Percent awake time "off" (hr)			
Change from baseline to Week 24	n=201	n=190	
Mean (SD)	-12.8 (19.72)	-1.8 (20.83)	<.0001
Median	-13.7	-1.3	
Total awake time "on" (hr)			
Change from baseline (LOCF)	n=201	n=190	
Mean (SD)	1.8 (3.24)	0.2 (3.34)	<.0001
Median	1.9	0.1	
Awake time "on" without dyskinesia			
Change from baseline	n=200	n=188	
Mean (SD)	1.9 (3.10)	0.4 (3.48)	<.0001
median	1.8	0.4	
Awake time "on" with dyskinesia			
Change from baseline	n=200	n=188	
Mean (SD)	-0.04 (1.05)	-0.23 (1.08)	
Median	0.00	0.00	
UPDRS Motor score			
Change from baseline	n=194	n=183	
Mean (SD)	-6.5 (9.65)	-1.9 (8.52)	<.0001
Median	-5.8	-1.0	
UPDRS ADL score			
Change from baseline	n=197	n=184	
Mean (SD)	-3.4 (4.27)	-0.8 (3.66)	<.0001
Median	-3.0	-0.5	
CGI			
Proportion of Responders	83/200 (42%)	27/189 (14%)	<.001
Requiring L-dopa reinstatement			
Proportion of reinstatement	14/191 (7%)	49/174 (28%)	<.001

3.1.1.3.5 Reviewer's Analysis

The reviewer found 3 patients without post-baseline measures "off" time while awake. Therefore, the primary analysis included 390 subjects. The efficacy results obtained by this reviewer agree with the ones obtained by the sponsor with minimal differences. Therefore, the results from reviewer's analyses are not presented.

The sponsor stated that the assumptions of normality and homogeneity of variance were checked. Diagnostic plots were examined and gave no reason to suspect that the underlying assumptions of the model were invalid. However, the Shapiro-Wilk's normal test used by the reviewer revealed a p-value of 0.002, indicating the assumption of normality was violated. Non-parametric analysis of ranked ANCOVA model was applied by the reviewer, and the results confirmed that ropinirole CR is superior to placebo with a p-value of less than 0.0001.

The relationship of treatment difference in awake time spent "off" and L-dopa dose reduction was examined. At the baseline, the mean L-dopa dose was 827 mg for the ropinirole CR group and 768 mg for the placebo group. At the last study visit, the mean reduction in L-dopa dose was 285 mg for the ropiniorle CR group and 179 mg for the placebo group. Adjusted by baseline L-dopa dose, this difference is statistically significant. With the available data, 182 of the 193 (94.3%) ropinirole CR-treated subjects and 136 of the 180 (75.6%) placebo-treated subjects had reduction in their baseline L-dopa dose.

3.1.2 Evaluation of Study 228

3.1.2.1 Description of the Study

This Phase IIIB study was a randomized, multicenter, double-blind, Sinemet-controlled, parallel group, flexible dose study to assess the effectiveness of ropinirole CR compared to Sinemet as adjunctive therapy to L-Dopa in patients whose symptoms of Parkinson's disease were not optimally controlled. Patients were randomized to double-blind (by double dummy) treatment of either add-on ropinirole CR (flexible dose 2-24 mg once daily) or Sinemet (50-1000 mg tid). A minimum of 15 visits were planned over the 107-week duration of the study.

The starting dose was 2mg of ropinirole CR, or 50mg of Sinemet (dose level 1). The dose titration regimen was followed until an optimal therapeutic dose was achieved. Once an optimal therapeutic dose was achieved, the subject was maintained on that dose for the remainder of the study unless further titration was necessary. The maximum recommended daily dose was 24mg of ropinirole CR or 1000mg of Sinemet (dose level 8) in addition to their baseline L-dopa dose. No reduction in the dose of baseline L-dopa was allowed. Subjects who did not experience an improvement in symptoms following upward titration through the 8 dose levels were withdrawn from the study.
The primary objective of the study was to evaluate the time to onset of dyskinesia over 2 years of treatment with ropinirole CR compared with Sinemet. The primary efficacy endpoint of the study was time to dyskinesia.

In September 2005, Study 228 was terminated for administrative reasons after a blinded review of the dyskinesia rate indicated that the study could not achieve its goals within a reasonable timeframe.

During the review process, the reviewer requested detailed information with regard to blinded review of the data, date of data lock and unblinding. The sponsor responded that the cumulative number of events was reviewed periodically in blinded fashion for reasons of evaluating futility and ended with the decision to terminate the study on September 28, 2005. The datasets were locked on May 4, 2006, and unblinding of data took place on May 5, 2006.

3.1.2.2 Study Population

The planned sample size for the study was 350 subjects (175 per treatment arm). At the time of study termination, 209 subjects were randomized. All but one subject were recorded as prematurely withdrawn; the majority (73%) of the premature withdrawal was because of the premature closure of the study by the sponsor. The most common reasons for early withdrawal, other than premature closure of the study, included AEs and dyskinesia. The following table presents a summary of patient dispositions. One subject randomized to ropinirole CR group did not receive study medication and is not included in the summary.

Table 6 Summary of Subject Discontinuation (Source: Table 7 of sponsor's study report)

	Number (%) Subjects		
Disposition	Ropinirole CR (N=104)	Sinemet (N=104)	Total (N=208)
Completed	0	1[2] (<1)	1 (<1)
Prematurely withdrawn	104 (100)	103 (>99)	207 (<99)
Adverse event	15 (14)	8 (8)	23 (11)
Lost to follow-up	1 (<1)	0	1 (<1)
Protocol violation	1 (<1)	1 (<1)	2 (<1)
Subject decided to withdraw	4 (4)	4 (4)	8 (4)
Lack of efficacy	1 (<1)	2 (2)	3 (1)
Sponsor terminated study	79 (76)	73 (70)	152 (73)
Dyskinesia	2 (2)	12 (12)	14 (7)[3]
Other[1]	1 (<1)	3 (3)	4 (2)

1. "Other" category includes 3 subjects withdrawn because of early closure of the study by the Sponsor and 1 subject withdrawn because of incarceration.
2. One subject in the Sinemet group who was withdrawn because of early termination of the study was erroneously recorded as a Study Completer on the End of Study CRF page. No subjects completed the study.
3. Seven other subjects were recorded with dyskinesia at follow-up after study termination.

3.1.2.3 Efficacy Results - Sponsor's Analysis

3.1.2.3.1 Analysis of Primary Efficacy Variable

The analysis of the primary efficacy endpoint, time to dyskinesia, was performed on the ITT patient population. Analysis on the per-protocol patient population was not performed by the sponsor due to the termination of the study.

The time to onset of dyskinesia was measured as the number of days from the date of randomization to the date at which a subject had the onset of dyskinesia. Subjects who did not experience dyskinesia were censored on the last day on which study medication was taken.

Twenty-one (21) subjects experienced dyskinesia, 3 in the ropinirole CR group and 18 in the Sinemet group. There was a statistically significant delay in the time to onset of dyskinesia for the ropinirole CR-treated subjects based on the log-rank test ($p<0.001$). The analysis of time to dyskinesia was not stratified by study entry L-dopa dose, as was planned in the RAP, due to a small number of events. The Kaplan-Meier plot of time to onset of dyskinesia is presented in Figure 1.

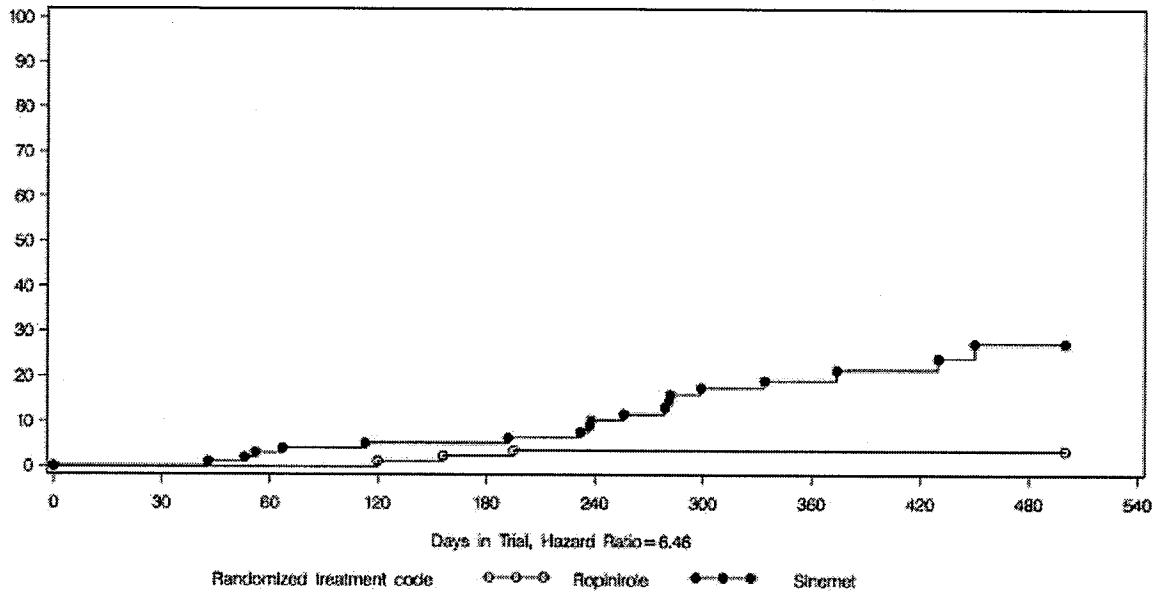

Figure 1 Kaplan-Meier Plot of Time to Onset of Dyskinesia (Source: Figure 2 of sponsor's study report)

Because Investigators were informed of GSK's decision to terminate the trial on 28 September 2005, a second Kaplan Meier analysis was performed post-hoc with censoring of observations after 28 September 2005 to evaluate any possible impact of termination on the primary endpoint. The results of this post-hoc analysis showed a similar delay in time to onset of dyskinesia for ropinirole CR-treated subjects ($p=0.002$) to that of the primary analysis above.

Further, post-hoc examination revealed that 8 subjects, 4 in each treatment group, reported some degree of dyskinesia on the UPDRS Part IV obtained at baseline. Two of these 8 subjects also had a subsequent dyskinesia event prior to study termination. Therefore, a third Kaplan-Meier analysis of time to onset of dyskinesia was conducted with censoring at study termination (as above) plus removal of the 8 subjects with evidence of dyskinesia per UPDRS assessment at baseline to determine if these subjects had an impact on the primary endpoint. The results of this post-hoc analysis showed a similar delay in time to onset of dyskinesia for ropinirole CR-treated subjects with a p-value of 0.004 for the treatment difference.

3.1.2.3.2 Analyses of Secondary Efficacy Variables

Secondary efficacy variables are summarized in descriptive statistics in the following table.

Table 7 Summary of Analysis Results from Secondary Efficacy Variables

Variable	Ropinirole CR	Sinemet
UPDRS ADL Score		
Change to Week 28 (OC)		
N	83	83
Mean (SD)	-1.5 (3.83)	-1.2 (3.92)
Median	-1.5	-1.0
Change to End of Study		
N	100	104
Mean (SD)	-1.0 (4.35)	-0.9 (3.62)
Median	-1.0	-1.0
UPDRS Motor Score		
Change to Week 28 (OC)		
N	83	81
Mean (SD)	-3.7 (9.32)	-3.5 (6.99)
Median	-3.0	-3.0
Change to End of Study		
N	98	102
Mean (SD)	-3.6 (9.16)	-3.3 (7.82)
Median	-3.0	-3.0
CGI Responders (Score 1 or 2)		
Number (%) at Week 28	35/83 (42%)	29/83 (35%0
Number (%) at End of Study	35/101 (35%)	35/104 (34%)

3.1.2.4 Reviewer's Analysis

The ITT patient population included 208 subjects, 104 in each treatment groups. No subjects completed the study at the time of study termination. There were 21 dyskinesia events in total, 3 in the ropinirole CR group and 18 in the Sinemet group. The following table presents detailed information for subjects who had dyskinesia during the study.

Table 8 Summary of Subjects Who had Dyskinesia during the Study (Source: Reviewer's summary)

Subject #	Treatment	Days to dyskinesia	Last dose	Dyskinesia observed by PI	Dyskinesia after 9/28/05
104	Ropinirole CR	120	6 mg	No	No
1256	Ropinirole CR	156	12 mg	Yes	No
1541	Ropinirole CR	195	12 mg	No	No
720	Sinemet	43	100 mg	Yes	No
522	Sinemet	53	50 mg	Yes	No
1200	Sinemet	56	200 mg	Yes	No
121	Sinemet	67	400 mg	Yes	No
620	Sinemet	113	200 mg	Yes	No
844	Sinemet	192	200 mg	Yes	No
889	Sinemet	232	600 mg	Yes	No
80	Sinemet	237	800 mg	No	No
887	Sinemet	238	200 mg	Yes	No
642	Sinemet	256	600 mg	Yes	No
1409	Sinemet	279	100 mg	Yes	**Yes**
1296	Sinemet	281	50 mg	Yes	No
360	Sinemet	282	150 mg	Yes	No
781	Sinemet	299	800 mg	No	No
942	Sinemet	334	600 mg	Yes	No
141	Sinemet	374	600 mg	No	No
481	Sinemet	430	200 mg	Yes	**Yes**
500	Sinemet	450	400 mg	Yes	No

The reviewer performed analysis of time to dyskinesia in 3 different censoring schemes, as was done by the sponsor. The sponsor's analysis results were confirmed:

First, subjects who did not have dyskinesia were censored at their last randomized treatment. A p-value of 0.0006 was obtained from the log-rank test in the treatment comparison with this censoring scheme. When subjects were censored after 28 September 2005, including the 2 subjects who experienced dyskinesia after the date, a p-value of 0.0017 was obtained. Finally, when subjects were censored after 28 September 2005, and 8 subjects who reported some degree of dyskinesia at baseline were removed, the analysis yielded a p-value of 0.0044. The analyses suggested that ropinirole CR may have an effect in delaying the onset of dyskinesia when compared to Sinemet.

Rigorous comparisons to evaluate the equivalency of ropiniorle CR and Sinemet in efficacy were not specified in the protocol. It appears that ropinirole CR and Sinemet were similar in efficacy measured by UPDRS ADL scores, UPDRS motor scores and response in CGI-I. However, inference in efficacy with regard to these variables could not be drawn without a rigorous pre-specified statistical method. This issue in addition to the issues from the early termination of the study needs to be concerned in interpreting the available data from the study.

3.1.3 Evaluation of Study 168

Study 168 and its results are described briefly in the following two sub-sections. No independent statistical analysis was performed by this reviewer.

3.1.3.1 Description of the Study

The primary objective of this study was to demonstrate the non-inferiority of ropinirole CR to the current marketed IR formulation in subjects with early phase Parkinson's disease.

This was a multicentre, randomised, double blind, three period, two treatment cross-over study to compare the efficacy of ropinirole CR with that of ropinirole IR as initial therapy in subjects with early phase Parkinson's disease. The study design is illustrated in Figure 2.

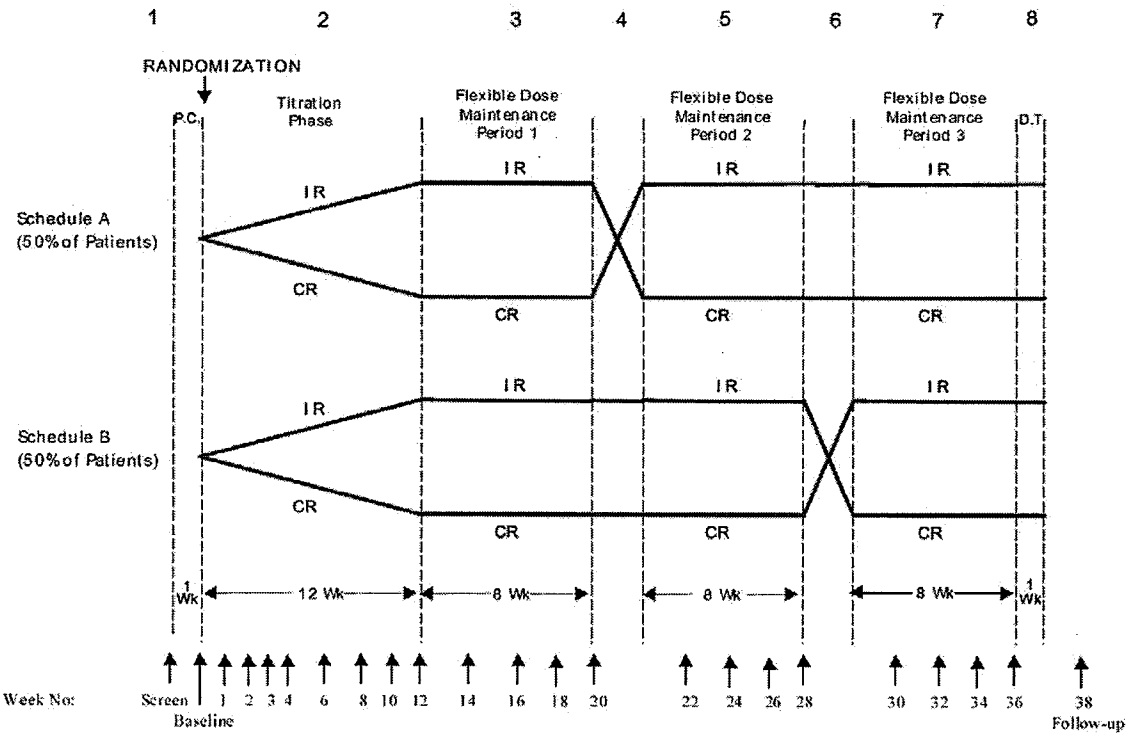

Figure 2 Outline of Study Design (Protocol 168)

At the baseline visit, subjects were randomized (1:1:1:1) to one of four sequences IR-CR-CR, CR-IR-IR, IR-IR-CR, CR-CR-IR. During the 12-week titration phase the subjects' dose was titrated upwards to achieve the optimal clinical response. Eligibility for a subject's continuation beyond the 12-week titration phase was dependent upon achieving a stable Unified Parkinson's disease Rating Scale (UPDRS) motor score.

Subjects who achieved a stable UPDRS motor score entered the first 8-week, flexible dose maintenance period (Period 1). At the end of the 8 weeks, 50% of the subjects were switched overnight to the alternative formulation of ropinirole (Schedule A), while the remaining 50% continued on the same treatment following a dummy overnight switch (Schedule B). Subjects then began the second flexible dose maintenance period (Period 2).

At the end of the flexible dose maintenance period 2, subjects in Schedule A had a dummy overnight switch and continued on the same treatment into the flexible dose maintenance period (Period 3). Subjects in Schedule B were switched overnight to the alternative ropinirole formulation prior to moving into maintenance Period 3.

In Periods 1 through 3, subjects could undergo dose adjustments during the first 4 weeks of the period if necessary.

3.1.3.2 Efficacy Results

The primary efficacy endpoint of this study was the change from period baseline in the UPDRS total motor score at the end of each flexible dose maintenance period. Each dose maintenance period had its own baseline know as the period baseline. The period baseline was the visit at which subjects entered the dose maintenance period, i.e., the Week 12 visit for period 1, the Week 20 visit for period 2, and the Week 28 visit for period 3.

A parametric analysis of variance techniques (SAS Proc Mixed) was used in primary analysis. The following table presents the results for the primary efficacy analysis reported by the sponsor. The reviewer did not perform an independent efficacy analysis for this study.

Table 9 Summary Statistics for Change from Period Baseline in UPDRS Total Motor Score at Each Time Point (Source: Table 31 of sponsor's study report)

UPDRS Total Motor Score	Ropinirole CR N=101		Ropinirole IR N=108	
	n	Mean (SD)	n	Mean (SD)
Up-titration Period				
Original Baseline (Week 0)	54	20.0 (8.59)	60	21.0 (9.29)
Week 12 OC	53	9.5 (7.12)	54	11.8 (8.13)
Change from Original Baseline [1,2]	53	-10.4 (6.06)	54	-8.9 (5.90)
Maintenance Period 1				
Period Baseline (Week 12)	53	9.5 (7.13)	53	12.0 (8.38)
Week 20 LOCF	51	9.4 (6.81)	50	12.2 (8.06)
Change from Period Baseline [1,2]	51	0.0 (4.00)	50	0.5 (3.08)
Maintenance Period 2				
Period Baseline (Week 20)	61	10.7 (8.01)	38	10.7 (5.57)
Week 28 LOCF	61	10.1 (7.64)	35	11.3 (6.16)
Change from Period Baseline [1,2]	60	-0.2 (3.84)	35	0.6 (2.73)
Maintenance Period 3				
Period Baseline (Week 28)	46	12.1 (7.85)	46	9.0 (6.10)
Week 36 LOCF	44	12.1 (7.35)	38	10.1 (6.53)
Change from Period Baseline [1,2]	43	-0.4 (3.03)	37	0.7 (2.45)

Data Source: Section 13, Table 7.1 and Table 7.2.

1. Change from period baseline was calculated for subjects who had both a period baseline score and a score at the end of the relevant period.
2. The total motor score of the UPDRS ranges from 0 to 108, where 0=normal/no symptoms and 108=worst possible case. A decrease from baseline in the score indicates an improvement.

3.2 Evaluation of Safety

Please refer to Clinical Review by Dr. Leonard Kapcala for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Analyses of primary efficacy endpoint by gender and age group were performed for Study 169 only. Subject's age was grouped by 18-64, 65-74, and >=75 years old. No discrepancies in terms of treatment difference were found among the subgroups in the subgroup analyses performed, except that the oldest age group showed a slightly smaller treatment gain from ropinirole CR compared to other age groups. Subgroup analysis by race was not performed since over 95% of the subjects were Caucasians and 3 of the other race groups did not have subjects in both treatment groups. The results are presented in the following table.

Table 10 Mean Change from Baseline in Total Time Awake Spent "Off" by Gender and Age Group - Study 169 (Source: Reviewer's analysis)

	Ropinirole CR	Placebo	Nominal p-value
Gender			
Male	N=117	N=129	
Mean (SD)	-2.20 (3.27)	-0.57 (3.47)	0.0002
Median	-2.63	-0.63	
Female	N=83	N=61	
Mean (SD)	-2.09 (2.99)	-0.38 (2.94)	0.0005
Median	-2.38	-0.13	
Age Group			
18-64 year	N=73	N=78	
Mean (SD)	-2.07 (3.24)	-0.31 (3.08)	0.0018
Median	-2.00	-0.44	
65-74	N=92	N=69	<.0001
Mean (SD)	-2.39 (3.31)	-0.53 (3.05)	
Median	-2.81	-0.13	
>=75	N=35	N=43	0.2467
Mean (SD)	-1.71 (2.45)	-0.83 (4.04)	
Median	-1.50	-0.88	

4.2 Other Special/Subgroup Populations

There were large differences in efficacy among the countries for Study 169. Four of the eight countries had small number of subjects enrolled. Poland and US contributed about two thirds of the patient population. Efficacy results from these two countries appear to be similar. The treatment difference in US reached significance level. The analysis of the primary endpoint, the change in the mean awake time spent "off" is presented in Table 11.

Table 11 Mean (SD) Change in the Awake Time Spent "Off" by Region and Country - Study 169 (Source: reviewer's analysis)

Region / Country	Ropinirole CR		Placebo		Nominal p-value
	N	Mean (SD)	N	Mean (SD)	
Region 1 - US	48	-2.18 (4.08)	40	-0.25	0.0087
Region 2 - Western Europe	24	-2.07 (3.41)	26	-1.59 (4.73)	0.5874
France	4	-3.84 (2.95)	5	1.70 (3.60)	0.1371
Belgium	7	-1.80 (3.68)	9	-3.40 (5.45)	0.4879
Italy	10	-1.38 (3.06)	10	-1.36 (4.47)	0.9184
Spain	3	-2.63 (5.35)	2	-2.81 (1.68)	0.3945
Region 3 - Eastern Europe	128	-2.16 (2.69)	124	-0.36 (2.97)	<.0001
Czech Republic	30	-2.29 (3.04)	28	-1.01 (3.49)	0.1272
Hungary	17	-2.01 (3.19)	16	-1.40 (2.57)	0.5489
Poland	81	-2.14 (2.47)	80	0.07 (2.78)	<.0001

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

An interaction between the treatment and prior exposure to ropinirole was observed in the primary efficacy analysis of total awake time spent "off". For subjects who had prior exposure of ropinirole, the mean change of total awake time spent "off" was similar between ropinirole CR-treated patients and placebo-treated patients. Due to a small number of observations, it is difficult to explain the discrepancy in the treatment differences between the subjects who had prior exposure of ropinirole CR and subjects who did not have prior exposure of ropinirole CR.

Study 228 provided some insight into the time course of development of dyskinesia. Data from Study 228 should be interpreted with caution since early termination of the study resulted in lower enrollment, a shorter period of observation and, as a result, a smaller number of events. In addition, rigorous comparisons to evaluate the equivalency of ropiniorle CR and Sinemet in efficacy were not specified in the protocol, and inference in efficacy could not be drawn.

5.2 Conclusions and Recommendations

The pivotal study 169 has demonstrated that ropinirole CR is superior to placebo as adjunctive therapy to L-dopa, assessed by the primary endpoint of change from baseline in awake time spent "off".

Data from Study 288 are suggestive of efficacy of ropinirole CR in delaying the onset of dyskinesia.

b(4)

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

/s/

Sharon Yan
11/15/2007 02:53:54 PM
BIOMETRICS

Kun Jin
11/15/2007 03:16:27 PM
BIOMETRICS

James Hung
12/5/2007 03:09:11 PM
BIOMETRICS