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APPLICATION NUMBER:

22-008

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22008
Submission Code	RS
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Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	12/6/07
Established Name	ropinirole extended-release
(Proposed) Trade Name	REQUIP XL
Therapeutic Class	Dopaminergic agonist
Applicant	Glaxo-Smith-Kline
Priority Designation	S
Formulation	Extended-release
Dosing Regimen	Once daily
Indication	Treatment of early and advanced Parkinson's Disease
Intended Population	Early and advanced Parkinson's Disease

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

- I conclude that extended-release ropinirole (ER ropinirole , ropinirole XL, REQUIP XL) is safe and effective for the signs and symptoms of Parkinson's Disease (advanced and early).

Effectiveness is based upon :

Reviewer Efficacy Conclusions for Study 169 (Randomized, Double-Blinded, Placebo-Controlled, Flexible Dose Titration Study of Adjunctive Treatment of Advanced Parkinson's Disease)

- I conclude that ER ropinirole is superior to placebo as adjunctive treatment (to levodopa) of "off" and provides a statistically significant and noteworthy therapeutic benefit vs placebo in patients with advanced Parkinson's Disease for the primary analysis of the primary efficacy endpoints as well as other similar secondary analyses.

- The therapeutic benefit by which ER ropinirole treatment appeared to decrease "off" appeared to be related primarily to an increase in "on" without troublesome dykinesia. This is a desirable goal of a drug developed to decreased "off" episodes.

- Although the dose range in the randomized, double-blinded, placebo-controlled, flexible dose-titration study was 2-24 mg, I am unable to conclude that the sponsor has demonstrated an optimal dosing regimen because dose-response was not characterized in a fixed, dose study in which patients were randomized to placebo or one of several fixed doses of ER ropinirole. In fact, I believe that results for studies 169 suggest that there is no clear suggestion of an additional clinical/therapeutic benefit of relatively higher daily doses of ER ropinirole (? > a mean dose of 8 or perhaps 14 mg/day depending on different analyses) which would be expected to increase the risk for the various and many types of toxicity from a dopaminergic drug. In study 168, the data suggest that there is no clear benefit for ER ropinirole (or IR ropinirole) above a mean dose of approximately 7-10 mg daily. I have outlined my concerns about excessive dosing in the Reviewer Comment section for efficacy results for studies 169 and 168.

- I am unable to conclude that an optimal titration schedule has been demonstrated for dosing ER ropinirole. Results from study 168 revealed that early Parkinson's Disease patients administered a slower and less aggressive rate of titration of IR

ropinirole (than ER ropinirole) ultimately resulted in a much lower "optimal" dose of ropinirole (~ 50 %) than the "optimal" dose of ER ropinirole after a more aggressive, rapid titration rate. My reasons for this concern are outlined in the Reviewer Comment section discussing efficacy results for study168.

- There does not appear to be any concern about the efficacy of ER ropinirole with respect to the subgroup analyses for age or gender or country. Of note, ER ropinirole clearly appeared to be of therapeutic benefit to patients studied in the U.S.

- I conclude that it would be highly desirable to characterize the dose-response of ER ropinirole (and ideally also study and compare IR ropinirole) by requiring a phase 4 commitment for a fixed, dose study.

Reviewer Efficacy Conclusions for Study 168 (Randomized, Double-Blinded, Comparator, Flexible Dose Titration Study of Monotherapy in Early Parkinson's Disease)

- Overall, I conclude that ER ropinirole appears to show similar efficacy to IR ropinirole in patients with early Parkinson's Disease who were treated with either formulation as monotherapy and then "crossed-over" to the other formulation.

- Although the results suggested that ER ropinirole is statistically non-inferior to IR ropinirole, I believe that the margin (3 points for change from baseline for UPDRS motor score) selected for the non-inferiority is probably excessive. The point estimates of the primary efficacy endpoints are similar for ER ropinirole and IR ropinirole.

- I believe that the data results raise the question that there is little to no clear additional therapeutic benefit of dosing patients with relatively high daily doses of ropinirole (i.e. for both ER ropinirole and IR ropinirole) above 10 mg up to 24 mg. I have outlined my reasons for this concern in the Reviewer Comment section discussing efficacy results for study168. Results from study 169 (for advanced Parkinson's Disease) also raise the question that dosing at > 10-24 mg daily does not provide any clear therapeutic benefit.

- I believe that the relatively rapid titration rate/scheme for ER ropinirole (vs the slower rate of titration for IR ropinirole recommended in the label) increases the chance that patients will titrate to a higher dose of ER ropinirole that is not clearly beneficial but which may be associated with an increased risk for toxicity.

Safety is based upon :

- I conclude that ER ropinirole is safe for the treatment of signs and symptoms of Parkinson's Disease (advanced and early) as a result of my review of the safety findings submitted in this NDA for early and advanced Parkinson's Disease.

- Overall, the safety profile of ER ropinirole is similar to that for IR ropinirole which is approved for the treatment of signs and symptoms of Parkinson's Disease (advanced and early. I did not identify any adverse reactions that appeared to be unique to ER ropinirole.

- Quantitative differences in the frequency of certain adverse reactions between ER ropinirole and IR ropinirole seem more likely to be related to differences in the titration rate of ER ropinirole that is considerably more rapid and aggressive than the titration rate for IR ropinirole described in its label. Although there may be some quantitative differences in the frequency of adverse reactions related to the different shape of the pharmacokinetic (PK) profile for each formulation, I was not able to identify or suggest specific adverse reactions that may have been related to this PK difference. Overall, Cmax and AUC are similar for both formulations. The main difference is Tmax that is much longer (median 6-10 hrs) than the Tmax for IR ropinirole (~ 1-2 hours).

1.2 Recommendation on Postmarketing Actions

- I recommend that the sponsor conduct post-marketing studies to characterize the dose-response curves for efficacy and safety for ER ropinirole in advanced and early Parkinson's Disease. This could be accomplished by conducting 2 randomized, double-blinded, placebo-controlled, parallel, fixed dose studies in early and advanced Parkinson's Disease.

  Ideally, I believe that 5 fixed doses (? 2, 4, 8, 12, 24 mg/day) of ER ropinirole should be included in each study for comparison with placebo to attempt to identify the lowest effective dose and the lowest, maximally therapeutic dose.

  It might also be desirable that multiple, fixed doses of IR ropinirole also be evaluated in these same studies to characterize the dose-response for IR ropinirole. However, it is not clear that this is necessary because our impression is that the same total dose of IR-ropinirole is essentially bioequivalent to ER ropinirole.

1.2.1 Risk Management Activity

- Not applicable. There is no risk management plan.

1.2.2 Required Phase 4 Commitments

- See section 1.2 for my recommendation for Phase 4 Commitments

1.2.3 Other Phase 4 Requests

- Not applicable

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The overall clinical development program consisted of several pharmacokinetic and clinical studies. Some studies focused on assessing the tolerability and safety of the initial starting dose of ER ropinirole and the early titration rate. Study 169 was the main study upon which the safety and efficacy was demonstrated in a randomized, double-blind, placebo-controlled trial in which ER ropinirole was investigated vs Placebo in advanced Parkinson's Disease. Study 168 was a randomized, double-blind, controlled study in which patients with early Parkinson's Disease were initially randomized to ER ropinirole or IR-ropinirole. After a titration period, patients were treated during a maintenance period followed by 2 additional maintenance periods in which patients continued on the same blinded treatment or crossed over to the alternative treatment.
Study 228 was randomized, double-blind, controlled study in which patients with Parkinson's Disease were treated with ER ropinirole or Sinemet and evaluated for the time to onset of dyskinesia. This study was terminated prematurely.

1.3.2 Efficacy

Study 169 : Comparison of ER ropinirole vs Placebo in Advanced Parkinson's Disease

Study 169 demonstrated that ER ropinirole is superior to placebo in patients with advanced Parkinson's Disease for the primary efficacy endpoint, the change from baseline in total "OFF" hours. These results are shown in the table below here.

Summary Statistics for Change from Baseline in Total Awake Time Spent "Off" at Week 24 LOCF (ITT Population: Study 169)

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, 16.0)	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)

Data Source: Section 13, Table 7.1 and Table 7.2.
1. A decrease from baseline indicates an improvement.

The following analyses show similar results for the primary efficacy endpoint for the modified ITT population based upon LOCF and observed case data, and also for observed case data in the Per Protocol population.

Adjusted Analysis of Change from Baseline in Total Awake Time Spent "Off" (Hours) at Week 24 by Population (Study 169)

Population	Ropinirole CR Adjusted[1] Mean (SE) Change from Baseline[2]	Placebo Adjusted[1] Mean (SE) Change from Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
ITT: Week 24 LOCF	n=201 -2.1 (0.32)	n=190 -0.3 (0.32)	-1.7	(-2.34, -1.09)	<0.0001
ITT: Week 24 OC	n=158 -2.8 (0.38)	n=126 -1.2 (0.40)	-1.6	(-2.30,-0.85)	<0.0001
PP: Week 24 LOCF	n=168 -2.4 (0.41)	n=156 -0.7 (0.40)	-1.8	(-2.46,-1.07)	<0.0001

Data Source: Section 13, Table 7.10, Table 7.11 and Table 7.14.
1. Adjusted for country and baseline score.
2. A decrease from baseline indicates an improvement.

The following table shows the results for each treatment over time, the adjusted treatment difference, 95 % CI for the treatment difference, and the respective p values.

Summary of the Adjusted Analysis of Change from Baseline in the Total Awake Time Spent "Off" (Hours) By Visit (ITT Population in Study 169)

Visit (OC)	Treatment	n	Adjusted[1] Mean (SE) Change From Baseline[2]		Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Week 1	Ropinirole CR	201	-0.8	(0.22)	-0.3	(-0.73, 0.13)	0.1741
	Placebo	188	-0.5	(0.22)			
Week 2	Ropinirole CR	197	-1.6	(0.22)	-0.7	(-1.09, -0.23)	0.0029
	Placebo	189	-1.0	(0.22)			
Week 3	Ropinirole CR	194	-2.0	(0.24)	-1.1	(-1.52, -0.59)	<0.0001
	Placebo	184	-1.0	(0.24)			
Week 4	Ropinirole CR	196	-2.1	(0.25)	-1.3	(-1.80, -0.79)	<0.0001
	Placebo	182	-0.8	(0.26)			
Week 6	Ropinirole CR	194	-2.1	(0.28)	-0.9	(-1.47, -0.39)	0.0008
	Placebo	178	-1.1	(0.28)			
Week 8	Ropinirole CR	189	-1.9	(0.30)	-1.5	(-2.05, -0.87)	<0.0001
	Placebo	175	-0.5	(0.31)			
Week 10	Ropinirole CR	190	-2.0	(0.30)	-1.4	(-1.93, -0.78)	<0.0001
	Placebo	167	-0.7	(0.31)			
Week 12	Ropinirole CR	189	-1.9	(0.32)	-1.6	(-2.21, -0.96)	<0.0001
	Placebo	163	-0.3	(0.34)			
Week 16	Ropinirole CR	182	-2.6	(0.32)	-1.3	(-1.88, -0.63)	0.0001
	Placebo	151	-1.3	(0.34)			
Week 20	Ropinirole CR	175	-2.6	(0.32)	-1.3	(-1.99, -0.69)	<0.0001
	Placebo	140	-1.2	(0.35)			
Week 24	Ropinirole CR	158	-2.8	(0.38)	-1.6	(-2.30,-0.85)	<0.0001
	Placebo	126	-1.2	(0.40)			

Data Source: Section 13, Table 7.10a.
1. Adjusted for country and baseline score.
2. A decrease from baseline indicates an improvement.

The following table shows the mean, median, and range of ER ropinirole doses (and for respective Placebo) over time. Reviewing these dosing data in conjunction with the above table of efficacy results over time shows that efficacy was suggested with a dose as low as 4 mg and that 8 mg may be the lowest, maximally effective dose.

Summary Statistics for the "Dose" of Ropinirole (or Placebo) at Each Visit (Safety Population: Study 169)

Dose (mg/day)		Ropinirole CR N=202	Placebo [1] N=191
Week 1	n	202	189
	Mean (SD)	2.0 (0.0)	2.0 (0.0)
	Median (Range)	2.0 (2 - 2)	2.0 (2 - 2)
Week 2	n	197	190
	Mean (SD)	4.0 (0.28)	4.0 (0.36)
	Median (Range)	4.0 (2 - 6)	4.0 (2 - 6)
Week 3	n	194	184
	Mean (SD)	5.9 (0.35)	6.0 (0.33)
	Median (Range)	6.0 (4 - 6)	6.0 (4 - 8)
Week 4	n	196	183
	Mean (SD)	7.9 (0.74)	8.0 (0.73)
	Median (Range)	8.0 (6 - 12)	8.0 (6 - 12)
Week 6	n	195	178
	Mean (SD)	11.3 (1.60)	11.8 (1.34)
	Median (Range)	12.0 (6 - 16)	12.0 (6 - 16)
Week 8	n	190	177
	Mean (SD)	14.3 (2.94)	15.2 (2.36)
	Median (Range)	16.0 (6 - 20)	16.0 (6 - 20)
Week 10	n	190	168
	Mean (SD)	16.8 (4.21)	18.2 (3.31)
	Median (Range)	20.0 (6 - 24)	20.0 (6 - 24)
Week 12	n	189	163
	Mean (SD)	19.0 (5.51)	20.7 (4.55)
	Median (Range)	20.0 (6 - 24)	24.0 (6 - 24)
Week 16	n	182	153
	Mean (SD)	19.4 (5.56)	21.0 (4.42)
	Median (Range)	22.0 (6 - 24)	24.0 (6 - 24)
Week 20	n	177	143
	Mean (SD)	19.5 (5.52)	21.1 (4.45)
	Median (Range)	24.0 (6 - 24)	24.0 (6 - 24)
Week 24	n	169	132
	Mean (SD)	19.5 (5.58)	21.2 (4.41)
	Median (Range)	24.0 (6 - 24)	24.0 (6 - 24)
Week 24 LOCF	n	202	191
	Mean (SD)	18.8 (6.26)	20.0 (5.62)
	Median (Range)	20.0 (2 - 24)	24.0 (2 - 24)
Down-Titration [2]	n	189	178
	Mean (SD)	6.6 (1.83)	6.9 (1.68)
	Median (Range)	8.0 (2 - 16)	8.0 (2 - 16)

Data Source: Section 12, Table 6.11.
1. Note that all subjects in the placebo group received 0 mg of active ingredient.
2. The dose reported is that taken during the second half of the down-titration period.

Study 168 : Comparison of ER ropinirole vs IR-ropinirole in Early Parkinson's Disease

In Study 168, patients were titrated to optimal doses of ropinirole. However, the titration schedule for ER ropinirole was faster, and more aggressive than the titration scheme used for IR-ropinirole. The primary efficacy endpoint was the change from period baseline in the UPDRS total motor score as recorded at the end of each flexible dose maintenance period. Primary inference with regards to the non-inferiority of ropinirole CR compared to ropinirole IR is based on the LOCF dataset for the PP population.

Summary statistics for the change from period baseline in UPDRS total motor score during each period of the study are shown in the following table.

Summary Statistics for Change from Period Baseline in UPDRS Total Motor Score at Each Time point (PP Population: Protocol SK&F-101468/168)

	Ropinirole CR N=101		Ropinirole IR N=108	
UPDRS Total Motor Score	**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.

The following table shows corresponding dosing information (e.g., mean, median, range) for ER ropinirole and IR-ropinirole at the end of the titration period and each of the 3 maintenance periods. Of significant interest, the mean change from baseline in total UPDRS motor score was relatively similar for both treatments at the end of the titration period, however, the mean "optimal" dose of IR-ropinirole (~ 7 mg) was much lower than the mean "optimal" dose of ER ropinirole (~ 18 mg). Of additional interest, there was relatively little change in the total UPDRS motor score for groups of patients as they switched from a similar dose of IR-ropinirole to ER ropinirole or from a similar dose of ER ropinirole to IR-ropinirole. These observations suggested that patients were maximally treated at mean ropinirole doses of ~ 7- 9 mg daily.

Summary Statistics for the Dose of Ropinirole at the End of Each Period by Sequence (Safety Population: Protocol SK&F-101468/168)

	Dose (mg/day)	CR-CR-IR N=41	IR-IR-CR N=43	CR-IR-IR N=34	IR-CR-CR N=43
Week 12 OC	n	39	40	32	40
	Mean (SD)	17.3 (6.25)	6.8 (2.22)	18.9 (5.00)	7.3 (2.01)
	Median	20.0	7.5	20.0	7.5
	Range	4.0 - 24.0	0.75 - 9.0	8.0 - 24.0	2.25 - 9.0
Week 20 LOCF	n	39	39	32	40
	Mean (SD)	17.8 (5.82)	9.0 (4.93)	19.6 (5.41)	8.9 (4.14)
	Median	20.0	7.5	20.0	9.0
	Range	4.0 - 24.0	1.5 - 21.0	8.0 - 24.0	2.25 - 21.0
Week 28 LOCF	n	39	33	27	35
	Mean (SD)	18.1 (5.94)	9.0 (5.74)	19.8 (5.13)	9.5 (4.86)
	Median	20.0	7.5	21.0	8.0
	Range	4.0 - 24.0	1.5 - 24.0	7.5 - 24.0	2.0 - 24.0
Week 36 LOCF	n	36	30	26	34
	Mean (SD)	17.9 (6.30)	9.4 (5.92)	20.1 (4.99)	9.8 (5.23)
	Median	21.0	8.0	21.0	8.0
	Range	4.5 - 24.0	2.0 - 24.0	7.5 - 24.0	2.0 - 24.0

Data Source: Section 12, Table 6.27.

Study 228 : Comparison of Time to Onset of Dyskinesia for ER ropinirole vs Sinemet

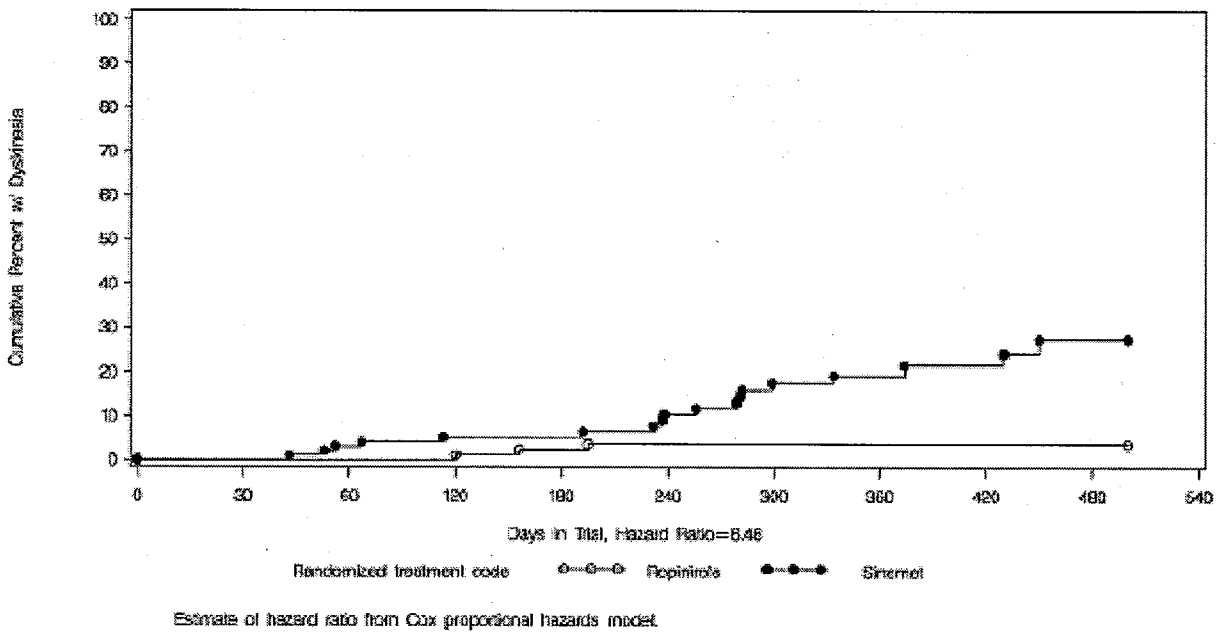
This Phase 3B study was a randomized, multicenter, double-blind, Sinemet-controlled, parallel group, flexible dose study to assess the effectiveness of adjunctive therapy with ropinirole CR and L-dopa at increasing the time to onset of dyskinesias in advanced Parkinson's disease patients, while adequately controlling PD symptoms. Screened patients were randomized to double-blind (by double dummy) treatment of either add-on ropinirole CR or Sinemet. A minimum of 15 visits were planned over the 107-week duration of the study. 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.

The DNP reviewed this study that was conducted without discussing its planning with the DNP. [redacted] b(4)

Brief efficacy results are presented.

The following figure shows the Kaplan-Meier plot of the time to onset of dyskinesia for ER ropinirole vs Sinemet and suggests that ER ropinirole delays the time to onset of dyskinesia.

Kaplan-Meier Plot of Time to Onset of Dyskinesia (ITT Population: Study 228)



Data Source: Section 14, Figure 7.1

Treatment-Emergent Adverse Reaction Incidence in a Double-Blind, Placebo-Controlled Trial in Advanced Stage Parkinson's Disease (With L-dopa) (Events ≥2% of Patients Treated with REQUIP XL and >% with Placebo)

Body System/Adverse Reaction	REQUIP XL (n = 202) %	Placebo (n = 191) %
Ear and labyrinth disorders		
Vertigo	4	2
Gastrointestinal disorders		
Nausea	11	4
Constipation	4	2
Abdominal pain/discomfort	6	3
Diarrhea	3	2
Dry Mouth	2	<1
General disorders		
Edema peripheral	4	1
Injury, poisoning, and procedural complications		
Fall*	2	1
Musculoskeletal and connective tissue disorders		
Back pain	3	2
Nervous system disorders		
Dyskinesia*	13	3
Dizziness	8	3
Somnolence	7	4
Psychiatric disorders		
Hallucination	7	3
Anxiety	2	1
Vascular disorders		
Orthostatic hypotension	5	1
Hypotension	2	0
Hypertension*	3	2

*Dose-related.

1.3.4 Dosing Regimen and Administration

The following information is what I believe and the DNP believes is appropriate for our recommendation for dosing regimen and administration.

Dosing for Parkinson's Disease

The starting dose is 2 mg taken once daily for 1 to 2 weeks, followed by increases of 2 mg per day at 1 [redacted] depending on therapeutic response and tolerability, up to a maximally recommended dose of 24 mg per day. b(4)

In clinical trials, dosage was initiated at 2 — and gradually titrated — therapeutic response and tolerability. Doses greater than 24 mg/day have not been studied in clinical trials. Patients should be assessed for therapeutic response and tolerability at a minimal interval of 1 week or longer after each dose increment. Caution should be exercised b(4)

during dose titration because too rapid a rate of titration — lead to dose selection that — not provide additional benefit, but that ——— the risk of adverse reactions. *[see Clinical Studies (14.2)]* Due to the flexible dosing design used in clinical studies, specific dose response information could not be determined. b(4)

When REQUIP XL is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be decreased gradually as tolerated. In the placebo-controlled advanced Parkinson's disease study, the L-dopa dose was reduced once patients reached a dose of REQUIP XL of 8 mg per day. Overall, L-dopa dose reduction was sustained in 93% of patients treated with REQUIP XL and in 72% of patients on placebo. On average the L-dopa dose was reduced by 34% in patients treated with REQUIP XL *[see Clinical Studies (14)]*

REQUIP XL should be discontinued gradually over a 7-day period.

Switching From Immediate-release Ropinirole Tablets to REQUIP XL

Patients may be switched directly from immediate-release ropinirole to REQUIP XL Tablets. The initial dose of REQUIP XL should most closely match the total daily dose of the immediate-release formulation of REQUIP, as shown in Table 1.

Table 1 Conversion from Immediate-release REQUIP to REQUIP XL

Immediate-release Ropinirole Tablets Total Daily Dose (mg)	REQUIP XL Tablets Total Daily Dose (mg)
0.75 to 2.25	2
3 to 4.5	4
6	6
7.5 to 9	8
12	12
15 to 18	16
21	20
24	24

Following conversion to REQUIP XL, the dose may be adjusted depending on therapeutic response and tolerability (see ——— 2.2). b(4)

1.3.5 Drug-Drug Interactions (DDIs)

- There were no new DDIs identified for ER ropinirole.

1.3.6 Special Populations

- There were no new or unique risks identified for treatment of any special population with Parkinson's Disease with ER ropinirole.

2 INTRODUCTION AND BACKGROUND

The new formulation, extended-release ropinirole is interchangeably referred to as ER ropinirole or controlled-release (CR) ropinirole in this NDA review. It is relevant to note that the sponsor subsequently began developing another controlled-release ropinirole formulation (CR ropinirole) for treatment of restless leg syndrome that is released over a shorter, extended period than the ER ropinirole that is released over a longer period, is dosed once daily, and is the subject of this NDA and review.

BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

Ropinirole IR tablets are indicated for the treatment of PD as monotherapy and as adjunctive therapy to L-dopa. Since the first approval in July 1996, ropinirole IR is now registered in over 60 countries worldwide. There is extensive clinical experience with ropinirole IR, and its safety profile is well characterized.

GlaxoSmithKline, in conjunction with SkyePharma, Inc., began developing a controlled-release
(CR) tablet of ropinirole in January 2000. The rationale for developing this CR tablet was to improve the profile of ropinirole by allowing once-daily dosing and a simpler dose titration regimen. Compared to ropinirole IR, once-daily dosing with ropinirole CR has the potential of affording subjects an improved tolerability and/or efficacy profile due to a slower rate of absorption and fewer fluctuations in drug plasma levels throughout the day. Compliance could also be improved with a once daily regimen versus a three times daily regimen.

2.1 Product Information

Ropinirole is a potent and highly selective non-ergoline dopamine agonist at D2/D3 receptors that is active both peripherally and centrally. Ropinirole immediate release (IR) tablets (REQUIP®) are indicated for the treatment of Parkinson's disease (PD) and, since the first approval in July 1996, are now available in over 60 countries worldwide for the treatment of PD. Ropinirole IR is effective as both monotherapy in early stage PD and as adjunctive therapy to L-dopa in subjects with advanced PD. Additionally, ropinirole IR has been approved for the treatment of moderate-to-severe primary restless legs syndrome (RLS). The first approval for this indication was obtained in June 2004, and approval was obtained in the United States (US) in May 2005. As of March 2006, the estimated cumulative worldwide exposure to ropinirole IR tablets had reached over 350 million patient days (>960,000 patient years).

GlaxoSmithKline (GSK), in conjunction with SkyePharma, began development of a controlled-release (CR) tablet formulation of ropinirole in January 2000. The controlled release
tablet formulation is referred to as 'ropinirole prolonged release tablets' in Europe (REQUIP-MODUTAB®) and International regions (REQUIP PD 24 HOUR®), and 'ropinirole extended release —— tablets' in the United States (REQUIP XL 24 HOUR®). b(4)

As described in the following sections, the clinical development program demonstrates that ropinirole CR is an effective agent with an acceptable safety and tolerability profile in the treatment of both early and advanced PD. The simplified titration regimen is well tolerated, while the once daily dosing is expected to improve compliance. Subjects who are already receiving ropinirole IR tablets can switch overnight to the nearest equivalent dose of ropinirole CR tablets and can take ropinirole CR tablets with or without food. No new safety concerns were identified for ropinirole CR tablets compared with ropinirole IR tablets and the proposed prescribing information provides appropriate information to allow for the safe and effective use of the drug in the treatment of signs and symptoms of idiopathic PD.

2.2 Currently Available Treatment for Indications

The aims of PD therapy are symptom control and improved quality of life. Current therapeutic strategies rely on the use of levodopa (L-dopa), monoamine oxidase (MAO)-B inhibitors and/or dopamine agonists to compensate for the dopaminergic deficit. The American Academy of Neurology issued evidence-based treatment guidelines for PD in 2002, which were re-affirmed in 2005. These guidelines suggest that in early PD, L-dopa or dopamine agonists should be used, although L-dopa is associated with a higher risk of dyskinesia. In later stage PD, motor fluctuations limit the response to therapy. Dopamine agonists, MAO-inhibitors, and catechol-O-methyl transferase (COMT) inhibitors are recognized therapies for reducing off-time in advanced Parkinson's Disease patients.

L-dopa is almost always given in combination with dose-sparing enzyme inhibitors, including peripherally acting dopa decarboxylase inhibitors (e.g. carbidopa or benserazide) and MAO inhibitors (e.g. selegiline, rasagiline) or COMT inhibitors (e.g. entacapone, tolcapone). However, long-term L-dopa therapy is associated with reduced efficacy and motor complications. Consequently, treatment guidelines generally recommend delaying, or minimizing, L-dopa therapy, particularly in younger subjects. Dopamine agonists are the primary alternative to L-dopa. They provide symptomatic relief of PD symptoms with a low risk of motor complications. Their use in early stage PD, as monotherapy or adjunct therapy with L-dopa, delays or reduces L-dopa-related adverse effects.

Dopamine agonists fall into two classes: ergoline agonists (e.g. pergolide, bromocriptine, lisuride, cabergoline and dihydroergocriptine) and non-ergoline agonists (e.g. ropinirole, pramipexole, and piribedil, plus apomorphine, which is only administered subcutaneously). All dopamine agonists require a relatively slow titration to an efficacious dose because of their dopaminergic side effects. These tend to occur most commonly within the first few weeks of treatment initiation. The ergoline agonists have the additional disadvantage of being specifically associated with rare cases of peripheral vasospasm, erythromelalgia and pleuropulmonary, or retroperitoneal fibrosis.

Dopamine agonists are generally administered two or three times per day. Compliance tends to be inversely related to the number of daily doses. Available compliance studies

in PD suggest that there is suboptimal compliance and erratic medicine taking and that the incidence of missed or mistimed doses of PD therapy can be high (51% and 82%, respectively). Ease of use is essential to enhance patient compliance and maximum therapeutic benefit.

To date, only the ergoline agonist, cabergoline, is available as a once daily oral formulation. The non-ergoline agonist, piribedil, is available as a sustained-release formulation administered as 1-5 times daily. A once a day sustained-release transdermal patch formulation of rotigotine is also now registered for monotherapy treatment in some markets. Some of these therapies are not yet available in the US. There is, therefore, an unmet medical need for an oral non-ergoline dopamine agonist with a simplified titration regimen and once daily dosing.

Sponsor's Rationale for Development of Controlled-Release Formulation of Ropinirole

The efficacy and safety of ropinirole IR tablets is well established and described in the original application for ropinirole IR tablets (New Drug Application (NDA) 20-658, approved September 1997). Ropinirole IR improves the clinical manifestations of Parkinson's Disease when used as monotherapy or as an adjunct to L-dopa in advanced cases of Parkinson's Disease. Furthermore, ropinirole IR may be associated with slower progression of PD than L-dopa and delayed development of dyskinesia associated with ropinirole IR monotherapy can be maintained for up to five years; these data seem to have been confirmed over the following five years despite the small patient population. Based on extensive clinical trials and post-marketing experience, ropinirole IR has been found to be well tolerated, and its safety profile well characterized, with most adverse events (AEs) being related to dopaminergic activity.

Ropinirole IR tablets are taken three times daily, starting with low doses (0.75mg/day) and a slow initial titration regimen of 0.75mg weekly increments over the first four weeks. In total, 13 dose levels are available up to the maximum dose of 24mg/day. The rationale for developing a CR formulation of ropinirole is to allow once-daily dosing and a simpler dose titration regimen. Compared to ropinirole IR, once-daily dosing with ropinirole CR has the potential of affording subjects an improved tolerability and/or efficacy profile due to a slower rate of absorption and fewer fluctuations in drug plasma levels throughout the day. Ropinirole CR tablets present a reduced pill-burden, simplified dosing regimen (eight versus 13 dose levels), higher starting dose (2mg/day versus 0.75mg/day) and faster achievement of effective dose (2mg versus 0.75mg weekly incremental increases over the first four weeks). Compliance might also be improved with a once daily regimen versus a three times daily regimen. Ropinirole CR will be the first non-ergoline dopamine agonist available as a once daily tablet for the treatment of PD.

The available dose range for both ropinirole IR and CR allows for potential up-titration as the disease progresses.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient (ropinirole) in ER ropinirole is immediate-release ropinirole marketed in the U.S. as Requip.

2.4 Important Issues With Pharmacologically Related Products

The typical issues associated with dopaminergic agonists are described in the ropinirole label.

2.5 Presubmission Regulatory Activity

The development program was discussed with the FDA at an End of Phase II meeting held on 6 February 2003. The following points highlight the comments and agreements reached at this meeting (based upon the sponsor's summary):

· The designs of biopharmaceutical studies were based on the Food and Drug Administration (FDA) draft guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products". Due to the potential dopaminergic side effects of single doses of ropinirole CR at the highest tablet strength of 8mg, the FDA and GSK agreed that it was appropriate to conduct the food effect, dose proportionality and dosage strength equivalence studies at steady state rather than as single-dose studies. These conditions are more likely to reflect the clinical use of ropinirole CR tablets in PD subjects.

· The FDA agreed in principle that a single clinical study of ropinirole CR tablets as adjunctive treatment could support approval of both adjunctive therapy and monotherapy in all stages of PD. However, it was critical to the justification for extrapolating these data to monotherapy that GSK evaluate the potential effect of food on the efficacy of the CR tablet formulation. In the planned confirmatory efficacy study (Study 169), the study was amended so that ropinirole CR tablets were to be taken once daily in the morning without regard to food.

· The FDA agreed with GSK's proposal to evaluate the weekly dose titration regimen (up to 8 mg) in a study.

· The FDA agreed with GSK's proposal for a single blood pressure measurement at each clinic visit in Study 169, with the exception that the evaluation be done no sooner than four hours post-dose rather than at least two hours post-dose as GSK proposed.

· The FDA agreed that a pharmacokinetic argument using results from Study 164 and other available data would be sufficient to support dosing guidance for switching from IR to CR, provided that the argument was sufficiently robust. The FDA also stated that any results available from Study 168 (cross over non-inferiority design study) could potentially provide additional support for IR to CR switching guidelines.

· The FDA agreed that the safety data from the ropinirole IR tablet program could be used to support the ropinirole CR tablet safety, unless any unusual findings were observed in the ropinirole CR tablet studies.

The sponsor submitted a supplement NDA (sNDA) 22008 to the Agency in 12/05 for ER ropinirole. After the sponsor became aware of numerous deficiencies in this sNDA, the sponsor withdrew the sNDA. The content and format of the Integrated Summary of Safety (ISS) and other analyses were discussed with the Agency at a meeting on 13 March 2006, with follow-up Agency correspondence received on 14 April, 17 April, and 18 April 2006. The DNP's recommendations for numerous analyses requested by the Agency were provided to the sponsor.

2.6 Other Relevant Background Information

Sponsor's Justification for the Use of Study 169 to Support Use of Ropinirole CR as Monotherapy in Early-Stage Parkinson's Disease

The principal efficacy study in this submission is Study 169, an adjunct study in advanced PD. The positive findings in this study may be used to infer that ropinirole CR is also efficacious as monotherapy in early-stage PD. This inference is justified for the following reasons:

· The pathophysiological basis of PD is the same in early and advanced stages, which represent a continuous progression in the natural history of the disease. The progressive dopaminergic deficit due to the degeneration of the neurons in the substantia nigra can be partially ameliorated by increasingly higher doses of L-dopa and/or dopamine agonists, which translates into improvement of the signs and symptoms of the disease.

· The pharmacodynamics of L-dopa and dopamine agonists are similar, as demonstrated by the L-dopa sparing activity by dopamine agonists in add-on studies in advanced PD. The dopaminergic deficit can be treated with L-dopa and/or dopamine agonists, and this is valid for all stages of disease and both for mono- and add-on therapy.

· A late-stage adjunct trial represents a more difficult population in which to demonstrate efficacy than an early-stage monotherapy trial. Advanced stage disease is more difficult to treat, late-stage PD, there is a narrower therapeutic window for dopaminergic therapy, so that a with more frequent motor complications. In adjunctive trials there are pharmacodynamic interactions with other dopaminergic agents and with the usual background L-dopa therapy. In treatment which produces successful results in this setting has greater leeway in earlier-stage patients for dose optimization. Prior experience demonstrates that dopamine agonists active in advanced PD are also active as a monotherapy in early Parkinson's Disease

.

Study 168 provides evidence that ropinirole CR is non-inferior to ropinirole IR in monotherapy treatment of early-stage PD; the efficacy of ropinirole IR has previously been demonstrated in a double-blind, placebo-controlled trial to be efficacious in the treatment of subjects with early stage PD.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The sponsor needed to address the standard issues/concerns associated with the development a and approval for a new formulation of an approved product. The CMC reviewer did not have any serious concerns with the NDA that have not been addressed. See the CMC review.

3.2 Animal Pharmacology/Toxicology

There were no new preclinical animal studies submitted to support this NDA. The Pharmacology/Toxicology reviewer did not have any significant concerns with this NDA. See the Pharmacology/Toxicology review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

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 :

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4.2 Tables of Clinical Studies

Table 1 Tabular Listing of Clinical Studies Contributing to Efficacy and Safety Data

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
SK&F-101468/166	To identify the maximum well-tolerated starting dose of ropinirole XL 24-hour. To compare the tolerability of once daily doses of ropinirole XL 24-hour with three times daily doses of 0.25mg ropinirole IR. To assess the PK profile of ropinirole XL 24-hour.	DB, AC, R, DR	Parkinson's disease patients	Ropinirole IR 0.25mg three times daily compared with Ropinirole XL 24-hour 1.0, 2.0 or 3.0mg once daily in sequential cohorts; oral; 1 week.	64	Complete
SK&F-101468/167	Primary: To compare the safety and tolerability of two titration regimens of ropinirole XL 24-hour using the standard titration regimen of ropinirole IR as a reference. Secondary: Preliminary assessment of efficacy for the XL 24-HOUR arms.	DB, AC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 3.0, 4.0, 6.0mg once daily (Titration Regimen A) or ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0mg once daily (Titration regimen B) or ropinirole IR 0.25, 0.5, 0.75, 1.0mg three times daily (standard titration regimen of ropinirole IR) during the first four weeks of treatment; oral; 4 weeks.	75	Complete

Table 1 (Continued) Tabular Listing of Clinical Studies Contributing to Efficacy and Safety Data

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
SK&F-101468/168	Primary: demonstrate non-inferiority of ropinirole XL 24-hour to IR. Secondary: evaluate the safety profile, assess the PK of ropinirole XL 24-hour, support dose switching from ropinirole IR to XL 24-HOUR, investigate the superiority of ropinirole XL 24-hour	DB, AC, XO, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or ropinirole IR 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0mg three times daily; oral; 36 weeks.	161	Complete
SK&F-101468/169	Primary: evaluate the efficacy of ropinirole XL 24-hour as adjunctive therapy to L-Dopa Secondary: evaluate the safety profile of ropinirole XL 24-hour , assess the PK of ropinirole XL 24-hour	DB, PLC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or placebo; oral; 24 weeks.	393	Complete

Table 1 (Continued) Tabular Listing of Clinical Studies Contributing to Efficacy and Safety Data

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
SK&F-101468/228	Primary: To evaluate the time to onset of dyskinesia with ropinirole XL 24-hour compared with Sinemet in patients already being treated with levodopa. Secondary: To evaluate the efficacy of ropinirole XL 24-hour compared to Sinemet on (a) symptomatic control of PD and (b) non-motor symptoms of PD.	DB, AC,R	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or Sinemet total daily doses of 50, 100, 150, 200, 400, 500, 800, 1000mg; oral; 2 years.	208	Complete
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
SK&F-101468/196	To obtain long-term exposure information on subjects with Parkinson's disease receiving ropinirole XL 24-hour.	O	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily; oral; 5 years currently (flexible).	83	Interim
SK&F-101468/248	Primary: To evaluate the safety profile of ropinirole XL 24-hour during long term treatment in patients with early and advanced Parkinson's disease. Secondary: To collect patient preference data regarding od versus tid study medication.	O	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily; oral; 3 years currently (flexible).	412	None

4.3 Review Strategy

Reviewer Comment

- My review focused particularly on studies 169, 168, and the ISS.

4.4 Data Quality and Integrity

Reviewer Comment

- The data appeared to be of reasonably good quality. I did not have any specific questions as to the integrity of the data contained in this NDA.

4.5 Compliance with Good Clinical Practices

The sponsor noted that all studies were undertaken in accordance with standard operating procedures of the GSK Group of Companies, SkyePharma and the contract research organizations, ——————— which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. b(4)

Informed consent was obtained from all subjects and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted, or the 1996 version. Where regulatory approval was required, this was obtained from the relevant health authority.

4.6 Financial Disclosures

The sponsor provided required information on financial disclosures.

Reviewer Comment

- I did not have nor discover any concerns with financial disclosures.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Sponsor's Biopharmaceutical Conclusions
• Ropinirole CR tablets have a slower rate of absorption and fewer fluctuations in ropinirole plasma concentrations over a 24-hour interval, compared with ropinirole IR tablets.
• In PD subjects, steady state ropinirole bioavailability is similar for the CR and IR tablets, supporting the proposed recommendations for formulation conversion.
• The lack of a clinically significant effect of food on bioavailability or drug-release rate confirms that ropinirole CR tablets can be taken with or without food.
• The ropinirole CR formulation was shown to be resistant to dose dumping in an alcohol environment.
• Dose-proportionality has been demonstrated using ropinirole CR tablet strengths over a range of 2mg to 8mg.

• Dosage strength equivalence has been demonstrated between one 8mg ropinirole CR tablet and four 2mg ropinirole CR tablets.

Sponsor's Pharmacokinetic Conclusions

· The results of the population pharmacokinetic analysis from the ropinirole CR tablet controlled Studies 169 and 168 are consistent with the results of the previous population pharmacokinetic analysis for ropinirole IR tablets.

· The population mean estimate of ropinirole oral clearance was 54.7L/h in subjects <65 years of age and 47.7L/h in subjects ≥65 years of age, when ropinirole was administered as the CR tablet. The inter-individual variability for oral clearance was approximately 47%. These are unlikely to be of any clinical relevance, especially because ropinirole is titrated to efficacy.

· Based on the population pharmacokinetic analysis, the pharmacokinetics of ropinirole are approximately linear up to a total daily dose of 24 mg.

Executive Summary Clinical Pharmacology Reviewer (Dr. Ta-Chen Wu)

The Sponsor (GlaxoSmithKline) is seeking approval for Requip (ropinirole hydrochloride) XL 24-Hour controlled-release formulations of 2 mg, 3 mg, 4 mg, and 8 mg strengths for the treatment of signs and symptoms of idiopathic Parkinson's disease (PD). The proposed extended release tablet formulations have an approximately 24 hours of release profile and are for allowing once-daily dosing.

The new XL formulation is claimed to provide a better tolerability (due to slower absorption) and a longer duration of action compared to the approved IR formulation. In addition, Parkinsons's patients already on immediate-release Requip Tablets may be switched directly from IR to the XL formulation. Therefore, it is important to bridge the two formulations through pharmacokinetics, relative bioavailability, exposure-response relationships, in addition to safety and efficacy.

The clinical pharmacology and biopharmaceutics program focused on single- and multiple-dose pharmacokinetics in healthy subjects and in patients with Parkinson's disease, relative bioavailability, food effects, dose-proportionality, dosage strength equivalence, exposure-response relationships based on Phase 3 trial, as well as generating individual estimates and sources of inter-subject variability based on population pharmacokinetics analysis on data from Phase 3 efficacy trials. The IVIVC model and prediction for the proposed formulation and a combined PK/PD assessment for QT in Parkinson's patients were also submitted, which have been previously reviewed. Other supporting data include in vitro dissolution data and in vitro evaluation for potential dose dumping.

Clinical Pharmacology Reviewer Recommendations

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 22-008 acceptable from an OCP

b(4)

perspective provided that the Sponsor agrees with the Phase IV commitment. The recommended Phase IV commitment pertaining to investigation of whether ropinirole is a P-glycoprotein substrate and has CYP induction potential has been previously conveyed to the Sponsor for the ——— application for Requip CR-RLS and should be applicable to the current submission. In addition, agreement on the labeling language should be reached between the Sponsor and the Agency.

Comments to be conveyed to the Sponsor:

- Since external predictability is inconclusive for 8 mg, we recommend additional evaluation of predictability with other strengths and data sets and submitted prior to full application of this IVIVC for biowaiver. You are using study specific UIR. While acceptable for this development and predictability, you should come up with reasonable estimates of UIR that can be used for future biowaiver.
- Since dissolution testing indicated a lack of significant impact of paddle speed on in-vitro dissolution profiles of the proposed ropinirole XL tablets, your selection of 100 rpm is acceptable. However, in future drug development programs, we recommend use of 50 rpm as paddle speed.

Clinical Pharmacology Reviewer Phase IV Commitment Recommendations

The Sponsor should commit to the following recommendations and submit results to the Agency within —— from the date of approval:

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- The Sponsor should evaluate whether ropinirole is a P-gp substrate and/or inducer for major CYP enzymes (e.g., CYP3A4) and, if so, any drug-drug interaction potential through either mechanism. This can be accomplished through comprehensive literature or in vitro study as a Phase IV commitment.

5.2 Pharmacodynamics

ER ropinirole appeared to be associated with the typical therapeutic effects and adverse reactions associated with dopaminergic agonists and in particular those associates with IR-ropinirole.

5.3 Exposure-Response Relationships

From Clinical Pharmacology Reviewer (Dr. Ta-Chen Wu)

Exposure-response relationships:

Population PK analysis: The population PK parameters, inter-individual variability, random residual variability and the covariance estimates for the Final Model were obtained using data from Studies 169, 168 and 164. The population mean estimate of ropinirole oral clearance (CL/F) was 54.7 L/h in patients <65 years of age and 47.7 L/h in patients ≥65 years of age. The inter-individual variability for CL/F was ~47%. The population mean estimate of ropinirole oral volume of distribution (V/F) was 641 L, with an inter-individual variability of 41%. The results of the analysis for ropinirole XL are similar to the results obtained with the previous analysis conducted for ropinirole IR.

Efficacy: The relationship between estimated ropinirole AUC(0-24,ss) and selected primary efficacy endpoints from Study 168 and Study 169 were constructed and analyzed by logistic regression. Graphical assessments of the exposure-response relationship showed that there was small decrease in awake time "off" in patients receiving placebo (~10%). The median percent decrease in awake time "off" was between ~40 to 50% in the ropinirole treated patients. Higher systemic exposures of ropinirole appeared to be associated with a greater decrease in awake time "off". Results of PK/PD analysis in patients with advanced stage Parkinson's disease suggested that higher doses of ropinirole up to 24 mg may lead to improved probability of clinical response, in parallel with possible reduction in L-dopa dose.

Graphical assessments of the relationship between systemic exposure to ropinirole and percent change from baseline in UPDRS motor score showed that there was a ≥30% decrease from baseline. The median decrease was ~50% over the entire ropinirole systemic range for both ropinirole XL and ropinirole IR. The analysis also demonstrated a flat exposure-response relationship for the UPDRS motor score over the entire ropinirole systemic exposure range that was included in the analysis, similar to that for IR. The probability of a patient being a responder to ropinirole was similar over the entire exposure range. The maximal efficacy is likely to be associated with AUC(0-24,ss) values in the range ~150–200 ng·h/mL, corresponding to approximately 8–12 mg/day doses of ropinirole XL, in patients with this early stage of Parkinson's disease.

Reviewer Comment

- I find it interesting that the exposure-response analysis/review of the Clinical Pharmacology reviewer (Dr.Wu) suggested that plasma ropinirole levels associated with doses of approximately 8-12 mg daily maximal efficacy in patients with early Parkinson's Disease when ropinirole was administered as monotherapy.

  Although Dr. Wu noted that increasing doses of ER ropinirole up to 24 mg daily may lead to improved probability of clinical response in parallel with possible reduction in levodopa doses, he did not refer to specific data. Nor did he specifically note that there might be greater reductions in "OFF" from baseline with progressively increasing doses of ER ropinirole up to 24 mg daily. My analyses of dose and response suggested that maximal efficacy might also occur at relatively low doses of ER ropinirole, perhaps 8-12 mg daily.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Based on the clinical studies presented in this submission, the sponsor has proposed that ropinirole ER tablets be indicated for treatment of the signs and symptoms of idiopathic Parkinson's Disease. In all clinical studies, treatment was initiated at subtherapeutic doses

and gradually titrated to therapeutic response. Doses should be increased to achieve a maximum therapeutic effect, balanced against tolerability.

Individual dose titration based on efficacy and tolerability, as specified in the controlled clinical studies (Studies 169, 168 and 228) that support this application, is recommended by the sponsor.

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The recommended initial ropinirole CR tablet dose is 2mg once daily for one [redacted]. Thereafter, the dose may be increased in 2mg increments, at least one week apart, [redacted]. The dose may be adjusted depending on the therapeutic response. The dose may be increased up to a maximum of 24mg once daily. Doses above 24mg/day have not been investigated in clinical trials. Ropinirole CR tablets should be taken once a day, [redacted] and may be taken with or without food.

The sponsor has also proposed that subjects already receiving ropinirole IR tablets may be converted overnight to ropinirole CR tablets. The dose of ropinirole CR tablets should be based on the closest total daily dose of ropinirole IR that the patient was taking. Following the conversion, the dose may be titrated, if required, per the recommendations previously discussed.
When ropinirole CR tablets are administered as adjunct therapy to L-dopa, it may be possible to reduce gradually the L-dopa dose, depending on the clinical response.

6.1.1 Methods

The main study supporting the approval of ER ropinirole (in NDA 22008) is Study SK&F 101468/169 (typically referred to as study 169) which provided the primary efficacy data in a randomized, double-blind, placebo-controlled study of patients with advanced Parkinson's Disease who had inadequate motor control consisting of "off" episodes (i.e. end of dose- wearing "off" and/or unpredictable "on"/"off" motor fluctuations) despite taking a stable dose of levodopa. I will focus on presenting efficacy results and other relevant findings related to and/or impacting on efficacy from study 169.

The sponsor also presented the results of 2 randomized, double-blind, active-controlled studies (SK&F-101468/168, and SK&F-101468/228, typically referred to as studies 168 and 228, respectively). Study 168 evaluated the effects of ER ropinirole vs immediate-release (IR) ropinirole, the approved product, on patients with early Parkinson's Disease (i.e. monotherapy). Study 228 evaluated effects of ER ropinirole (vs levodopa/carbidopa - Sinemet) on the time to onset of dyskinesia in patients with relatively early Parkinson's Disease. **Although, I will present some efficacy results from these studies (168, and 228), I stress again that my focus will be on presenting efficacy results of study 169, the critical, and most important study supporting NDA 22008.**

Overview of Ropinirole CR/ER Parkinson's Disease Clinical Development Program

The ropinirole CR clinical development program assessed the efficacy and safety of ropinirole CR tablets in PD. The program comprised 13 studies. Studies 161 through 167 and 219 were Phase I and II studies to establish the tolerability of the CR formulation and a new titration schedule.

This efficacy summary presents data from two completed Phase III studies with ropinirole CR in PD: 1) Study 169, an adjunctive therapy study in PD subjects classified as Hoehn and Yahr (H&Y) stage II-IV to demonstrate superiority to placebo and 2) Study 168, a monotherapy study in PD subjects classified as H&Y stage I-III to demonstrate the non-inferiority of ropinirole CR to ropinirole IR. In addition, limited efficacy data from a terminated phase IIIb study with ropinirole CR in advanced PD is included (Study 228 [an adjunctive therapy, onset of dyskinesia study in PD subjects classified as H&Y stage IIII]).

Study 168 (comparing IR vs ER ropinirole) is presented as pivotal support for use of ropinirole CR/ER as monotherapy in early-stage PD in addition to adjunctive therapy to L-dopa in later stage Parkinson's Disease (study 169). At the February 6, 2003 End-of-Phase 2 meeting to discuss the clinical development of ropinirole CR, the Agency agreed in principle that results from a study of adjunctive treatment in later-stage disease could support monotherapy treatment in early-stage PD, provided appropriate medical rationale was provided.

In addition, it had to be demonstrated that efficacy of ropinirole CR is maintained in the presence or absence of food, since preliminary data suggested that the pharmacokinetics of ropinirole CR was affected by food.

Study 168 provides support for the use of ropinirole as monotherapy in early stage disease. In addition, Study 168 provides support for switching patients from the IR to the CR formulations of ropinirole. **This study was conducted by the sponsor without any specific discussion with the DNP as to the desirability, design, or analysis of this study. The End of Phase 2 meeting minutes do not reflect discussion of the planning of this study.**

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. Although the study was terminated early and was based on a smaller number of subjects than originally planned, Study 228 provides insight into the time course of development of dyskinesia, a complication of therapy. Data on the primary endpoint only are presented in this summary document and should be interpreted with caution because early termination of the study resulted in lower enrolment, a shorter period of observation and, as a result, a smaller number of events.

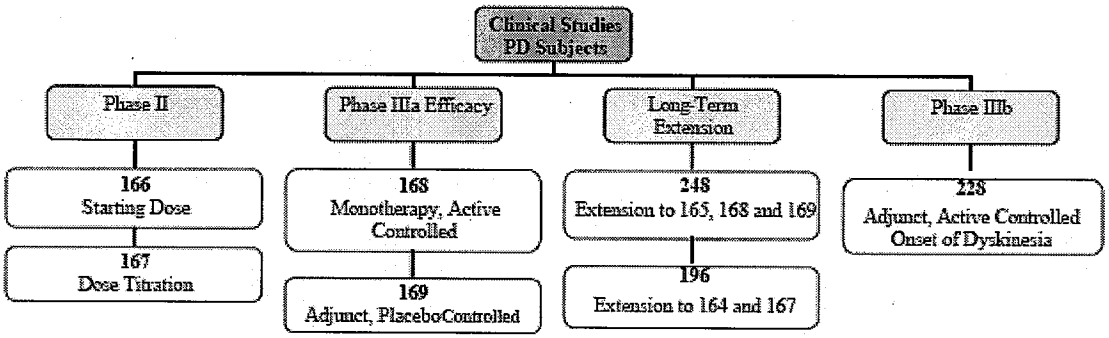
Additional studies in healthy volunteers and PD subjects were conducted to evaluate the relative bioavailability, dose proportionality, and food effect of the ropinirole CR tablet for treatment of PD. These clinical pharmacology studies (Studies 161, 162, 163, 164, 165 and 219) are presented in detail in the clinical study reports.

Two Phase II studies (Studies 166 and 167) were conducted to determine the optimal starting dose and titration regimen, respectively, to use in the pivotal efficacy studies and the primary evaluations were of safety and tolerability.

Two ongoing long-term open-label extension studies are being conducted to assess long-term
safety of ropinirole CR (Studies 196 and 248).

An overview of these clinical studies is provided in Figure 1.

Figure 1 Clinical Studies for Ropinirole CR/ER



6.1.2 General Discussion of Endpoints

The sponsor noted that the majority of outcome measures used for Studies 169, 168 and 228 are established endpoints used for the development of symptomatic treatments for PD. The scales used to determine these disease-specific endpoints included objective and subjective data. The sponsor also noted that most of the endpoints used within Studies 169 and 168 were similar to those used in the original NDA submission for ropinirole IR tablets (NDA 20-658, approved September 1997).

Primary Efficacy Variables

For study 169 in advanced Parkinson's Disease, the primary efficacy variable was the **mean change from baseline in awake time "off"** (e.g. total hours) at Week 24 last observation carried forward (LOCF), and was analyzed in terms of absolute change from baseline.

The primary efficacy variable for the controlled, comparator study 168 in early Parkinson's Disease was the difference between ropinirole IR and CR in the **change from period baseline in the UPDRS motor score** as recorded at the end of each flexible dose maintenance period (Each flexible dose maintenance period has its own baseline known as the period baseline. This was the visit at which subjects entered the flexible 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.). For the primary endpoint, the non-inferiority of

ropinirole CR to ropinirole IR was assessed by comparing the confidence interval for the treatment difference with a non-inferiority margin of 3 points. Based on data from a previous ropinirole IR study (study 056) where ropinirole IR was compared to L-dopa, a difference of 3 points or less between ropinirole CR and ropinirole IR is not considered as clinically significant. In addition, the use of a 3-point non-inferiority margin on the UPDRS motor score was endorsed by the key opinion leader advisory panel who worked with GSK on the study design.

The primary efficacy variable for study 228 (adjunctive treatment in advanced Parkinson's Disease) was **time to onset of dyskinesia**. 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 event of interest.

The approval of IR ropinirole was based primarily on 3 pivotal studies (two in "early" and one in "advanced" Parkinson's Disease). In one monotherapy study in early Parkinson's Disease, the primary measure of effectiveness was the mean percent reduction (improvement) from baseline in the UPDRS Motor Score. In the other pivotal study in early Parkinson's Disease, the primary efficacy outcome measure was the proportion of patients experiencing a decrease (compared to baseline) of at least 30% in the UPDRS motor score. In the advanced Parkinson's Disease pivotal study, the primary outcome was the proportion of responders, defined as patients who were able both to achieve a decrease (compared to baseline) of at least 20% in their L-dopa dose and a decrease of at least 20% in the proportion of the time awake in the "off" condition (a period of time during the day when patients are particularly immobile), as determined by patient diary. Thus, the primary efficacy endpoints in studies 168 and 169 (for ER ropinirole in early and advanced Parkinson's Disease) were not the same/identical as the primary efficacy endpoints for IR ropinirole in early and advanced Parkinson's Disease in the main pivotal studies supporting the approval of IR ropinirole. The sponsor did not appear to make a direct comparison across these studies with respect to the primary efficacy endpoints.

The primary efficacy endpoints used in these studies (169, 168, 228) were reasonable primary efficacy outcomes. In my experience, common primary efficacy endpoints in early Parkinson's Disease is the change from baseline in UPDRS motor scale (part III), or in UPDRS Activities of Daily Living (ADL, part II) + UPDRS motor scale (part III) or in UPDRS mentation (part I) + ADL (part II) + UPDRS motor scale (part III) (this combined endpoint of 3 UPDRS subscales is often noted as "total" UPDRS). The change from baseline in total "OFF" time (hours) is a common primary efficacy endpoint advanced Parkinson's Disease.

b(4)

Secondary Efficacy Variables

The sponsor included numerous secondary efficacy endpoints in all of these 3 studies and provided analyses without adjustment for multiplicity. Some secondary efficacy

endpoints in these studies were similar to the primary efficacy endpoints in the pivotal studies used to support the approval of IR ropinirole.

Of interest, in study 169, the sponsor analyzed the change from baseline with respect to : 1) total time "ON"; 2) total time "ON" without troublesome dyskinesias; 3) total time "ON" with troublesome dyskinesias; and 4) total time sleeping at the end of the study. Analyses of these endpoints were useful to indicate that a reduction in total "OFF" time was related primarily to an increase in total "ON" time (especially without troublesome dyskinesias) and not substantially related in an increase in total sleep time.

Key Efficacy Measures/Endpoints

A brief overview of the key efficacy measures/endpoints used in Studies 169, 168 and 228 and
presented in this document is provided here.

Diary cards (Absolute awake time "Off", "On", "On with Troublesome Dyskinesia" and Asleep) [Study 169]

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, if subjects experienced troublesome dyskinesia during "on" periods this was recorded in the diary. Prior to entry into the study, the investigator (or designee) discussed with the subject the definition of "off/on" periods and the definition of "troublesome dyskinesia" :

· The general definition of "off" includes a lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity. Subjects individually defined what constituted an "off" period in discussions with the investigator.

· The general definition of an "on" period is when medication is working and provides benefit in regards to mobility, tremor and rigidity.

· Dyskinesias are involuntary twisting, turning movements caused by medication, which occur during "on" time. The general definition of troublesome dyskinesia provided in the 169 protocol was those movements that interfered with function and caused meaningful discomfort. The total number of hours spent "off", "on", asleep and "on" with troublesome dyskinesia during each 24 hour period was summed by the investigator and entered into the CRF. The mean of the two 24 hour periods were used for all analyses and summaries.

Diary cards for 'off/on' periods were utilized in Study 169 only.

Dyskinesias

The principal assessment measure of the time to onset of dyskinesia endpoint in Study 228 was the completion of the dyskinesia CRF page at each clinic visit. The Principal Investigator (PI) or trained sub-investigator in consultation with the PI completed the dyskinesia page of the CRF by checking either yes or no for the presence of dyskinesia.

If the PI checked yes for the presence of dyskinesia, then a subsection was completed by the investigator that identified how the investigator determined that dyskinesia was present. One of the following applied; Dyskinesia present at clinic visit and observed by PI; Dyskinesia history is unequivocal; or History suspicious and reported at 2 visits. The date of onset of the dyskinesia was determined by the investigator and recorded in the CRF. Time to onset of dyskinesia and the dyskinesia CRF page were only collected in Study 228.

6.1.3 Study Design

6.1.3.1 Description of Study 169 Design

Primary Objective :

· To evaluate the efficacy of ER ropinirole as adjunctive therapy to L-dopa in subjects with Parkinson's disease.

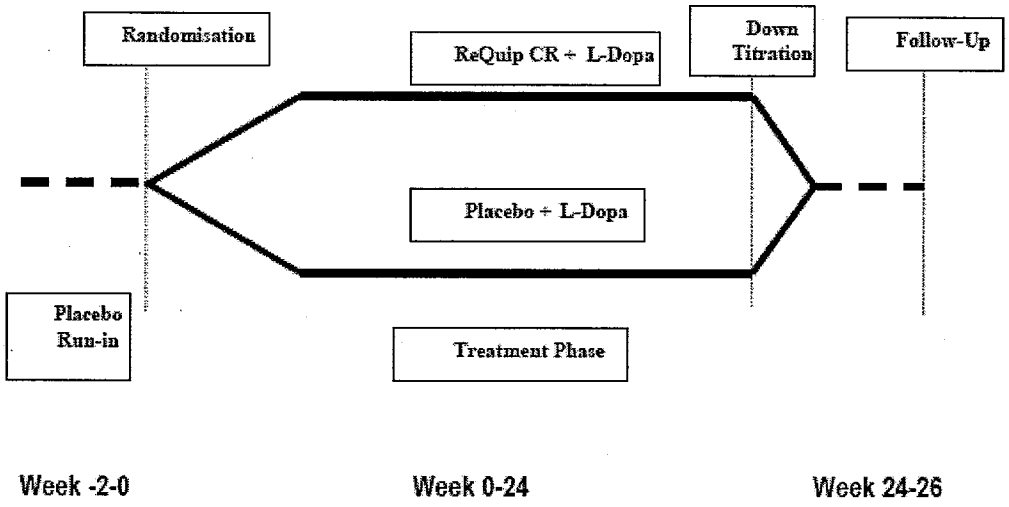
Secondary Objectives :

· To evaluate the safety profile of ropinirole CR as adjunctive therapy to L-dopa in subjects with Parkinson's disease.

· To assess the pharmacokinetics of ropinirole CR in subjects with Parkinson's disease on L-dopa.

This was a multicenter, randomized, double-blind, parallel group, flexible dose titration, placebo-controlled study to compare the efficacy of 6-months therapy of ER ropinirole ropinirole with that of placebo as adjunctive therapy to L-dopa in Parkinson's disease subjects not optimally controlled on L-dopa. The study design is illustrated in Figure 2.

Figure 2 Outline of Study Design (Protocol SK&F-101468/169, Study 169)



Screening/Placebo Run-in
Subjects diagnosed with advanced stage Parkinson's disease (according to modified Hoehn and Yahr criteria Stages II-IV), not optimally controlled on L-dopa and who fulfilled the study entry criteria were eligible for the study. Following screening, eligible subjects entered a 14 day single-blind placebo run-in period in addition to their background L-dopa.

Treatment Phase
At the baseline visit (Week 0), subjects who completed the placebo run-in period and continued to meet study eligibility requirements were randomized (1:1) to double-blind treatment with either ropinirole CR tablets (2-24 mg once daily) or placebo tablets for 24 weeks. During the 24-week treatment phase subjects were required to attend the clinic at several specified times.

All subjects were started on a 2 mg/day dose of ropinirole CR or placebo equivalent. Subjects were to be progressed through the first three dose levels (2 mg at start, 4 mg at week 1, and 6 mg at week 2) during the first three weeks of the study. At later clinic visits starting at week 3, the dose could be increased to 8 mg and then by 4 mg increments at subsequent clinic visits at weeks 6, 8, and 10. If the patient was not optimally treated and tolerated the treatment, dose level 8 at which 24 mg would be started could be achieved at the week 10 visit. The titration dosing guidelines are shown below here. Thereafter, the dose titration regimen was to be followed until an optimal therapeutic dose was achieved. In all instances subjects had to reach a minimum dose of 6 mg/day ropinirole CR or matching placebo. The maximum dose was 24 mg/day ropinirole CR or matching placebo. Subjects may have titrated more slowly than this schedule by not increasing dose at each scheduled clinic visit. Subjects may have also titrated more quickly by attending unscheduled visits at which time dose may have been increased. If loss of symptom control persisted then subjects were to have their study

medication up-titrated an additional dose level and could return to the clinic at weekly intervals, if necessary for these up-titration visits. 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.

Dosing Guidelines

Dose Level	CR Daily Dose (mg/day)	Matching Placebo
1	2 mg (2.0)	Placebo
2	4 mg (2.0 + 2.0)	Placebo
3[1]	6 mg (2.0 + 2.0 + 2.0)	Placebo
4	8 mg (4.0 + 4.0)	Placebo
5	12 mg (4.0 + 4.0 + 4.0)	Placebo
6	16 mg (8.0 + 8.0)	Placebo
7	20 mg (8.0 + 8.0 + 4.0)	Placebo
8	24 mg (8.0 + 8.0 + 8.0)	Placebo

1. Titration to dose level 3 was required.

Once 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.

Down-Titration

For all subjects who completed the study or withdrew from the study prematurely, study medication was down-titrated over a 7-day period as shown here.

Down Titration Schedule

CR Daily Dose (mg) at End of Treatment Phase (or Matching Placebo)	Down Titration Schedule CR Daily Dose (mg) (or Matching Placebo)	
	4 Days @	3 Days @
2.0	No treatment	No treatment
4.0	2.0	No treatment
6.0	4.0	2.0
8.0	6.0	4.0
12.0	8.0	4.0
16.0	12.0	6.0
20.0	12.0	6.0
24.0	16.0	8.0

Follow-up

All subjects were to attend a follow-up visit 4 to 14 days after their last dose of study medication (this did not include down titration medication). Generally, this visit was scheduled to occur on the last day of the 7-day down-titration period.

Selection of Study Population

Patients with advanced stage Parkinson's disease were supposed to be included in the study if they met the following inclusion and exclusion criteria.

Inclusion Criteria :

Subjects were included in the study if all of the following criteria were met :

- Men or non-pregnant/non-breast-feeding women of at least 30 years of age at screening. Women of child-bearing potential must have been practicing a clinically accepted method of contraception (such as oral contraception, surgical sterilization, intrauterine device [IUD], or diaphragm *in addition* to spermicidal foam and condom on male partner, or systemic contraception [i.e. Norplant system]), during the study and for at least one month prior to randomization and one month following completion of the study.
- Diagnosis of idiopathic Parkinson's disease (according to modified Hoehn & Yahr criteria Stages II-IV) and demonstrating lack of control with L-dopa therapy (e.g. end of dose akinesia, simple on/off fluctuations).
- Subjects receiving a stable dose of L-dopa for at least four weeks prior to screening.
- Subjects provided written informed consent for the study.
- A minimum of 3 hours awake time "off" for each diary day was recorded during the placebo run-in period.
- Subjects were willing and able to comply with study procedures, including diary card completion and follow-up clinic visits.

Exclusion Criteria :

A subject was not eligible for inclusion in the study if any of the following criteria were met :

- Late stage advanced subjects demonstrating incapacitating peak dose or biphasic dyskinesia on their stable dose of L-dopa.
- Presence, or history within the previous 3 months, of significant and/or uncontrolled psychiatric, hematological, renal, hepatic, endocrinological, neurological (other than Parkinson's disease), or cardiovascular disease or active malignancy (other than basal cell cancer).

- Any abnormality, at screening, that the investigator deems to be clinically relevant on history, physical examination and in diagnostic laboratory tests including ECG.
- Recent history of severe dizziness or fainting due to postural hypotension on standing.
- Clinical dementia that in the judgment of the investigator would preclude assessment of the subject.
- Recent history or current evidence of drug abuse or alcoholism.
- Consumption of any dopamine agonist within four weeks of the screening visit.
- Definite or suspected personal or family history of clinically significant adverse reactions or hypersensitivity to ropinirole (or to drugs with a similar chemical structure) that would preclude long-term dosing with ropinirole CR.
- Withdrawal, introduction, or change in dose of HRT and/or any drug known to substantially inhibit CYP1A2 (e.g. ciprofloxacin, fluvoxamine, cimetidine, ethinyloestradiol) or induce CYP1A2 (e.g. tobacco, omeprazole) within 7 days prior to enrolment. Subjects already on chronic therapy with any of these agents may be enrolled but must remain on stable doses of the agent from 7 days prior to enrolment through the end of the treatment period.
- Use of an investigational drug within 30 days or 5 half-lives (whichever is longer).

Subject Withdrawal From the Investigational Product and Study
All subjects who withdrew from the study were to receive a one week down-titration of their study medication.

A subject was considered to have completed the study if they completed the treatment phase of the study (i.e. completed all visits up to the end of Week 24). A withdrawal was any subject who had been randomized to receive double-blind study medication but did not complete the treatment phase of the study (whether or not the subject received study medication). This was based on the investigator's response to the study conclusion question in the study conclusion panel of the CRF.

A subject could withdraw (or be withdrawn) from the study prematurely for the following reasons:

· Adverse event (AE) (the AE or serious adverse event [SAE] section of the CRF was to be completed).
· Lack of efficacy.
· Protocol violation.
· Subject decided to withdraw from the study.
· Lost to follow-up.
· Sponsor terminated study.
· Non-compliance
· Other (must be specified).

The reason for termination was to be recorded in the Study Conclusion section of the CRF.

At the early withdrawal visit, subjects were dispensed down-titration medication. Every attempt was made to complete the assessments scheduled for Week 24 at the early withdrawal visit (with the exception of pharmacokinetic sampling if the subject had stopped taking study medication). A follow-up visit was still to take place for all subjects who withdrew prematurely, 4 to 14 days after the last dose of study medication (not including down-titration).

Withdrawn subjects were not replaced.

Dose Rationale
The starting dose of ropinirole CR 2 mg/day and a titration schedule of 2 mg/day, 4 mg/day, 6 mg/day and 8 mg/day were determined from earlier studies (166 and 167). The dose range (2-24 mg) and down-titration schedule were based on approved ropinirole IR labeling, but allowed once daily dosing and a simpler titration regimen in accordance with the objectives for the development of this formulation.

Blinding
Active ER ropinirole and placebo tablets were identical in appearance and were packaged to be indistinguishable irrespective of treatment to maintain the double-blind nature of the study. In order to achieve blinding, dosages were referred to as levels 1 through to 8. Placebo subjects were dosed similarly to the ropinirole group, e.g. subjects received one placebo tablet for dosage level 1. The investigator and subject were not blinded to the dose level. Only in an emergency, when knowledge of the investigational product was essential for clinical management/welfare of the subject, an investigator could unblind a specific patient treatment assignment.

Treatment Assignment
Subjects were randomized to one of two treatments on a 1:1 ratio, ropinirole : placebo, for up to 24 weeks (Weeks 1-24), according to a computer-generated randomization schedule. To ensure balance with respect to the number of subjects assigned to each treatment group, the allocation schedule was generated in blocks using the sponsor's Coding Memo System.

Assessment of Compliance
Every effort was made to encourage subject compliance with the dosage regimen as per protocol. All subjects were instructed to return their medication pack, with any unused study medication, to the investigator at each visit. A record of the supplies dispensed, taken and returned was made in the CRF at each visit.

Subjects who were not compliant during the placebo run-in phase, i.e. < 80% or > 120% were not eligible to be randomized and were withdrawn from the study. If there were any significant irregularities in compliance during the on treatment phase of the study, in the

opinion of the investigator, the subject was to be withdrawn from the study. The compliance of subjects with respect to study medication was defined in two ways :

· Tablet compliance: Subjects were considered to be compliant if the calculation for overall compliance (based on an algorithm for tablets dispensed and returned in relation to number of days at each dosage level) was ≥80% and ≤120%.
· Interruption in study drug: Subjects were considered to be compliant if they had not had a break in study medication for more than three consecutive days. (This was based on the investigator's response).

To be overall compliant, the subject must have a tablet compliance of ≥ 80% and ≤ 120% and must not have missed >3 consecutive days of study medication.

Prior and Concomitant Medications and Non-Drug Therapies
At the screening visit, investigators were requested to record all Parkinson's disease medications, all L-dopa medication, and all other medications, including over-the-counter (OTC) products, taken within the 30 days prior to the study. This information was recorded in the CRF with indication, daily dose and dates of administration.

Permitted Medications
Selegiline, amantadine, anticholinergics, and catechol-O-methyl-transferase (COMT) inhibitors were permitted provided the dose was stable for at least four weeks prior to screening. Doses of selegiline, amantadine and anticholinergics, if used, were to remain stable throughout the study. **Introduction of these medications during the conduct of the study was not permitted.** Subjects were to continue to take their L-dopa medication. The dose and frequency of L-dopa was to remain stable for at least four weeks prior to screening and was to remain stable until L-dopa was reduced as required by the protocol. Subjects were not to switch between controlled-release and immediate-release L-dopa formulations.

L-dopa Reduction
When each subject was titrated to study medication dose level 4 (8 mg/day), the background total daily dose of L-dopa was reduced. This was accomplished by reducing, for example, the number of Sinemet or Sinemet CR tablets by ½ tablet or 1 tablet. If a subject was taking six or more Sinemet tablets per day, a reduction of greater than one tablet was permitted (e.g. 1 and ½ tablets, 2 tablets, 2 and ½ tablets, 3 tablets). Decrements smaller than ½ tablet were not permitted. For subjects taking Sinemet and Sinemet CR, the CR dose was reduced first.

If symptom control was maintained following the first reduction in L-dopa dose, the total dose of L-dopa was reduced by an additional ½ tablet or 1 tablet (or more for subjects on > 6 tablets of Sinemet) when the subject was titrated to the next higher level of study medication. **At each upward titration of study medication, the dose of L-dopa was reduced as above.** If loss of symptom control occurred with the reduction in the background L-dopa dose, the dose of study medication was increased to the next higher

dose level with no adjustment in the dose of L-dopa. If loss of symptoms control persisted, subjects were titrated up an additional dose level. If necessary, subjects could return to the clinic at weekly intervals to have study medication up-titrated rather than waiting until the next study visit. Subjects who did not experience an improvement in symptoms following upward titration by 2 dose levels of study medication, were "rescued" with L-dopa. **The dose of L-dopa could be increased to baseline levels but not 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.**

Modification to Dosing Regimen (Study Medication and L-dopa) in the Event of Unacceptable Dopaminergic Side Effects
In the event of unacceptable dopaminergic side effects relative to baseline modifications to dosing regimen (study medication and L-dopa) were made as follows :

Step 1: Study medication dose was maintained and the unit dose of L-dopa was reduced (e.g. 250 mg to 200 mg). If unacceptable dopaminergic side effects persisted, then Step 2 was carried out.

Step 2: Study medication dose was maintained and the frequency of L-dopa administration was reduced (e.g. from five to four times per day). If unacceptable side effects persisted, Steps 1 or 2 were repeated before progression to Step 3.

Step 3 Study medication dose was reduced. If Step 1 and 2 reduced dopaminergic side effects, the dose of study medication could be increased at subsequent visits.

Prohibited Medications
Subjects previously treated with a dopamine agonist must have discontinued treatment a minimum of four weeks prior to screening. Neuroleptics and rescue anti-emetics were not permitted.

Study Assessments and Procedures Including Data Collection
The time and events schedule for the study is shown in Table 2.

Table 2 Time and Events Schedule (Protocol SK&F-101468/169)

Assessments	Study Period															
	Screening (start of placebo run-in)		Randomisation and Baseline												Follow-up[1]	Early Withdrawal[2]
Week	-2	-1	0	1	2	3	4	6	8	10	12	16	20	24	26	
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Written Informed Consent	X															
Medical History	X															
PD staging (Mod. Hoehn & Yahr)	X															
Review prior PD meds	X															
Physical Examination	X														X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X													X		X
Inclusion/exclusion criteria	X	X	X													
12-Lead ECG	X		X			X			X		X			X	X	X
Clinical Chemistry, Haematology, Urinalysis	X													X		X
Supply Diary Cards	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review Diary Cards Awake Time "Off/On"		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI			X[3]		X		X	X	X	X	X	X	X	X	X	X
UPDRS			X				X				X			X	X	X
PDQ-39			X								X			X		X
BDI-II			X								X			X		X
Epworth Sleepiness Scale			X								X			X		X
PD Sleep Scale			X								X			X		X
PK Sampling[4]											X	X	X	X		
Dispense Study Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Compliance check		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Baseline signs/symptoms, Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Visit is 4 to 14 days after the last dose of study medication.
2. Subjects were dispensed down-titration medication at the early withdrawal visit and were scheduled to return for a follow up visit 4 to 14 days after the last dose of study medication.
3. CGI-S only.
4. Ropinirole plasma concentrations: blood samples for PK analysis were collected at Week 12, 16, 20, and 24. A morning sample collection was taken at Week 12. For Week 16, 20 and 24, there were two afternoon visits and one morning visit. The scheduling of these visits was made at the subject's and clinic's convenience.

Protocol Amendments

The original protocol was dated 10 March 2003 and the first subject was enrolled on 7 July 2003. The protocol was amended three times, as follows :

Amendment 1: Issue Date 16 December 2003

The following changes were made to the protocol and were applicable to all centers:

· **Exclusion criterion #8 was removed to allow for the inclusion of subjects who had prior exposure to ropinirole thus treating it in the same way as other dopamine agonists. Exclusion criterion (#8) had been the primary reason for subject noneligibility.**

· The composite endpoint (proportion of responders, where a responder was defined as a subject who had at least a 20% reduction from baseline in awake time spent "off" and at least a 20% reduction from baseline in L-dopa dose), was mistakenly classified as an 'other endpoint' rather than a 'secondary endpoint'. This was corrected.

· Subjects may have experienced a loss of symptom control when their L-dopa dose was reduced (starting at dose level 4). Rather than waiting for the next scheduled visit to

increase the dose of study medication, this amendment allowed subjects to return to the clinic at weekly intervals, if necessary, to have the dose of study medication up-titrated.

· An open-label extension study (SK&F-101468/248) was developed for subjects completing at least 12 weeks of randomized treatment in study SK&F-101468/169 was added.

The following clarifications to the protocol were made:

· The original protocol did not stipulate a timeframe for Unified Parkinson's Disease Rating Scale (UPDRS) assessments, but ideally, it should have been done when the subject was "off" rather than "on". In practice, it would be difficult to ensure that subjects were "off" when this assessment was done. Therefore, a more practical timeframe for assessing UPDRS, by anchoring it in a window relative to the previous L-dopa dose, was provided. This amendment specified that UPDRS assessments must be conducted within a window of at least 2 hours after the previous L-dopa dose and prior to the next scheduled L-dopa dose.

· The Beck Depression Inventory (BDI)-II was utilized in this study, not the BDI-I.

· A timeframe for the initial up-titration to dose level 3 was not provided in the original protocol. In this amendment, the investigator was asked to progress subjects through the first 3 dose levels during the first three weeks of the study.

· This amendment clarified that L-dopa could be increased during the down-titration of study medication, but should not exceed baseline levels.

· In the original protocol, the dose of catechol-O-methyl-transferase (COMT) inhibitors must have remained stable throughout the study. In this amendment, if a dose of L-dopa was completely eliminated during the L-dopa dose reduction, the corresponding dose of the COMT inhibitor should also be eliminated since these drugs do not provide an antiparkinsonism effect on their own. A paragraph regarding L-dopa medication was also added to the permitted medications section.

· The prohibited medications section of the protocol was revised to take into account the amended eligibility criteria regarding prior exposure to ropinirole.

· The final versions of the rating scales were not available for the original protocol. The rating scales were updated and the final versions were added.

Amendment 2: Issue Date 05 March 2004

The following changes were made to the protocol and were applicable to all centers:

· The protocol was amended to collect additional electrocardiogram (ECG) data in subjects with Parkinson's disease treated with ropinirole CR. This amendment was implemented in anticipation of the need to provide increased ECG data to regulatory agencies; it was not implemented due to a specific clinical signal. Additional ECG measurements were added to the baseline, Week 3, Week 8, Week 12 and follow-up visits, where possible.

· An additional safety endpoint "Mean maximal change from screening in QTcF, QTcB and uncorrected QT intervals" was added.

Amendment 3: Issue Date 24 November 2004

The protocol was amended to add two secondary endpoints:

· Mean change from baseline in amount of awake time spent "on" without troublesome dyskinesia.

· Mean change from baseline in percent awake time spent "on" without troublesome dyskinesia. In addition, two ECG parameters that were no longer considered to be part of current measurements in ECG analysis (axis and atrial rate) were deleted.

Data Analysis Methods

Timings of Planned Analyses

Once all subjects had completed the study, all data were in-house and had been quality assured,
and the protocol violators had been determined, the data were unblinded. The database was then frozen and the analyses described in this section were performed.

Interim Analyses and Data Monitoring

No interim analyses were planned or conducted.

Changes in the Conduct of the Study or Planned Analyses

Planned analyses were conducted as specified in the Reporting and Analysis Plan/Statistical Analysis Plan (RAP/SAP), with the following additions :

· **An additional category of study conduct violation was identified during a review of protocol violations on blinded data. It was noted that some patients 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.**

· An analysis of the change from baseline in the total awake time spent "off", by visit, was conducted.

· Summary statistics for the change from baseline in the total awake time spent "off" at Week 24 LOCF, by dose, were produced.

· Summary statistics for disabling dyskinesia (question 33 of the UPDRS questionnaire), and change from baseline for disabling dyskinesia, were produced.

· Summary statistics for dyskinesia: duration, disability and pain (questions 32, 33 and 34 of the UPDRS questionnaire), and change from baseline for these questions, were produced.

· A summary of the proportion of subjects who were minimally depressed (BDI-II score of 0-13), mildly depressed (BDI-II score of 14-19), moderately depressed (BDI-II score of 20-28) and severely depressed (BDI-II score of 29-63), by visit, was produced.

· Summary statistics for the PDQ-39 summary index score, and change from baseline for this score, were produced. The PDQ-39 summary index was calculated by summing all eight of the PDQ-39 domains and standardizing the score on a scale of 0-100.

· A summary of subjects with follow-up visits, and whether they were on-treatment (by dose) or off-treatment at this follow-up visit, was produced.

Sample Size Considerations

Data from a previous study in ropinirole immediate-release-IR (SK&F-101468/044), a published study [Rinne, 1998] in addition to input from consultants was used to obtain estimates of what difference in the reduction of awake time spent "off" was considered to be clinically relevant. Data from Study 044 was also used to obtain the estimated standard deviation for this study.

The sample size calculation was based on the mean change from baseline to endpoint in awake time "off". A difference of 1.2 hours between ER ropinirole and placebo in the reduction of awake time spent "off" was considered to be clinically relevant based on feedback from key opinion leaders and regulatory authorities.

A total of 133 subjects per treatment group evaluable for the primary analysis (266 overall) were therefore required in order to detect a difference of 1.2 hours with a standard deviation of 3 hours, for a two-sided test with 90% power and a 5% level of significance. The total number of subjects to be randomized was 368, assuming an drop-out/attrition rate of 27%.

Subjects were to be randomized in approximately 62 centers with approximately 4-8 subjects planned for randomization at each center.

Sample Size Sensitivity

The robustness and sensitivity of the sample size calculation was explored to assess the impact on the power of the study if the observed standard deviation was larger or smaller than expected.

Changes to the standard deviation will affect the power of the study to detect the difference of 1.2 hours in the mean change from baseline in awake time spent "off", given the fixed sample size of 133 subjects per treatment group, as shown in the following table. This table also shows the number of evaluable subjects required to maintain the power at 90% and the corresponding numbers of subjects that would need to be randomized.

Standard Deviation	Power (%) with 133 evaluable subjects per group	Number of evaluable subjects required (per treatment group) for 90% power	Number Randomized[a]
2.0	>99	60	168
2.5	97	93	256
3.0	90	133	368
3.5	79	180	496
4.0	68	235	644

a Assuming 27% attrition rate

Analysis Populations

Two populations were to be evaluated for efficacy.

Intent-To-Treat (ITT) Population :
The ITT population is defined as consisting of all randomized subjects who received at least one dose of study medication and had at least one post-baseline efficacy assessment.

Per Protocol (PP) Population :
The PP population was to consist of all subjects included in the ITT population but who also meet the following criteria:

- No major protocol violation existing with regard to inclusion or exclusion criteria.
- No major protocol violation between randomization and completion of the active treatment phase of the study (Weeks 1-24).
- No more than three consecutive days of study medication have been missed throughout active treatment phase of the study

The primary inferences concerning the efficacy of ropinirole were to be made using the ITT population. The primary efficacy variable was also to be analyzed using the PP population.

Any differences between the PP and ITT analyses were to be discussed in the clinical report, however, primary inference will be based on the results from the ITT analysis. The PP population was not to be analyzed if this population comprises > 95%, or < 50% of the ITT population. Subjects excluded from the PP efficacy analysis were to be identified before the randomization code was broken.

Data Sets
For the ITT and PP populations, where appropriate, the primary inference was to be based on the last observation carried forward (LOCF) dataset at the protocol defined Week 24 endpoint.

In the LOCF dataset, the last available on-therapy observation for a subject was to be used to estimate missing data points. In the observed case (OC) dataset, efficacy data are evaluated only at the time point when they were collected, i.e. no data are carried forward to estimate missing data points.

All appropriate primary and secondary variables were to be summarized using the Week 24 LOCF dataset and at each visit using the OC dataset.

General Considerations for Data Analysis

Tests of Significance
All hypothesis tests were to be two-sided and performed at the 5% level of significance. Due to the low power of the study to detect an interaction, the effect of interactions (e.g. treatment by center) was to be assessed at the 10% level of significance.
Withdrawal

The number and percentage of subjects withdrawing early from the study, for all reasons and for each individual reason, together with the number of completers, were to be tabulated for the Safety, ITT and PP populations.

Missing Data

For variables measured at the Week 24 endpoint, missing data were to be imputed using the
LOCF technique, i.e. the last available on therapy observation for a subject is used to estimate the missing data point.
Techniques for handling missing data from the rating scales were to be detailed in the Reporting and Analysis Plan (RAP)/Statistical Analysis Plan (SAP).

Primary Analysis

The primary efficacy variable/endpoint was :
• Mean change from baseline in awake time spent "off" at Week 24 LOCF.

Secondary Analysis

Secondary efficacy variables/endpoints were :
· Mean change from baseline in amount of awake time spent "on"
· Mean change from baseline in percent awake time spent "on"
· Mean change from baseline in amount of awake time spent "on" without troublesome dyskinesia.
· Mean change from baseline in percent awake time spent "on" without troublesome dyskinesia.
· Mean change from baseline in percent awake time spent "off"
· Mean change from baseline in UPDRS total motor score
· Mean change from baseline 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
· Proportion of subjects requiring reinstatement of L-dopa following reduction in dose
· Time to reinstatement of L-dopa following reduction in dose
· Mean change from baseline in the depression scores of the Beck Depression Inventory
· Mean change from baseline in the Parkinson's Disease Quality of life scores (PDQ39)
· Mean change from baseline in the Daytime Sleepiness scores of the Epworth Sleep Scale
· Mean change from baseline in the night-time quality of sleep scores of the Parkinson's Disease Sleep Scale
· Proportion of responders, where a responder is defined as a subject who has at least a 20% reduction from baseline in awake time spent 'off' and at least a 20% reduction from baseline in L-dopa dose. (This analysis will enable comparison to the previous IR program).

These secondary efficacy endpoints were to be analyzed as described in the RAP/SAP without statistical adjustment for multiplicity.

Other Efficacy Analysis

Any additional efficacy analyses were be discussed in the RAP/SAP.

Primary Efficacy Analysis(es) from Statistical Analysis Plan (SAP)

Model Specification

The change from baseline to study endpoint for the amount of awake time "off" was to be analyzed using errors). The assumptions of normality and homogeneity of variance, underlying the statistical analysis were to be checked. If these assumptions were not met, additional analysis of the data were to be performed in order to assess the robustness of the conclusions drawn from the primary analysis. This plan would entail use of a nonparametric analysis of covariance, utilizing the SAS macro NparCov.

The statistical model on which the primary inference was to be based was to include terms for center, baseline absolute amount of awake time "off" and treatment group, regardless of their significance. No interaction terms were to be included in this primary model. Centers were to be grouped as described

If the assumptions of the analysis of covariance are met, the results were to be presented as the adjusted mean change for each treatment group, and the mean and 95% confidence interval for the difference between ropinirole CR and placebo.

Robustness of the Primary Analysis

Exploratory analyses to assess the robustness of the primary model were to be undertaken; interactions between treatment and center, and treatment and baseline amount of awake time "off" were to be investigated separately. Each interaction was to be fitted in turn to the primary model, the statistical significance being assessed at the 10% level. In the event that one or more interaction term was found to be statistically significant, attempts were to be made to establish the cause of the heterogeneity, e.g. joint modeling of significant interaction terms if more than one exist (fitting >1 interaction term in a single model to see if they remain significant) and investigation of other demographic characteristics.

Significant interactions were to be investigated further to determine their overall effect on the results using graphical and analytical methods if appropriate. Also, if appropriate, results were to be reported for each level of the covariate. However, the primary inference was to be based on the model excluding interactions. Investigation of interaction terms was to be confined to the primary endpoint (mean change from baseline in amount of awake time "off"), using the LOCF dataset for the ITT population.

Diagnostics

The assumptions of normality and homogeneity of variance was to be assessed for the primary model by inspection of the following plots:

- Normal probability plot.
- Standardized residual plot against predicted values.
- Standardized residual plot against continuous covariates.

In addition, the model was to be re-fitted excluding observations with large residuals or which are strongly influencing the fit of the model to the data (defined as a standardized residual with an absolute value > 3). The importance of changes to the results on exclusion of these observations was to be assessed and any important differences were to be reported in the Statistical Appendix. However, the primary inference was to be based on the primary model with any influential outliers included.

Presentation of the Primary Model Results

A table of summary statistics (adjusted mean, standard error of mean and N) for the mean change from baseline in the awake time "off", by treatment group, together with the estimate of the adjusted difference in means (including 95% CI and P-value) between ropinirole CR and placebo, was to be presented.

Summaries and Further Analyses of the Absolute Awake Time "off"

The mean change from baseline to Week 24 OC for the absolute awake time "off", for the ITT population, and the change from baseline to Week 24 LOCF for the PP population were also to be analyzed using the model defined to support the primary analysis. The PP population was not to be analyzed if it comprises >95%, or <50% of the ITT population.

Summary statistics (n, mean, standard deviation, median, min and max) of the observed and mean change from baseline awake times "off" were to be provided. These statistics were to be produced for the LOCF Week 24 endpoint and at each time point for the OC data.

Additionally, mean value and mean change from baseline were to be presented graphically at each time point.

Summary statistics (n, mean, standard deviation, median, min and max) of the mean change from baseline to Week 24 LOCF for the absolute awake time "off" were to be presented by country, and by each of the covariates detailed for the ITT population.

Analysis of Additional Covariates

An analysis was to be performed to establish the significance of the following covariates and their interactions with treatment, on the primary endpoint, change from baseline in awake time "off", for the ITT population, using the Week 24 LOCF data:

- gender.
- age group (18-64, 65-74, ≥75).
- race (provided no more than 95% of subjects are in any one category).
- pre/post protocol amendment 1.
- prior exposure to dopamine agonists.
- prior exposure to ropinirole.
- ropinirole CR (or matching placebo) taken with/without food.

Each covariate was to be fitted in turn to the model containing centre, baseline awake time "off" and treatment group. The main effect was to be tested first at the 5% level of significance. Once the main effect of the covariate was established, the treatment by

covariate interaction was to be added and tested at the 10% level of significance. This procedure was to be repeated for each of the seven covariates listed above.

Any significant treatment by covariate interactions was to be investigated further and discussed in the Statistical Appendix to the Clinical Study Report (CSR).

6.1.3.2 Description of Study 168 Design

This study was conducted by the sponsor without any specific discussion with the DNP as to the desirability, design, or analysis of this study. The End of Phase 2 meeting minutes do not reflect discussion of the planning of this study.

Primary Objective

• To demonstrate the non-inferiority of ropinirole CR to the current marketed IR formulation in subjects with early phase Parkinson's disease.

Secondary Objectives

· To evaluate the safety profile of ropinirole CR in subjects with early phase Parkinson's disease.

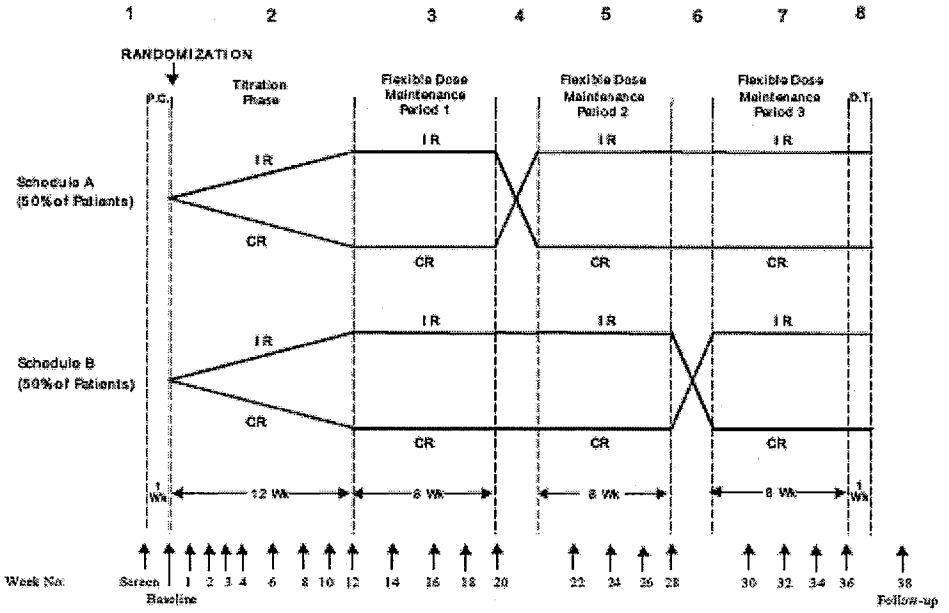
· To assess the pharmacokinetics of ropinirole CR in subjects with early phase Parkinson's disease.

· To collect data on dose switching from ropinirole IR to ropinirole CR in subjects with early phase Parkinson's disease.

· To investigate the superiority of ropinirole CR in comparison to ropinirole IR in subjects with early phase Parkinson's disease.

This was a multicenter, randomized, 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 3.

Figure 3 Schematic Study Design (Protocol SK&F-101468/168)



PC = Placebo, IR = Immediate Release, CR = Controlled Release, DT = Down-Titration
Note that each vertical arrow represents a study visit.

Placebo Run In

Subjects diagnosed with early phase Parkinson's disease (according to modified Hoehn and Yahr criteria Stages I-III), and who fulfilled the study entry criteria were eligible for the study. Following screening, eligible subjects entered a 7-day placebo run-in period.

Titration Phase

At the baseline visit (Week 0), subjects who successfully completed the placebo run-in period were randomized (1:1:1:1) to one of four sequences IR-CR-CR, CR-IR-IR, IR-IRCR, CR-CR-IR. At the start of the titration phase, the groups randomized to initially receive the CR treatment were started on a 2 mg once daily (od/qd) (2 mg/day) dose and the groups randomized to initially receive IR treatment were started on a 0.25 mg three times daily (tid) (0.75 mg/day) dose. During the 12-week titration phase the subjects' dose was titrated upwards to achieve the optimal clinical response (Table 3). The investigator was asked to progress all subjects through the first four dose levels during the first four weeks of the titration period, provided no tolerability issues arose. If there were tolerability issues the subject could remain on the same dose. If absolutely required, the dose could have been decreased during the first four weeks, however the decrease in dose had to be discussed with the medical monitor and approval had to be obtained before the dose was decreased.

Beyond Week 4, the particular titration schedule used was dependent on the response/tolerance of each individual subject. During the titration phase, although encouraged to progress through the first four dose levels during the first four weeks of the

study, there was no stipulation regarding a minimum dose which must have been achieved in order to progress in the study. However, 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 (a stable UPDRS motor score was defined as a score that did not change by more than ± 2 points during at least the final two visits of the titration phase, i.e. Weeks 10 and 12).

Table 3 Ropinirole IR and CR Titration Schedules

Dose Level[1]	IR Daily Dose (mg) or matching placebo	CR Daily Dose (mg) or matching placebo
1	0.75 (0.25 + 0.25 + 0.25)	2.0 (2.0)
2	1.5 (0.5 + 0.5 + 0.5)	4.0 (2.0 + 2.0)
3	2.25 (0.75 + 0.75 + 0.75)	6.0 (2.0 + 2.0+ 2.0)
4	3.0 (1.0 + 1.0 + 1.0)	8.0 (4.0 + 4.0)
5	4.5 (0.75+0.75) + (0.75+0.75) + (0.75+0.75)	12.0 (4.0 + 4.0 + 4.0)
6	6.0 (2.0 + 2.0 + 2.0)	16.0 (8.0 + 8.0)
7	7.5 (2.5 + 2.5 + 2.5)	20.0 (8.0 + 8.0 + 4.0)
8	9.0 (3.0 + 3.0 + 3.0)	24.0 (8.0 + 8.0 + 8.0)
9	12.0 (2.0+2.0) + (2.0+ 2.0) + (2.0+ 2.0)	24.0 (8.0 + 8.0 + 8.0)
10	15.0 (5.0 + 5.0 + 5.0)	24.0 (8.0 + 8.0 + 8.0)
11	18.0 (3.0+3.0) + (3.0+3.0)+ (3.0+ 3.0)	24.0 (8.0 + 8.0 + 8.0)
12	21.0 (5.0+2.0) + (5.0+2.0) + (5.0+2.0)	24.0 (8.0 + 8.0+ 8.0)
13	24.0 (5.0+3.0) + (5.0+3.0) + (5.0+3.0)	24.0 (8.0 + 8.0 + 8.0)

1. Dose levels can differ following switching (see Table 4 and Table 5).

Flexible Dose Maintenance Period 1
Subjects who achieved a stable UPDRS motor score entered the first 8-week, flexible dose maintenance period (Period 1). During the first 4 weeks subjects could undergo dose adjustments, if needed. 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).

Flexible Dose Maintenance Period 2
Subjects could undergo dose adjustments if needed during the first 4 weeks of 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 3 (Period 3). Subjects in Schedule B were switched overnight to the alternative ropinirole formulation prior to moving into maintenance Period 3.

Flexible Dose Maintenance Period 3
As in Periods 1 and 2, subjects could undergo dose adjustments during the first 4 weeks of Period 3 if necessary.

Dose Switching
When the subjects were switched between ropinirole formulations, as far as practically possible, the protocol ensured that the total daily dose remained constant. Although all

doses were assigned in a blind fashion, and the investigator did not choose the particular dose of IR or CR to switch between, the following information is provided as background on the switching rationale between the two formulations.

For certain doses, the switch was straightforward (e.g. 4 mg IR tid is equivalent to 12 mg CR od). However, an equal switch was not always possible due to tablet strengths (e.g., there was no equivalent for a 7.5 mg IR dose in the CR tablet strengths) and the recommended CR titration regimen (e.g. unlike the previous example it would be possible to make up an 18 mg dose from the available CR tablet strengths, however the 18 mg dose did not exist within the recommended CR regimen). In such cases, the nearest equivalent dose was used.

Table 4 and Table 5 show the dose switches between the IR and CR formulations.

Table 4 Daily Dose Switches from IR to CR Formulation

IR Daily Dose (mg)	CR Daily Dose (mg)
0.75	2.0
1.5	2.0
2.25	2.0
3.0	4.0
4.5	4.0
6.0	6.0
7.5	8.0
9.0	8.0
12.0	12.0
15.0	16.0
18.0	16.0
21.0	20.0
24.0	24.0

Table 5 Daily Dose Switches from CR to IR Formulation

CR Daily Dose (mg)	IR Daily Dose (mg)
2.0	2.25
4.0	4.5
6.0	6.0
8.0	7.5
12.0	12.0
16.0	15.0
20.0	21.0
24.0	24.0

Doses Levels and Dose Level Reductions Prior to and After the Treatment Switch
The actual dose and dose reductions for subjects prior to or after the treatment switch is shown **in Table 6. For example**, a subject randomized to CR medication prior to the switch, who received a 24 mg dose (dose level 8 to 13 inclusive), received a 20 mg dose following a single dose reduction. Similarly, a subject randomized to CR medication after the switch who received a 2 mg dose (dose levels 2 and 3) received placebo following a single dose reduction and a subject who received an 8 mg dose of CR (dose level 7 and 8) received a 6 mg dose following a single dose reduction. Subjects randomized to receive either CR or IR medication that required a dose level reduction for dose level 1, either prior to or after the switch, were withdrawn from the study.

Table 6 Doses and Dose Level Reductions Prior to and After the Treatment Switch

	PRIOR TO SWITCH				AFTER SWITCH			
Dose Level	Titration Phase & Flexible Dose Maintenance Periods: Prior to Switch		Single Dose Level Reduction: Prior to Switch		Flexible Dose Maintenance Periods: After Switch		Single Dose Level Reduction: After Switch	
	CR	IR	CR	IR	CR	IR	CR	IR
1	2.0	0.75	Withdraw Subject	Withdraw Subject	2.0	2.25	Withdraw Subject	Withdraw Subject
2	4.0	1.5	2.0	0.75	2.0	4.5	Placebo	3.0
3	6.0	2.25	4.0	1.5	2.0	6.0	Placebo	4.5
4	8.0	3.0	6.0	2.25	4.0	7.5	2.0	6.0
5	12.0	4.5	8.0	3.0	4.0	12.0	2.0	9.0
6	16.0	6.0	12.0	4.5	6.0	15.0	4.0	12.0
7	20.0	7.5	16.0	6.0	8.0	21.0	6.0	18.0
8	24.0	9.0	20.0	7.5	8.0	24.0	6.0	21.0
9	24.0	12.0	20.0	9.0	12.0	24.0	8.0	21.0
10	24.0	15.0	20.0	12.0	16.0	24.0	12.0	21.0
11	24.0	18.0	20.0	15.0	16.0	24.0	12.0	21.0
12	24.0	21.0	20.0	18.0	20.0	24.0	16.0	21.0
13	24.0	24.0	20.0	21.0	24.0	24.0	20.0	21.0

Dose Rationale

During this study, ropinirole IR was dosed in accordance with approved labeling. The sponsor noted that the dosing regimen for ropinirole CR covered the same dose range, but allowed once daily dosing and a simpler titration regimen in accordance with the objectives for the development of this formulation.

Down-Titration

For all subjects who completed the study or withdrew from the study prematurely, investigational product was down-titrated over a 7-day period.

Follow-up

All subjects were to attend a follow-up visit four to fourteen days after their last dose of investigational product. In practice, this visit was usually scheduled to occur at the end of the one week down-titration period.

Extension Study

Subjects who completed study SK&F-101468/168 (including the 1 week down-titration of investigational product) were eligible to receive open-label treatment with ropinirole CR (2-24 mg/day) in an extension study (SK&F-101468/248).

Study Procedures

The time and events schedule for study SK&F-101468/168 is summarized in Table 7. All assessments were performed in the clinic by the investigator or their designee (unless otherwise stated). All assessments had to be performed at least two hours after the first dose of investigational product on that particular day, the only exception to this was for blood pressure assessments which had to be conducted at least 4 hours post-dose.

Table 7 Time and Events Schedule (Protocol SK&F-101468

Assessments	Study Period							
	Screening (start of placebo run-in)	Randomisation and Baseline	Up-titration	Maintenance Period 1	Maintenance Period 2	Maintenance Period 3	Follow-up[1]	Early Withdrawal[8]
Visits (Weeks)	-1	0	1-4, 6, 8, 10, 12	14, 16, 18[7], 20	22, 24, 26[7], 28	30, 32, 34[7], 36	38	
Written Informed Consent	X							
Medical History	X							
PD staging (modified Hoehn & Yahr)	X							
Review prior PD meds	X							
Physical Examination	X					X[2]		X
Vital Signs	X	X	X	X	X	X	X	X
Pregnancy Test	X					X[2]		X
Inclusion/Exclusion Criteria	X	X						
12-Lead ECG	X		X[3]			X[3]		X
Clinical Chemistry, Haematology, Urinalysis	X		X[3]			X[3]		X
CGI		X	X	X	X	X		X
UPDRS		X	X[4]	X[4]	X[4]	X[4]		X
BDI		X	X[5]	X[5]	X[5]	X[5]		X
ESS		X	X[5]	X[5]	X[5]	X[5]		X
PDSS		X	X[5]	X[5]	X[5]	X[5]		X
PK Sampling[6]				X[6]		X[6]		
Dispense Investigational Product	X	X	X	X	X	X		X
Compliance Check		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Baseline Signs/Symptoms, AEs		X	X	X	X	X	X	X
Study Conclusion						X[9]		X[9]

1. Visit was 4 to 14 days after the last dose of investigational product.
2. Collected at end of flexible dose maintenance period 3 only (Week 36).
3. Performed at the end of titration and end of treatment (Weeks 12 and 36).
4. Collected at every visit during titration (Weeks 1-12) and at end of each flexible dose maintenance period (Weeks 20, 28 and 36).
5. Collected at end of titration (Week 12) and at end of each flexible dose maintenance period (Week 20, 28 and 36).
6. Ropinirole plasma concentrations: blood samples for PK analysis were collected at Weeks 14, 16, 20, 30, 32 and 36. Morning sample collection (Weeks 14 and 30). If a subject attended a morning visit at Week 16 or Week 32, they were to attend an afternoon clinic at Week 20 and Week 36 and vice versa.
7. The visits at Weeks 18, 26 and 34 were dispensing visits only. Other than drug dispensing and reconciliation no other assessments were conducted at these visits.
8. Subjects were dispensed down-titration medication at the early withdrawal visit and were scheduled to return for a follow up visit 4 to 14 days after the last dose of investigational product.
9. The study conclusion page was completed at the Week 36 visit or at early withdrawal. An additional question was included to determine whether subjects generally took their medication with or without food during the study.

AE = adverse event; BDI = Beck Depression Inventory; CGI = Clinical Global Impression; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; PD = Parkinson's disease; PDSS = Parkinson's Disease Sleep Scale; PK = pharmacokinetic; UPDRS = Unified Parkinson's Disease Rating Scale.

This was a monotherapy study with a three period cross-over design to demonstrate the non-inferiority of ropinirole CR to the currently marketed IR formulation. The sponsor noted that this design was considered to be more efficient at estimating treatment effects compared to a standard two period (AB/BA) design, as it allows any carryover effect that may be present to be determined and accounted for when determining the treatment effect This is because each subject receives a treatment which is preceded by both itself and by the alternative treatment. This design offers considerable economy in subject numbers versus a parallel study design (that would require in the order of 570 randomized subjects).

Protocol Amendments (The original protocol was dated 26 February 2003.)

Amendment 1: Issue Date 7 August 2003

The following changes were made to the protocol and were applicable to all centers except the U.K. (U.K. centers were covered by Protocol Amendment 2):

Sample Size: An error was detected in the sample size for the study, caused by incorrect use of a sample size program. The number of evaluable subjects required per sequence was actually 20, rather than the 38 that was given previously.

Attrition Rate: The protocol assumed an attrition rate of 30%. This was based on data from previous studies in ropinirole IR. However, in this study subjects were to be withdrawn if they did not have a stable UPDRS motor score at the end of the titration phase. The rate of attrition was therefore expected to be higher than in previous studies due to this additional criterion, and was increased to 40%.

Time to maintained response: This endpoint was to be used for exploratory purposes only and had been reclassified as an 'other' endpoint, rather than as a 'secondary' endpoint.

Method of analysis for dichotomous efficacy variables: The methodology for analyzing the dichotomous efficacy variables in the study was changed to reflect recent advances in analysis software. A new procedure in SAS Version 8, PROC NLMIXED was used to analyze dichotomous endpoints.

Extension Study: An open-label extension study (study SK&F-101468/248) was developed for subjects completing study SK&F-101468/168.

Amendment 2: Issue Date 7 August 2003

In addition to the changes in Amendment 1, the following changes were made to the protocol and were applicable to U.K. centers only.

MREC comments on exclusion criteria: Some comments from the MREC which were conditional for approval in the U.K. were addressed:

· The use of an investigational drug 30 days prior to enrolment (exclusion criterion #12) was increased to 3 months prior to enrolment.

· The addition of exclusion criterion #13 to exclude subjects who were already receiving effective treatment for their Parkinson's disease symptoms. If there was a clinical rationale, such subjects could be temporarily withdrawn from such treatment in order to participate in the study.

Selection of Study Population

Patients with early stage Parkinson's disease were supposed to be included in the study if they met the following inclusion and exclusion criteria.

Inclusion Criteria

Subjects were included in the study if all of the following criteria were met :

1. Subjects were aged 30 years or greater at screening.
2. Women of child-bearing potential were practicing a clinically accepted method of contraception during the study and for at least one month prior to randomization and one month following completion of the study. Acceptable contraceptive methods include oral

contraception, surgical sterilization, intrauterine device [IUD], or diaphragm IN ADDITION to spermicidal foam and condom on male partner, or systemic contraception [e.g. Norplant System].
3. Diagnosis of idiopathic Parkinson's disease (according to modified Hoehn & Yahr criteria Stages I-III.)
4. Limited prior exposure to low or moderate doses of L-dopa (up to 3 months in total) or dopamine agonists (up to 6 months in total) provided treatment was discontinued for a minimum of 2 weeks prior to screening.
5. No prior exposure to ropinirole.
6. Provided written informed consent for this study.
7. Were willing and able to comply with study procedures.

Exclusion Criteria
A subject was not eligible for inclusion in the study if any of the following criteria were met :
1. De novo untreated subjects with Parkinson's disease in whom dopaminergic therapy was not warranted at the time of enrollment.
2. Subjects with severe, clinically significant condition(s) other than Parkinson's disease which, in the opinion of the investigator, would render the subject unsuitable for the study (e.g. psychiatric, hematological, renal, hepatic, endocrinology, neurological [other than Parkinson's disease], cardiovascular, or active malignancy [other than basal cell carcinoma]).
3. Subjects with clinically significant abnormalities in laboratory or ECG tests at screening.
4. Subjects with severe dizziness or fainting due to postural hypotension on standing.
5. Subjects with prior or current major psychosis (e.g. schizophrenia or psychotic depression) e.g. scoring 3 or 4 on UPDRS item 2 [thought disorder] or item 3 [depression].
6. Subjects with severe clinical dementia e.g. scoring 3 or 4 on UPDRS item 1 [mentation].
7. Subjects with neurotic behavior, crippling degenerative arthritis or limb amputations, which would preclude efficacy or safety assessments.
8. Previous or current alcohol or drug dependence.
9. Definite or suspected personal or family history of clinically significant adverse reactions or hypersensitivity to ropinirole (or to drugs with a similar chemical structure) that would preclude long-term dosing with ropinirole.
10. Withdrawal, introduction, or change in dose of hormone replacement therapy and/or any drug known to substantially inhibit CYP1A2 (e.g. ciprofloxacine, fluvoxamine, cimetidine, ethinyloestradiol) or induce CYP1A2 (e.g. tobacco, omeprazole) within 7 days prior to enrolment. Subjects already on chronic therapy with any of these agents may be enrolled but doses must have remained stable from 7 days prior to enrolment through the end of the treatment period.
11. Women who are pregnant or breast-feeding.
12. Use of an investigational drug from 30 days (3 months for UK centers, see amendment 2) prior to enrolment through to the end of the treatment period.

13. Subjects who were already receiving effective treatment for their Parkinson's disease symptoms (subjects should only be temporarily withdrawn from such treatment in order to participate in the study if there was a clinical rationale to do so). Applicable to UK centers only (see amendment 2).

Planned analyses were conducted as specified in the Reporting and Analysis Plan (RAP). In addition, the following additional analyses, summary tabulations and plots were retrospectively defined. Some additional efficacy analyses were :

Retrospectively Defined Analyses

· Summary of analysis of covariance of the percentage change from period baseline in the total motor score of the UPDRS (PP and ITT Populations).
· Summary of analysis of covariance of the change from original baseline in the total motor score of the UPDRS at Week 20 LOCF (ITT Population).
· Summary of analysis of responders according to the CGI-I at Week 20 LOCF (ITT Population).

Sample Size Considerations

Data interpolated from the previous ropinirole IR program indicated that 20 evaluable subjects in each of the four treatment sequences (IR-CR-CR, CR-IR-IR, IR-IR-CR, CR-CR-IR) were required in order to demonstrate non-inferiority of ropinirole CR compared with IR using a non-inferiority margin of 3 points on the UPDRS motor score (i.e. a conclusion of non-inferior efficacy of ropinirole CR was to be drawn if the upper limit of the 95% confidence interval for the difference in the UPDRS motor score (CR - IR) was $\leq$ 3). This calculation was for a one-sided test, with 90% power and a 2.5% level of significance, based on a within-subject standard deviation of 3.96. To account for an estimated 40% attrition rate, 136 subjects were to be randomized to treatment.

A non-inferiority margin of 3 points on the UPDRS motor score was selected as this difference is considered not to be clinically meaningful. The sponsor noted that results of a previous ropinirole IR study, study SK&F-101468/056 suggest this 3 point non-inferiority margin. A 3-point difference between treatment groups (ropinirole and L-dopa) was observed in this study. According to the sponsor this difference was not considered to be clinically relevant The sponsor commented also that selection of a 3-point non-inferiority margin was also supported by an advisory panel of key opinion leaders.

Analysis Populations

Three populations were evaluated, the Safety population, the Intent-to-Treat (ITT) population and the Per Protocol (PP) population. The ITT and Safety populations were similar to those used for study 169.

Per Protocol (PP) Population

The PP population consisted of all subjects who were included in the ITT population, but who also met the following criteria:

· No major protocol violation existed with regard to inclusion or exclusion criteria.
· No major protocol violation between randomization and completion of the active treatment phase of the study (Weeks 1-36).
· No more than 3 consecutive days of investigational product had been missed throughout the active treatment phase of the study.

Major protocol violations that led to exclusion from the PP population were defined in more detail.

Subjects to be excluded from the PP population were identified prior to the unbinding of the study. Subjects to be excluded were identified programmatically and/or by clinical review of relevant data; specific details of the method of identification for each category of protocol violation can be found in the RAP.

Treatment Comparisons

The primary inferences regarding the non-inferiority of ropinirole CR compared to ropinirole IR (based on the primary endpoint) were made using the PP population. Within the context of non-inferiority, where the desired outcome was finding no difference between treatment groups, the sponsor noted that PP population generally provides a more conservative estimate of the treatment effects.

The primary efficacy variable was also analyzed using the ITT population. Any differences between the PP and ITT analyses were to be discussed in the report; however, primary inference regarding non-inferiority was based on the results from the PP analysis. Assessments of the superiority of ropinirole CR to ropinirole IR were based on the ITT population.

All secondary efficacy variables were analyzed using both the ITT and PP populations. For the assessment of non-inferiority based on the CGI global improvement, the PP population was considered primary. For all other assessments, the ITT population was considered primary.

Other Strata and Covariates

As this study was a cross-over study, subjects acted as their own controls and therefore for all primary and secondary analyses no strata or covariates were included in the model. For the other efficacy analysis, time to maintained response, the following terms were included in the statistical model regardless of their statistical significance :

· centre/centre group
· treatment group

6.1.3.3 Description of Study 228 Design

This Phase IIIB study was a randomized, multicenter, double-blind, Sinemet-controlled, parallel group, flexible dose study to assess the effectiveness of adjunctive therapy with ropinirole CR and L-dopa at increasing the time to onset of dyskinesias in advanced Parkinson's disease patients, while adequately controlling PD symptoms. Screened patients were randomized to double-blind (by double dummy) treatment of either add-on

ropinirole CR or Sinemet. A minimum of 15 visits were planned over the 107-week (2 years and 3 weeks) duration of the study. The study design is illustrated in Figure 4.

Treatment Phase

Following Screening, subjects who successfully completed the Screening and Baseline visits were randomized (1:1) to double-blind treatment of either ropinirole CR (2-24mg once daily [od/qd]) or Sinemet (50–1000 mg tid) for 104 weeks. At the beginning of the Treatment Phase, the group randomized to ropinirole CR treatment were started on a 2mg/day od dose. During the Treatment Phase, the subject's dose was adjusted according to the dosing table to achieve an optimal therapeutic response. Subjects who did not experience an improvement in symptoms following upward titration through dose level 8 were withdrawn from the study. Calls to the patient by the physician or designee (frequency determined by Principle Investigator [PI]) were made to ensure that the dose of drug was adjusted according to symptom control and tolerability. Dose adjustments were made on a weekly basis as needed. Subjects who required an increase in their dose between scheduled study visits visited the study site for dispensing study medication. At this unscheduled visit, assessments were conducted as specified (Table 8). Subjects who experienced dyskinesias met the primary study endpoint and were withdrawn. Treatment of dyskinesia was at the discretion of the treating physician.

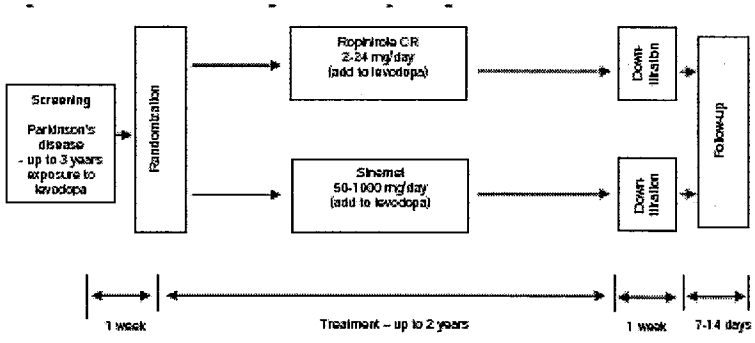
Down-titration Phase

For all subjects who completed the study or withdrew from the study prematurely, study medication was down-titrated over a 7-day period.

Follow-up Phase

Subjects attended a Follow-up visit 7 to 14 days after their last dose of study medication during the Down-titration Phase.

Figure 4Schematic Diagram of Study Design for SK&F-101468/228



A summary of the required protocol-related activities is provided in the Time and Events schedule (Table 1). The window around the weekly visits was ±3 days.

Table 8 Schedule of Time and Events for Study 228

Assessments	Study Period																
	Screening	Randomization and Baseline													Unscheduled	Early-Withdrawal	Follow-up
Visit**	0	1	2	3	4	5	6	7	8	9	10	11	12	13			14
Week	-1	0*	1	4	8	16	28	40	52	64	76	88	96	104			106
Informed Consent	X																
Inclusion/exclusion	X	X															
Randomization/Drug dispensing		X[a,b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Physical Examination	X																
Neurological Examination	X																
MMSE	X													X		X	
Weight		X												X		X	X
Medical History	X																
Dyskinesias		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
UPDRS Part II-IV		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
UPDRS Part V	X																
PDQ-39 – Questionnaire		X					X		X		X			X		X	
Beck Depression Inventory		X					X		X		X			X		X	
PD Psychosis scale (PPRS)		X					X		X		X			X		X	
Fatigue/sleep Scales (ESS/PDSS)		X					X		X		X			X		X	
Assessment of Time to Wearing Off		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-I Questionnaire			X	X	X	X	X	X	X						X[d]	X[d]	
CGI-S Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X						X									X	X
Pregnancy test	X	X					X							X		X	X[e]
Pharmacogenetic sampling							X[f]									X[f]	X[f]
12-lead ECG	X	X	X	X	X		X		X		X		X	X		X	X
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-study PD medications	X																
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Randomization.
b. Drug dispensing.
c. Vital signs included Heart rate, supine and standing diastolic and systolic BP, i.e., orthostatic BP.
d. If visit occurs within first year.
e. Also test at 30 days post dose.
f. Only one sample was needed, collected at any one of these indicated visits, as appropriate.
*Visit 1 was the Baseline visit/randomization visit.
** Calls to the patient by the physician or designee (frequency determined by PI) were made to ensure that the dose of drug was adjusted according to symptom control and tolerability. Dose adjustments were made on a weekly basis.
Note: CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity of Illness, ESS = Epworth Sleepiness Scale, MMSE = Mini Mental State Exam, PD = Parkinson's disease, PDQ = Parkinson's Disease Questionnaire, PDSS = Parkinson's Disease Sleep Scale, PPRS = Parkinson's Psychosis Rating Scale, UPDRS = Unified Parkinson's Disease.

The initial treatment of Parkinson's disease by general neurologists and family practitioners commonly involves placing the patient on L-dopa. Dopamine agonists are effective monotherapy agents and are useful as adjunctive treatment. The initial use of dopamine agonists compared to levodopa has been reported to reduce the incidence of dyskinesias in Parkinson's disease patients. Subjects in the current study have Parkinson's disease without dyskinesias, but are at risk for early development of motor complications. The sponsor indicated that data presently do not exist to show whether dopamine agonists are effective in reducing the incidence of dyskinesia in a population of PD patients that have short-term exposure to L-dopa. The present study was designed to determine whether ropinirole CR is useful in increasing the time to onset of dyskinesia in a population of Parkinson's Disease patients that are already receiving L-dopa for up to 3 years or less and are on $\leq$ 600mg/day of L-dopa.

Protocol Amendment(s)

Amendment 1: Issue Date 10 June 2004

The first amendment, introduced 8 months after study initiation, modified the inclusion criteria to include subjects that had been on L-dopa for up to 3 years .It allowed suitably trained sub-Investigators to administer the dyskinesia assessment in consultation with the PI, added 10 additional ECGs, modified the study title, and added a down-titration arm for the Sinemet-treated subjects. Specific changes in Amendment 1 included :

- Inclusion of subjects on $\leq$ 600mg of L-dopa therapy for $\leq$ 3 years, instead of $\leq$ 2 years.
- Provided that subjects assigned to Sinemet would be down titrated over a 7-day period, with a decrease in the total daily dose occurring every 2 days for the first 6 days, followed by a final reduction on Day 7, instead of no specified down titration. Thus, all subjects were down titrated for both the ropinirole CR and Sinemet.
- Allowed the PI or suitably trained sub-Investigator in consultation with the PI to complete the dyskinesia page of the CRF by checking either yes or no for the presence of dyskinesia, instead of requiring the PI to perform this determination.
- Specified that a 12-lead ECG would be taken at Screening, Baseline, Week 1, Week 4, Week 8, Week 28, Week 52, Week 76, Week 96, Week 104 (or on early withdrawal) and Follow-up, increased from evaluation at Screening only. Site personnel recorded the results of the ECG (normal, abnormal but not clinically significant, or abnormal and clinically significant). Any clinically significant worsening was recorded on the adverse event (AE) or severe adverse event (SAE) page of the CRF. Manual reading and interpretation by an external cardiologist/vendor was coordinated by GSK. All ECGs would be read blinded. The conduction intervals entered into the database would be those read by the external cardiologist/vendor.
- Modified the language in requirements for transmission of expedited safety reports to IRBs and IECs and corrected minor typographical and editorial errors in the original protocol. As a result of this amendment, subjects with longer prior exposures to levodopa were admitted to the study, enriching the population with subjects at greater risk for early development of dyskinesia. The amendment allowed detailed evaluation of the effects of study medications on serial ECGs. As a result of this amendment, some subjects had pretreatment ECGs at Baseline while others did not, while all subjects had Screening ECGs. For that reason, comparisons of ECG results between on-treatment and pretreatment values were made to the Screening ECGs.

Amendment 2: Issue Date 14 June 2005

The second amendment, introduced 20 months after study initiation, added disease genetics and pharmacogenomics components to the study. Specific changes in Amendment 2 included :

- Incorporated disease genetics aspects to the protocol to identify if a genetic component of dyskinesia may exist in Parkinson's disease.
- Incorporated a pharmacogenetics sub-study to the protocol. No changes in subject eligibility or analyses of already planned endpoints were expected to result from this amendment.

Study Closure

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. Although the study was terminated early and was based on a smaller number of subjects than originally planned, Study 228 provides insight into the time course of development of dykinesia, a possible complication of therapy. In order to maximize the number of subjects used in analyses of secondary endpoints, planned analyses were based on the Week 28 (approximately 6 month) assessment, the first post-Baseline assessment at which all questionnaires were completed before Week 52.

Subjects who were enrolled into the trial at least 22 weeks prior to the data cut-off date (last subject/last visit) of 7 December 2005 were to be included in the Evaluable population with those subjects who completed their Week 28 assessment according to the assessment window. Analyses of the Evaluable population may be included in a subsequent report. The Evaluable population was only to be used for the statistical analyses of secondary endpoints. All intent-to-treat (ITT) subjects were included in the summaries of the secondary endpoints and the analyses of dyskinesia.

Selection of Study Population
Patients with early stage Parkinson's disease were supposed to be included in the study if they met the following inclusion and exclusion criteria

Inclusion Criteria
A subject was eligible for inclusion in this study only if all of the following criteria applied :
1. Men or non-pregnant/non-breast-feeding women of at least 30 years of age but no older than 70 years of age at Screening. Women of childbearing potential must have been practicing a clinically accepted method of contraception (such as oral contraception, surgical sterilization, intrauterine device [IUD], or diaphragm IN ADDITION to spermicidal foam and condom on male partner, or systemic contraception [i.e., Norplant System]), during the study and for at least 1 month prior to randomization and 1 month following completion of the study.
2. Diagnosis of idiopathic Parkinson's disease (according to modified Hoehn & Yahr criteria Stages I-III) and demonstrating lack of control with L-dopa therapy (e.g., mild wearing off, simple on/off fluctuations).
3. Patients on 600mg or less of L-dopa therapy for 3 years or less. Patients receiving combination therapy such as COMTAN/L-dopa or Stalevo were also eligible.
4. Subjects receiving a stable dose of L-dopa for at least 4 weeks prior to Screening.
5. Provide written informed consent for this study.
6. Be willing and able to comply with study procedures, including Follow-up clinic visits.

Exclusion Criteria
A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. Any stage of Parkinson's disease in which the subject demonstrated or had a history consistent with dyskinesia.
2. Presence, or history within the previous 3 months, of significant and/or uncontrolled psychiatric, hematological, renal, hepatic, endocrinological, neurological (other than Parkinson's disease), or cardiovascular disease or active malignancy (other than basal cell carcinoma).
3. Any abnormality, at Screening, that the Investigator deemed to be clinically relevant on history, physical examination and in diagnostic laboratory tests including ECG.
4. Recent history of severe dizziness or fainting due to postural hypotension on standing.
5. Clinically relevant dementia or a MMSE score of <26.
6. Recent history or current evidence of alcohol or drug abuse at the time of enrollment.
7. Use of monoamine oxidase (MAO) inhibitors within 3 weeks of the Screening visit except for the selective MAO-B inhibitor, selegiline.
8. Definite or suspected personal or family history of clinically significant adverse reactions or hypersensitivity to ropinirole (or to drugs with a similar chemical structure) that would have precluded long-term dosing with ropinirole CR.
9. Withdrawal, introduction, or change in dose of hormone replacement therapy and/or any drug known to substantially inhibit CYP1A2 (e.g., ciprofloxacin, fluvoxamine, cimetidine, ethinyloestradiol) or induce CYP1A2 (e.g., tobacco, omeprazole) within 7 days prior to enrollment. Subjects already on chronic therapy with any of these agents could have been enrolled, but must have remained on stable doses of the agent from 7 days prior to enrollment through the end of the Treatment Period.
10. Use of an investigational drug within 30 days or 5-half-lives (which ever was longer).

Changes in the Conduct of the Study or Planned Analyses

The protocol was amended twice. Amendment 1 (10 June 2004) modified the inclusion criteria to include subjects that had been on L-dopa for up to 3 years. It allowed suitably trained sub-PIs to administer the dyskinesia assessment in consultation with the PI, and added additional ECGs. It modified the study title and added a down-titration arm for Sinemet. Amendment 2 (14 June 2005) added disease genetics and pharmacogenomics components to the study.

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. Although the study was terminated early and was based on a smaller number of subjects than originally planned, Study 228 provides insight into the time course of development of dyskinesia, a possible complication of therapy. Data 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. Planned analyses were conducted as specified in the in the RAP with three exceptions. First, no Per Protocol (PP) population was constructed and planned analyses using the PP population were not performed. Second, the analysis of time to dyskinesia (primary endpoint) was not stratified by study entry L-dopa dose, as was planned in the RAP, due to a small number of observed events. Third, although the RAP specified statistical inferences would be drawn for the secondary efficacy endpoints using analyses of

covariance, they are summarized only with descriptive statistics in this report due to early termination of the trial.

Sample Size Considerations
Data from a previous study of ropinirole and recommendations from consultants were used to estimate the rate of dyskinesia in this population and the difference that would be considered clinically meaningful. It was assumed that 50% of subjects on L-dopa treatment and 30% of subjects on ropinirole treatment experience dyskinesia within 2 years. Under these assumptions, 135 subjects/arm would be necessary to test the null hypothesis that the incidence rates in the 2-treatment arms were equal, with 90% power and a 5% Type 1 error rate. Assuming an exponential time to dyskinesia, the hazard ratio with these parameters is 1.943. It was postulated that the early withdrawal rate over 2 years in this population could be as high as 30%. Treating early withdrawals as censored observations, a log-rank test of the equality of the survival curves over 2 years with 175 subjects/arm would achieve a power of about 93% with a 2-sided 5% Type 1 error rate test.

The final sample size of 175 subjects randomized to each treatment arm was chosen to account for early withdrawal, non-evaluable subjects, and other incorrect assumptions.

Analysis Populations
Four subject populations (the ITT, Safety, Evaluable, Per Protocol-PP) were planned. The ITT and Safety were similar as described for study 169. However, analyses of the Evaluable and PP populations were not done for this report due to premature study termination.

Treatment Comparisons
The primary comparison of interest was ropinirole CR versus Sinemet for the time to onset of dyskinesia endpoint. All treatment comparisons, including the primary comparison, were made at the 5% level of significance. The primary population for analysis was the ITT population.

The Kaplan-Meier method was used to obtain log-rank p-values to compare survival curves for ropinirole CR and Sinemet treatment groups.

6.1.4 Efficacy Findings

6.1.4.1 Study 169 Efficacy Findings

Disposition of Subjects

The disposition of all randomized subjects in study 169 is summarized in Table 9.

Table 9 Summary of Subject Disposition (All Subjects: Study 169)

Study Stage / Population	Ropinirole CR		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Randomised	202	(100)	191	(100)	393	(100)
Safety population: received at least one dose of investigational product	202	(100)	191[1]	(100)	393	(100)
ITT population: received at least one dose of investigational product and attended at least one post-baseline assessment	201	(>99)	190[1]	(>99)	391	(>99)
Completed	168	(83)	134	(70)	302	(77)

Data Source: Section 12, Table 6.1 and Table 6.2.

1. One subject in the placebo group (subject 4825) received ropinirole CR for 4 weeks due to a dispensing error (details can be found at the end of Section 6.1 under Dispensing Errors).

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 (subject 6061) in the ER ropinirole group and one subject (subject 4850) in the placebo group did not have at least one post-baseline assessment and these subjects were excluded from the ITT population.

Of the 391 subjects in the ITT population, subjects were enrolled at multiple centers in the following counties such as 16 subjects in Belgium, 58 subjects in the Czech Republic, 9 subjects in France, 33 subjects in Hungary, 20 subjects in Italy, 162 subjects in Poland, 5 subjects in Spain, and 88 subjects in the US.

Subjects in the Safety population (i.e. those who received at least one dose of study medication) who discontinued from the study prematurely are summarized in Table 10, by reason for withdrawal.

Table 10 Summary of Reason for Study Discontinuation (Safety Population : Study 169)

	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)

Data Source: Section 12, Table 6.2.

1. *Primary* reason for discontinuation, as documented by the investigator on the end of study record.
2. Other reasons for discontinuation included: (i) sponsor requested withdrawal of subject (3 subjects) due to study conduct violation; (ii) necessary to increase dose of L-dopa above baseline level (1 subject); (iii) subject enrolled in study SK&F-101468/248 after completing 12 weeks of double-blind treatment (1 subject); (iv) subject leaving for winter (1 subject); (v) safety of patient (1 subject).
3. The investigator selected this category as the primary reason for premature discontinuation of the subject, although the study was not terminated by the sponsor.

Of the 393 subjects in the Safety population, overall 91 (23%) patients were discontinued from the study prematurely. A larger proportion of subjects discontinued prematurely from the placebo group than from the ER ropinirole group (30% versus 17%).
The most common reason for premature discontinuation was lack of efficacy, primary reason for 33 subjects (8%) in both treatment groups. A larger proportion of subjects discontinued from the placebo group than from the ER ropinirole group due to lack of efficacy (14% versus 3%).

Adverse event was cited as the *primary* reason for premature discontinuation on the end of study record for a similar proportion of subjects in each treatment group (12 subjects, 6% for ER ropinirole; 10 subjects, 5% for placebo). One of the withdrawn subjects in each treatment group (ropinirole CR: subject 4659; placebo: subject 6006) was withdrawn during the post-follow-up phase, due to an SAE. One additional subject in the placebo group (subject 6064) was reported to have withdrawn from the study due to an AE, based on the AE pages of the CRF. This subject had an AE of Parkinson's disease and "subject decided to withdraw from the study" was cited as the *primary* reason for premature discontinuation on the end of study record.

A total 374 subjects (ropinirole CR: 190/202 subjects; placebo: 184/191 subjects) had a follow-up visit, of which 308 (ropinirole CR: 168 subjects, 88%; placebo: 140 subjects, 76%) were still on-treatment. The reason for this is that subjects completing study SK&F-101468/169 were eligible for an open-label follow-up study (study SK&F-101468/248).

To avoid a break in treatment, follow-up visits were, therefore, generally scheduled for the end of the down-titration phase in study 169.

Follow-up

All subjects were to attend a follow-up visit 4 to 14 days after their last dose of study medication (this did not include down titration medication). Generally, this visit was scheduled to occur on the last day of the 7-day down-titration period.

Protocol Deviations

Major Protocol Deviations

The number (%) of subjects in the ITT population with major protocol deviations (≥ 1/patient) leading to exclusion from the PP population are summarized in Table 11. A similar proportion of subjects were excluded from the PP population due to major protocol deviation in the ER ropinirole ropinirole group (16%) and the placebo group (18%). The most common protocol deviation leading to exclusion from the PP population in both treatment groups was the withdrawal, introduction or change in dose of HRT and/or CYP1A2 inhibitors/inducers (ropinirole CR: 4%; placebo: 4%).

Table 11 Number of Subjects with Major Protocol Deviations Leading to Exclusion for the PP Population (ITT Population: Study 169)

	Ropinirole CR N=201		Placebo N=190		Total N=391	
	n	(%)	n	(%)	n	(%)
Subjects with at Least One Protocol Deviation Leading to Exclusion[1]	33	(16)	34	(18)	67	(17)
Withdrawal, introduction or change in dose of HRT and/or CYP1A2 inhibitors/inducers	9	(4)	8	(4)	17	(4)
Missed >3 consecutive days of study medication during the active treatment phase	6	(3)	6	(3)	12	(3)
Reached dose level 4 of study medication but did not reduce total daily dose of L-dopa	4	(2)	7	(4)	11	(3)
Significant changes to Parkinson's disease medication during study	4	(2)	5	(3)	9	(2)
Not 80-120% study medication compliant during the active treatment phase	6	(3)	3	(2)	9	(2)
Took significant amount of prohibited concomitant medications	3	(1)	3	(2)	6	(2)
Less than 3 hours awake time "off" on any diary day during placebo run-in	1	(<1)	4	(2)	5	(1)
Total daily dose of L-dopa increased above baseline value	2	(<1)	2	(1)	4	(1)
Consumption of any dopamine agonist within 4 weeks of screening	2	(<1)	1	(<1)	3	(<1)
Not receiving stable dose of L-dopa for at least 4 weeks before screening	0		1	(<1)	1	(<1)

Data Source: Section 12, Table 6.4.
1. Subjects may have had more than one protocol violation leading to exclusion.

Minor Protocol Deviations

The number (%) of patients in the ITT population with minor protocol deviations (which

did not lead to exclusion from the PP population) was similar proportion of subjects with minor in each treatment group (ER ropinirole: 102 subjects, 51%; placebo: 90 subjects, 47%). All of the subjects with a minor protocol deviation had irregular diary completion reported (i.e. diary not completed on the same 2 days of each week). This was categorized as a minor protocol deviation as the sponsor noted that this protocol violation was not considered to impact on the evaluation of efficacy.

Demographic Characteristics

Demographic characteristics for the ITT population are summarized in Table 12. The treatment groups were considered generally well-balanced for Parkinson's disease history at screening. However, there was a larger proportion of subjects with stage III disease in the ER ropinirole group compared to the placebo group (44% vs 34%) and a smaller proportion with stage IV disease (4% vs 13%).

Table 12 Summary of Demographic Characteristics (ITT Population : Study 169)

	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	

Data Source: Section 12, Table 6.18.
PD = Parkinson's disease.

Prior Parkinson's Disease Medications

The percentage of patients with previous dopaminergic agonist treatment was similar in both treatment groups (32 % placebo; 30 % ER ropinirole). In addition, the proportion of patients with previous ropinirole treatment was also (5 placebo; 6 % ER ropinirole).

Concomitant Medications

The percentages of different concomitant medications (including Parkinson's Disease medications was generally similar in both treatment groups (Table 13).

Table 13 Number (%) of Subjects Who Received the Most Common (≥ 5% in Either Treatment Group) On-Treatment Concomitant Medications (Safety Population: Study 169)

	Ropinirole CR N=202		Placebo N=191	
Ingredient	n	(%)	n	(%)
Any On-Treatment Concomitant Medication	202	(100)	191	(100)
Levodopa + Benserazide Hydrochloride	113	(56)	100	(52)
Levodopa + Carbidopa	98	(49)	96	(50)
Acetylsalicylic Acid	46	(23)	46	(24)
Entacapone	42	(21)	40	(21)
Selegiline Hydrochloride	33	(16)	21	(11)
Amantadine Sulphate	21	(10)	21	(11)
Amantadine Hydrochloride	14	(7)	20	(10)
Selegiline	18	(9)	15	(8)
Biperiden	17	(8)	13	(7)
Tocopherol	18	(9)	12	(6)
Paracetamol	11	(5)	15	(8)
Vitamins NOS	13	(6)	10	(5)
Atenolol	7	(3)	14	(7)
Metoprolol Tartrate	10	(5)	10	(5)
Citalopram	12	(6)	8	(4)
Clonazepam	13	(6)	7	(4)
Atorvastatin Calcium	8	(4)	10	(5)
Furosemide	8	(4)	10	(5)
Piracetam	10	(5)	8	(4)
Ascorbic Acid	11	(5)	7	(4)
Amlodipine Besilate	7	(3)	9	(5)
Omeprazole	10	(5)	5	(3)
Alprazolam	10	(5)	4	(2)

Data Source: Section 14, Table 8.30.
NOS = not otherwise specified.

Treatment Compliance

Treatment compliance (overall) was similar in each group (95 % placebo; 94 % ER ropinirole).

Titration

Dosing started at 2 mg ER ropinirole, or placebo equivalent, and was titrated upward (depending on the response/tolerability) of each individual subject . The dose titration regimen was to be followed until an optimal therapeutic dose was achieved.

Dosing Guidelines

Dose Level	CR Daily Dose (mg/day)	Matching Placebo
1	2 mg (2.0)	Placebo
2	4 mg (2.0 + 2.0)	Placebo
3[1]	6 mg (2.0 + 2.0 + 2.0)	Placebo
4	8 mg (4.0 + 4.0)	Placebo
5	12 mg (4.0 + 4.0 + 4.0)	Placebo
6	16 mg (8.0 + 8.0)	Placebo
7	20 mg (8.0 + 8.0 + 4.0)	Placebo
8	24 mg (8.0 + 8.0 + 8.0)	Placebo

1. Titration to dose level 3 was required.

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 ER ropinirole group and for 56% (107/191) of subjects in the placebo group. The "dose" of each treatment was generally similar throughout the whole study (Table 14).

Table 14 Summary Statistics for the "Dose" of Ropinirole (or Placebo) at Each Visit (Safety Population: Study 169)

Dose (mg/day)		Ropinirole CR N=202	Placebo [1] N=191
Week 1	n	202	189
	Mean (SD)	2.0 (0.0)	2.0 (0.0)
	Median (Range)	2.0 (2 - 2)	2.0 (2 - 2)
Week 2	n	197	190
	Mean (SD)	4.0 (0.28)	4.0 (0.36)
	Median (Range)	4.0 (2 - 6)	4.0 (2 - 6)
Week 3	n	194	184
	Mean (SD)	5.9 (0.35)	6.0 (0.33)
	Median (Range)	6.0 (4 - 6)	6.0 (4 - 8)
Week 4	n	196	183
	Mean (SD)	7.9 (0.74)	8.0 (0.73)
	Median (Range)	8.0 (6 - 12)	8.0 (6 - 12)
Week 6	n	195	178
	Mean (SD)	11.3 (1.60)	11.8 (1.34)
	Median (Range)	12.0 (6 - 16)	12.0 (6 - 16)
Week 8	n	190	177
	Mean (SD)	14.3 (2.94)	15.2 (2.36)
	Median (Range)	16.0 (6 - 20)	16.0 (6 - 20)
Week 10	n	190	168
	Mean (SD)	16.8 (4.21)	18.2 (3.31)
	Median (Range)	20.0 (6 - 24)	20.0 (6 - 24)
Week 12	n	189	163
	Mean (SD)	19.0 (5.51)	20.7 (4.55)
	Median (Range)	20.0 (6 - 24)	24.0 (6 - 24)
Week 16	n	182	153
	Mean (SD)	19.4 (5.56)	21.0 (4.42)
	Median (Range)	22.0 (6 - 24)	24.0 (6 - 24)
Week 20	n	177	143
	Mean (SD)	19.5 (5.52)	21.1 (4.45)
	Median (Range)	24.0 (6 - 24)	24.0 (6 - 24)
Week 24	n	169	132
	Mean (SD)	19.5 (5.58)	21.2 (4.41)
	Median (Range)	24.0 (6 - 24)	24.0 (6 - 24)
Week 24 LOCF	n	202	191
	Mean (SD)	18.8 (6.26)	20.0 (5.62)
	Median (Range)	20.0 (2 - 24)	24.0 (2 - 24)
Down-Titration [2]	n	189	178
	Mean (SD)	6.6 (1.83)	6.9 (1.68)
	Median (Range)	8.0 (2 - 16)	8.0 (2 - 16)

Data Source: Section 12, Table 6.11.
1. Note that all subjects in the placebo group received 0 mg of active ingredient.
2. The dose reported is that taken during the second half of the down-titration period.

EFFICACY RESULTS

Primary Efficacy Results

Change from Baseline in Total Awake Time Spent "Off" at Week 24

The primary efficacy endpoint was the mean change from baseline in total awake time spent "off" at Week 24. Primary inference by the sponsor with regards to the superiority of ER ropinirole compared to placebo is based on the LOCF dataset for the ITT population. Summary statistics for this endpoint are presented in Table 15.

Table 15 Summary Statistics for Change from Baseline in Total Awake Time Spent "Off" at Week 24 LOCF (ITT Population: Study 169)

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)

Data Source: Section 13, Table 7.1 and Table 7.2.
1. A decrease from baseline indicates an improvement.

At baseline the mean total awake time spent "off" was approximately 7 hours in each treatment group. In the ropinirole CR group, total awake time spent "off" had decreased, on average, by approximately 2 hours at Week 24 LOCF. In the placebo group, total awake time spent "off" had decreased, on average, by approximately half an hour at Week 24 LOCF. Similar results were observed for the PP population. The adjusted analysis (adjusted for country and baseline "off") of total awake time spent "off" can be found in Table 16.

Table 16 Adjusted Analysis of Change from Baseline in Total Awake Time Spent "Off" (Hours) at Week 24 by Population (Study 169)

Population	Ropinirole CR Adjusted[1] Mean (SE) Change from Baseline[2]	Placebo Adjusted[1] Mean (SE) Change from Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
ITT: Week 24 LOCF	n=201 -2.1 (0.32)	n=190 -0.3 (0.32)	-1.7	(-2.34, -1.09)	<0.0001
ITT: Week 24 OC	n=158 -2.8 (0.38)	n=126 -1.2 (0.40)	-1.6	(-2.30,-0.85)	<0.0001
PP: Week 24 LOCF	n=168 -2.4 (0.41)	n=156 -0.7 (0.40)	-1.8	(-2.46,-1.07)	<0.0001

Data Source: Section 13, Table 7.10, Table 7.11 and Table 7.14.
1. Adjusted for country and baseline score.
2. A decrease from baseline indicates an improvement.

The mean change from baseline in awake time spent "off" by visit is shown in Figure 5.

Statistical analyses of awake time spent "off" at each time point can be found in Table 17. A plot of the treatment difference for change from baseline in awake time spent "off" by visit is shown in Figure 6. The sponsor noted that a clinically relevant and "statistically" significant treatment effect (i.e. **nominal p values not adjusted for multiplicity**) was observed at all visits from Week 2 onwards.

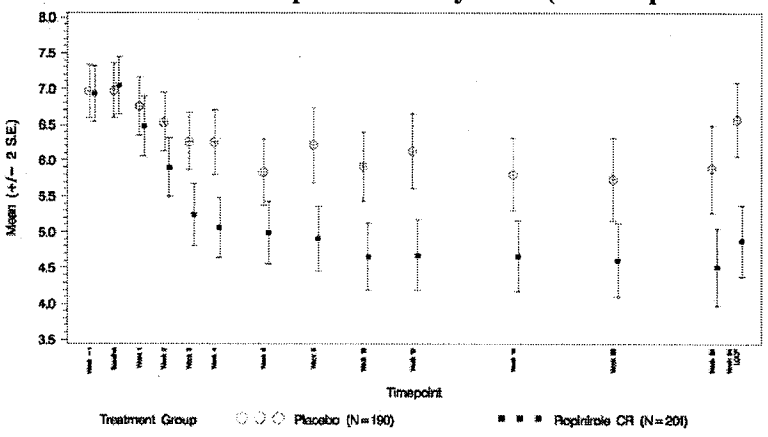
Table 17 Summary of the Adjusted Analysis of Change from Baseline in the Total Awake Time Spent "Off" (Hours) By Visit (ITT Population in Study 169)

Visit (OC)	Treatment	n	Adjusted[1] Mean (SE) Change From Baseline[2]		Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Week 1	Ropinirole CR	201	-0.8	(0.22)	-0.3	(-0.73, 0.13)	0.1741
	Placebo	188	-0.5	(0.22)			
Week 2	Ropinirole CR	197	-1.6	(0.22)	-0.7	(-1.09, -0.23)	0.0029
	Placebo	189	-1.0	(0.22)			
Week 3	Ropinirole CR	194	-2.0	(0.24)	-1.1	(-1.52, -0.59)	<0.0001
	Placebo	184	-1.0	(0.24)			
Week 4	Ropinirole CR	196	-2.1	(0.25)	-1.3	(-1.80, -0.79)	<0.0001
	Placebo	182	-0.8	(0.26)			
Week 6	Ropinirole CR	194	-2.1	(0.28)	-0.9	(-1.47, -0.39)	0.0008
	Placebo	178	-1.1	(0.28)			
Week 8	Ropinirole CR	189	-1.9	(0.30)	-1.5	(-2.05, -0.87)	<0.0001
	Placebo	175	-0.5	(0.31)			
Week 10	Ropinirole CR	190	-2.0	(0.30)	-1.4	(-1.93, -0.78)	<0.0001
	Placebo	167	-0.7	(0.31)			
Week 12	Ropinirole CR	189	-1.9	(0.32)	-1.6	(-2.21, -0.96)	<0.0001
	Placebo	163	-0.3	(0.34)			
Week 16	Ropinirole CR	182	-2.6	(0.32)	-1.3	(-1.88, -0.63)	0.0001
	Placebo	151	-1.3	(0.34)			
Week 20	Ropinirole CR	175	-2.6	(0.32)	-1.3	(-1.99, -0.69)	<0.0001
	Placebo	140	-1.2	(0.35)			
Week 24	Ropinirole CR	158	-2.8	(0.38)	-1.6	(-2.30,-0.85)	<0.0001
	Placebo	126	-1.2	(0.40)			

Data Source: Section 13, Table 7.109.
1. Adjusted for country and baseline score.
2. A decrease from baseline indicates an improvement.

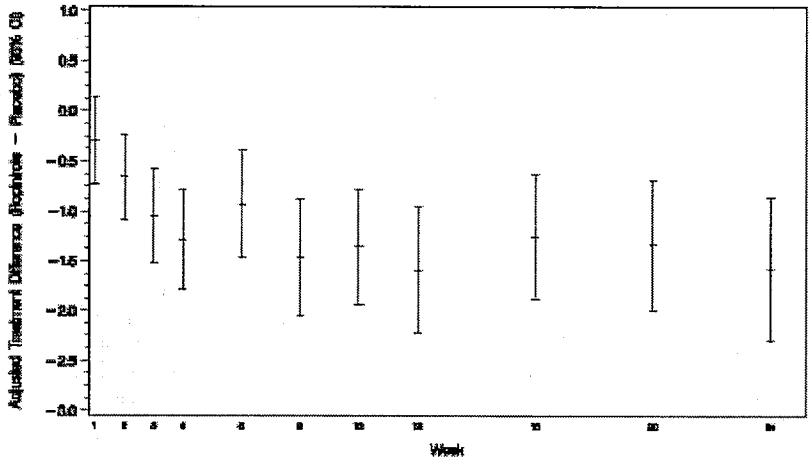
Of interest, the mean maximal adjusted treatment effect/difference ~ 1.5 was reached at 8 weeks (Table 17) when the mean daily ER ropinirole dose was ~ 14 mg/day (Table 14). The mean maximal ER ropinirole daily dose was not achieved until 12 weeks of treatment suggesting the possibility the maximal treatment effect was reached at lower daily doses and that higher doses were not providing any additional therapeutic benefit but merely potentially increased toxicity.

Figure 5 Mean Change From Baseline (± 2 SE) Absolute Awake Time Spent "Off" by Visit (ITT Population : Study 169)



Data Source: Section 13, Figure 7.1.

Figure 6 Adjusted Mean Treatment Difference for Change From Baseline (95% Confidence Interval) Absolute Awake Time Spent "Off" by Visit (ITT Population: Study 169)



Data Source: Section 13, Figure 7.5.

ITT Population

In the primary population of interest, the ITT population at Week 24 LOCF, 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. It should be noted that this study was powered to detect a difference of 1.2 hours in awake time spent "off", a value considered to be highly clinically relevant by the sponsor. The observed difference was greater than this.

Observed Case and PP Population

To assess the robustness of the primary analysis, the model was refitted for the ITT population at Week 24 observed case (OC) and the per protocol (PP) population at Week 24 LOCF. The results from these analyses (Table 16) were similar and supported those obtained from the primary analysis (i.e. ropinirole CR was demonstrated to be statistically significantly superior to placebo). More specifically, the mean adjusted treatment difference in "off" hours was – 1.6 for patients who completed 24 weeks of treatment (N = 158 ropinirole CR; N = 126 Placebo), - 1.7 in the primary ITT population (using LOCF), and -1.8 in the PP population (using LOCF).

Interactions

To further assess the robustness of the primary analysis, the statistical significance of treatment by country and treatment by baseline awake time "off" interactions was assessed for the ITT population at Week 24 LOCF. Each interaction was fitted separately to the primary model and assessed at the 10% level. Neither the treatment by country, nor the treatment by baseline awake time "off" interactions were statistically significant (p=0.1887 and p=0.8051, respectively).

Retrospectively-Defined Analysis of Change of "OFF", By Visit

An analysis of the change from baseline in total awake time spent "off", by visit (i.e. for OC population), was retrospectively defined (i.e. conducted as a post-hoc analysis not prospectively defined in the protocol or RAP/SAP). A summary of this analysis is shown in Table 18 that shows similar data as reflected in Figure 5 and Figure 6.

Table 18 Summary of the Adjusted Analysis of Change from Baseline in the Total Awake Time Spent "Off" (Hours) By Visit (ITT Population in Protocol SK&F-101468/169)

Visit (OC)	Treatment	n	Adjusted[1] Mean (SE) Change From Baseline[2]		Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Week 1	Ropinirole CR	201	-0.8	(0.22)	-0.3	(-0.73, 0.13)	0.1741
	Placebo	188	-0.5	(0.22)			
Week 2	Ropinirole CR	197	-1.6	(0.22)	-0.7	(-1.09, -0.23)	0.0029
	Placebo	189	-1.0	(0.22)			
Week 3	Ropinirole CR	194	-2.0	(0.24)	-1.1	(-1.52, -0.59)	<0.0001
	Placebo	184	-1.0	(0.24)			
Week 4	Ropinirole CR	196	-2.1	(0.25)	-1.3	(-1.80, -0.79)	<0.0001
	Placebo	182	-0.8	(0.26)			
Week 6	Ropinirole CR	194	-2.1	(0.28)	-0.9	(-1.47, -0.39)	0.0008
	Placebo	178	-1.1	(0.28)			
Week 8	Ropinirole CR	189	-1.9	(0.30)	-1.5	(-2.05, -0.87)	<0.0001
	Placebo	175	-0.5	(0.31)			
Week 10	Ropinirole CR	190	-2.0	(0.30)	-1.4	(-1.93, -0.78)	<0.0001
	Placebo	167	-0.7	(0.31)			
Week 12	Ropinirole CR	189	-1.9	(0.32)	-1.6	(-2.21, -0.96)	<0.0001
	Placebo	163	-0.3	(0.34)			
Week 16	Ropinirole CR	182	-2.6	(0.32)	-1.3	(-1.88, -0.63)	0.0001
	Placebo	151	-1.3	(0.34)			
Week 20	Ropinirole CR	175	-2.6	(0.32)	-1.3	(-1.99, -0.69)	<0.0001
	Placebo	140	-1.2	(0.35)			
Week 24	Ropinirole CR	158	-2.8	(0.38)	-1.6	(-2.30,-0.85)	<0.0001
	Placebo	126	-1.2	(0.40)			

Data Source: Section 13, Table 7.109.
1. Adjusted for country and baseline score.
2. A decrease from baseline indicates an improvement.

Analysis of Additional Covariates

The statistical significance of each of the additional covariates and their interactions with treatment was assessed for the primary endpoint, for the ITT population at Week 24 LOCF. The effect of race was not assessed as > 95% of subjects were White/Caucasian. The effect of food was assessed, although it should be noted that investigational product was taken without regard to food. The majority of subjects (ropinirole CR: 192 subjects, 96%; placebo: 181 subjects, 95%) reported that they took their medication within 2 hours of a meal.

Each main effect was assessed at the 5% level of significance; each interaction was assessed at the 10% level of significance. The statistical significance of each main effect and their interaction with treatment is shown in Table 19.

Table 19 Results from the Analyses of Additional Covariates on the Change from Baseline in Awake Time Spent "Off" (Hours) at Week 24 LOCF (ITT Population in Study 169)

	Main Effect (Only)			Interaction with Treatment (in the Presence of the Main Effect)[1]		
Effect	DF	F-Value	P-Value	DF	F-Value	P-Value
Gender	1	0.19	0.6650	1	0.03	0.8607
Age Group	2	0.17	0.8466	2	0.62	0.5386
Pre/Post Protocol Amendment 1	1	2.79	0.0954	1	1.32	0.2519
Prior Exposure to Dopamine Agonists	1	0.58	0.4456	1	0.98	0.3221
Prior Exposure to Ropinirole	1	0.74	0.3898	1	4.25	0.0400[3]
Study Medication Taken With/Without Food [2]	1	0.36	0.5504	1	0.09	0.7599

Data Source: Attachment 2.
1. After adjusting for country, baseline awake time spent "off", and treatment.
2. With food was defined as the subject generally took investigational product within 2 hours of a meal.
3. Effect statistically significant.

No main effects were found to be statistically significant, however, 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 (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**. The results are shown in Table 20.

Table 20 Adjusted Treatment Differences and 95% Confidence Intervals for the Change from Baseline in Awake Time Spent "Off" (Hours) at Week 24 LOCF for Subjects With and Without Prior Exposure to Ropinirole (ITT Population in Study 169)

Population	Ropinirole CR Adjusted[1] Mean (SE) Change from Baseline[2]	Placebo Adjusted[1] Mean (SE) Change from Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
No Prior Exposure	n=189 -1.9 (0.34)	n=181 -0.1 (0.35)	-1.9	(-2.52, -1.23)	<0.0001
Prior Exposure	n=12 -2.3 (1.38)	n=9 -2.5 (1.07)	0.2	(-2.84, 3.28)	0.8799

Data Source: Attachment 2.
1. Adjusted for country and baseline score.
2. A decrease from baseline indicates an improvement.

For subjects without prior exposure to ropinirole, the results obtained were similar to those obtained from the analysis containing all subjects. There was a statistically significant difference in favor of ropinirole CR and the estimated treatment difference was considered comparable. There were too few subjects with prior exposure to ropinirole (21 subjects in total) to draw any conclusions regarding this data.

Reviewer Comment

- **Of interest, there did not appear to be any benefit of ropinirole CR in patients who had previously been treated with ropinirole IR.** Although the number of patients with prior exposure to ropinirole IR was relatively small in each treatment group (N = 12 for ropinirole CR; N = 9 for Placebo), the treatment difference was + 0.2 hours (i.e. a slight incremental change in "off" hours) for patients previously treated with ropinirole compared to – 1.9 hours (i.e. marked treatment benefit) in patients with who had never been treated with ropinirole. The reason for this apparent effect is not clear.

Secondary Efficacy Results

I have presented selected secondary efficacy results/analyses that I have deemed of interest. All results showing p values for statistical analyses/comparison represent nominal p values that have NOT been adjusted/corrected for multiplicity.

Change from Baseline in Percent Awake Time Spent "Off"

Summary statistics for change from baseline in the percent awake time spent "off" are presented in Table 21.

Table 21 Summary Statistics for Change from Baseline in Percent Awake Time Spent "Off" at Week 24 LOCF (ITT Population: Study 169)

Percent Awake Time Spent "Off"	Ropinirole CR N=201	Placebo N=190
Baseline	n=201	n=190
Mean (SD)	43.8 (16.42)	43.6 (15.42)
Median (Min, Max)	42.2 (18.5, 100.0)	42.5 (20.0, 100.0)
Week 24 LOCF	n=201	n=190
Mean (SD)	30.6 (21.69)	41.9 (22.85)
Median (Min, Max)	28.8 (0.0, 100.0)	43.5 (0.0, 100.0)
Change from Baseline to Week 24 LOCF[1]	n=201	n=190
Mean (SD)	-12.8 (19.72)	-1.8 (20.83)
Median (Min, Max)	-13.7 (-79.3, 76.2)	-1.3 (-87.3, 74.8)

Data Source: Section 13, Table 7.21 and Table 7.22.
1. A decrease from baseline indicates an improvement.

At baseline, in each treatment group subjects spent just less than half their **awake time** "off", on average. In the ropinirole CR group, percent awake time spent "off" had decreased, on average, to approximately 30 % at Week 24 LOCF, while in the placebo group there was little change.

A summary of the adjusted mean change from baseline, adjusted treatment difference, confidence interval and p-value for the change from baseline in percent awake time spent "off" is presented in Table 22. These data show a significant decrease in % awake time spent in the "Off" state with a treatment difference of ~ 11%.

Table 22 Adjusted Analysis of Change from Baseline in Percent Awake Time Spent "Off" at Week 24 LOCF (ITT Population: Study 169)

Population	Ropinirole CR Adjusted[1] Mean (SE) Change from Baseline[2]	Placebo Adjusted[1] Mean (SE) Change from Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Week 24 LOCF	n=201 -12.1 (2.01)	n=190 -0.9 (2.02)	-11.2	(-15.13, -7.21)	<0.0001

Data Source: Section 13, Table 7.23.
1. Adjusted for country and baseline score
2. A decrease from baseline indicates an improvement.

The change from baseline in total "Off" time (hours) for patients completing the study at week 24 (i.e. "completers") showed similar results for these observed case data as those for all modified ITT populations patients applying LOCF and per protocol patients applying LOCF (Table 16).

Change from Baseline in Total Awake Time Spent "On"

Summary statistics for change from baseline in total awake time spent "on" are shown in Table 23.

Table 23 Summary Statistics for Change from Baseline in Total Awake Time Spent "On" (Hours) at Week 24 LOCF (ITT Population: Study 169)

Total Awake Time Spent "On"	Ropinirole CR N=201	Placebo N=190
Baseline	n=201	n=190
Mean (SD)	9.0 (2.75)	9.1 (2.69)
Median (Min, Max)	9.3 (0.0, 17.0)	9.3 (0.0, 15.8)
Week 24 LOCF	n=201	n=190
Mean (SD)	10.9 (3.48)	9.2 (3.68)
Median (Min, Max)	11.3 (0.0, 18.3)	9.0 (0.0, 17.8)
Change from Baseline to Week 24 LOCF[1]	n=201	n=190
Mean (SD)	1.8 (3.24)	0.2 (3.34)
Median (Min, Max)	1.9 (-12.8, 13.9)	0.1 (-11.6, 13.1)

Data Source: Section 13, Table 7.18 and Table 7.19.
1. An increase from baseline indicates an improvement.

At baseline the total awake time spent "on" was approximately 9 hours, on average, in each treatment group. In the ropinirole CR group, total awake time spent "on" had increased to approximately 11 hours, on average, at Week 24 LOCF, while in the placebo group there was little change in total awake time spent "on". A summary of the adjusted mean change from baseline, adjusted treatment difference, confidence interval and p-value for total awake time spent "on" at Week 24 LOCF is shown in Table 24. There was a statistically significant benefit of ropinirole CR over placebo for the total awake time spent "on" at Week 24 LOCF.

Table 24 Adjusted Analysis of Change from Baseline in Total Awake Time Spent "On" (Hours) at Week 24 LOCF (ITT Population: Study 169)

Population	Ropinirole CR Adjusted[1] Mean (SE) Change from Baseline[2]	Placebo Adjusted[1] Mean (SE) Change from Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Week 24 LOCF	n=201 1.6 (0.32)	n=190 -0.1 (0.32)	1.7	(1.06, 2.33)	<0.0001

Data Source: Section 13, Table 7.20
1. Adjusted for centre/country group and baseline score.
2. An increase from baseline indicates an improvement.

An analysis that I requested for "completers" at 24 weeks showed a treatment effect/difference (Table 25) for the change from baseline in total awake time spent "on" that was similar to that for the modified ITT population (LOCF).

Table 25 Summary of Analysis of Covariance of the Change from Baseline in the Total Awake Time Spent 'On' at Week 24 OC

Treatment	Adjusted Mean	SE of Adjusted Mean	Difference vs Placebo	95% CI for Treatment Difference	P-Value for Treatment Difference
Ropinirole CR	2.2	0.38	1.4	[0.68,2.13]	0.0002
Placebo	0.8	0.41			

Change from Baseline in Percent Awake Time Spent "On"

At baseline, in each treatment group subjects spent, on average, just over half (i.e. ~ 56 %) their **awake time** "on". In the ropinirole CR group, percent awake time spent "on" had increased to approximately 70%, on average, at Week 24 LOCF, while in the placebo group there was little change. A summary of the adjusted mean change from baseline, adjusted treatment difference, confidence interval and p-value for the change from baseline in percent awake time spent "on" is presented in Table 26. There was a statistically significant benefit of ropinirole CR over placebo for the percent total awake time spent "on" at Week 24 LOCF.

Table 26 Adjusted Analysis of Change from Baseline in Percent Awake Time Spent "On" at Week 24 LOCF (ITT Population: Study 169)

Population	Ropinirole CR Adjusted[1] Mean (SE) Change from Baseline[2]	Placebo Adjusted[1] Mean (SE) Change from Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Week 24 LOCF	n=201 12.1 (2.00)	n=190 1.00 (2.02)	11.1	(7.17,15.08)	<0.0001

Data Source: Section 13, Table 7.29.
1. Adjusted for country and baseline score.
2. An increase from baseline indicates an improvement.

Change from Baseline in Total Awake Time Spent "On" Without Troublesome Dyskinesia

At baseline the total awake time spent "on" without troublesome dyskinesia was approximately 8.5 hours, on average, in each treatment group. In the ropinirole CR group, total awake time spent "on" without troublesome dyskinesia had increased to approximately 10.5 hours, on average at Week 24 LOCF, while in the placebo group total awake time spent "on" had increased to 8.8 hours. A summary of the adjusted mean change from baseline, adjusted treatment difference, confidence interval and p-value for the change from baseline in total awake time spent "on" without troublesome dyskinesia at Week 24 LOCF is presented in Table 27. There was a statistically significant benefit of ropinirole CR over placebo for the total awake time spent "on" without troublesome dyskinesia at Week 24 LOCF.

Table 27 Adjusted Analysis of Change from Baseline in Total Awake Time Spent "On" Without Troublesome Dyskinesia (Hours) at Week 24 LOCF (ITT Population: Study 169)

Population	Ropinirole CR Adjusted[1] Mean (SE) Change from Baseline[2]	Placebo Adjusted[1] Mean (SE) Change from Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Week 24 LOCF	n=200 1.6 (0.32)	n=188 0.1 (0.33)	1.5	(0.85,2.13)	<0.0001

Data Source: Section 13, Table 7.17.
1. Adjusted for country and baseline score.
2. An increase from baseline indicates an improvement.

An analysis that I requested for study "completers" (at 24 weeks) for the change from baseline in the total time spent "on" **without troublesome dsykinesia** showed a substantial and statistically significant treatment effect/difference (Table 28) for ER ropinirole (vs placebo). This analysis was similar to the ITT population analysis (Table 27). Both of these analyses indicated that the vast majority of the decrease in mean "off" time was related to an increase in "on" time without troublesome dyskinesia, a desirable therapeutic effect/goal.

Table 28 Summary of Analysis of Covariance of the Change from Baseline in the Total Awake Time Spent "On" Without Troublesome Dyskinesia at Week 24 OC

Treatment	Adjusted Mean	SE of Adjusted Mean	Difference vs Placebo	95% CI for Treatment Difference	P-Value for Treatment Difference
Ropinirole CR	2.2	0.39	1.2	(0.45,1.92)	0.0016
Placebo	1.1	0.41			

Change From Baseline in Total Awake Time Spent "On" With Troublesome Dyskinesia

At baseline the total awake time spent "on" **with troublesome dyskinesia** was 0.5 hours, on average, in the ropinirole CR group and 0.61 hours, on average, in the placebo group. At Week 24 LOCF the total awake time spent "on" with troublesome dyskinesia was 0.46

hours, on average, in the ropinirole CR group and 0.35 hours, on average in the placebo group. There was no substantial treatment effect on the total awake time spent "on" with troublesome dyskinesia.

The analysis (that I requested) for "completers" at 24 weeks showed no **substantial** mean treatment effect/difference (Table 29) in the total "on" hours spent with troublesome dyskinesia. Although there was a positive treatment effect/difference (+ 0.2 hrs) for ER ropinirole treatment (vs placebo), and this difference was statistically significant, this mean treatment effect/difference was minor in absolute terms and only amounted to ~ 12 minutes.

Table 29 Summary of Analysis of Covariance of the Change from Baseline in the Total Awake Time Spent 'On' With Troublesome Dyskinesia at Week 24 OC

Treatment	Adjusted Mean	SE of Adjusted Mean	Difference vs Placebo	95% CI for Treatment Difference	P-Value for Treatment Difference
Ropinirole CR	-0.1	0.11	0.2	(0.01,0.42)	0.0435
Placebo	-0.3	0.11			

Change from Baseline in Total Time Asleep

In the ITT population, at baseline the mean total time asleep per day was 8.0 hours in each treatment group. At Week 24 LOCF, there was little change in total time asleep in either treatment group; the mean total time asleep per day was 8.2 hours in the ropinirole CR group and 8.3 hours in the placebo group. A formal, adjusted analysis of change from baseline in total time asleep was not planned or conducted.

An analysis (that I requested) for "completers" at 24 weeks showed no **substantial** mean treatment effect/difference (Table 30) in the total sleep time (i.e. hours) associated with ER ropinirole treatment (vs placebo).

Table 30 Summary of Analysis of Covariance of the Change from Baseline in the Total Sleep Time at Week 24 OC

Treatment	Adjusted Mean	SE of Adjusted Mean	Difference vs Placebo	95% CI for Treatment Difference	P-Value for Treatment Difference
Ropinirole CR	0.6	0.18	0.1	(-0.21,0.49)	0.4410
Placebo	0.4	0.20			

Change from Baseline in UPDRS Motor Score

UPDRS assessments were conducted within a window of at least 2 hours after the previous L-dopa dose and prior to the next scheduled L-dopa dose. Subjects may have been evaluated in either the "on" and "off" states and summaries of the UPDRS motor score at each visit were also produced separately for each state (e.g. "off" or "on"). The last on-treatment value was carried forward regardless of the state.

At baseline the mean UPDRS motor score was similar in each treatment group (approximately 30 points). At Week 24 LOCF the mean UPDRS motor score had