improved (decreased) in the ropinirole CR group to 23.4 points, and to 28.8 points in the placebo group. A summary of the adjusted mean change from baseline, adjusted treatment difference, confidence interval and p-value for UPDRS motor score, regardless of state, at Week 24 LOCF is shown in Table 31. There was a statistically significant benefit of ropinirole CR over placebo for the change from baseline in the UPDRS motor score at Week 24 LOCF.

Table 31 Adjusted Analysis of Change from Baseline in UPDRS Motor Score 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=194 -6.5 (0.90)	n=183 -1.7 (0.92)	-4.8	(-6.56,-2.98)	<0.0001

Data Source: Section 13, Table 7.36.
1. Adjusted for country and baseline score.
2. The total motor score of the UPDRS ranged from 0 to 108, where 0=normal/no symptoms and 108=worst possible case. A decrease from baseline indicates an improvement.

Other analyses of mean change of UPDRS motor score with respect to being "on" or "off" were also conducted. The mean arithmetic treatment effect/difference (ER ropinirole – Placebo) for change from baseline for UPDRS motor score in the "on" state was – 2.9 for the observed case patients (ER ropinirole, N=131; Placebo, N=101) at 24 weeks and the mean treatment effect/difference for the LOCF analysis at 24 weeks was – 4.2 (ER ropinirole, N=163; Placebo, N=139). The mean arithmetic treatment effect/difference (ER ropinirole – Placebo) for change from baseline for UPDRS motor score in the "off" state was – 4.7 for the observed case patients (ER ropinirole, N=27; Placebo, N=25) at 24 weeks and the mean treatment effect/difference for the LOCF analysis at 24 weeks was – 1.9 (ER ropinirole, N=139; Placebo, N=163). Thus, the adjusted mean LOCF analysis of the ITT population for the treatment effect/difference (-4.8; Table 31) for the mean change from baseline for UPDRS motor score without regard to "on" or "off" state was numerically greater than any of the mean arithmetic treatment effects/differences with respect to "on" or "off" state.

Change from Baseline in Average Total Activities of Daily Living Score of the UPDRS

Subjects may have had responses in both the "on" and "off" states and summaries of the ADL score at each visit were produced separately for each state. An average ADL score was calculated by the sponsor from the "on" and "off" score for each subject at each visit. If only the "on" or "off" score was available, then this was considered the average. The analysis for the change from baseline in the ADL score at Week 24 LOCF was performed on this average score.

At baseline the mean UPDRS ADL score was similar in each treatment group (approximately 14 points). At Week 24 LOCF the mean UPDRS ADL score had improved in the ropinirole CR group to 10.6 points, and was 13.3 points in the placebo group. A summary of the adjusted mean change from baseline, adjusted treatment

difference, confidence interval and p-value for the ADL Score of the UPDRS at Week 24 LOCF is presented in Table 32.

There was a statistically significant benefit of ropinirole CR over placebo for the change from baseline in the UPDRS ADL score at Week 24 LOCF.

Table 32 Adjusted Analysis of Change from Baseline in UPDRS ADL Score 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=197 -3.5 (0.39)	n=184 -0.9 (0.40)	-2.6	(-3.36,-1.83)	<0.0001

Data Source: Section 13, Table 7.41.
1. Adjusted for country and baseline score.
2. The total ADL Score of the UPDRS ranged from 0 to 52, where 0=normal/no symptoms and 52=worst possible case. A decrease from baseline indicates an improvement.

Proportion of Subjects with a Score of Much Improved or Very Much Improved on the CGI Global Improvement Scale

A summary of the number (%) of responders, defined as subjects with a CGI-I score of 1 (very much improved) or 2 (much improved), in the ITT population was determined. From Week 2 onwards, the proportion of responders on the CGI-I scale was greater for subjects receiving ropinirole CR than for subjects receiving placebo. From Week 4 to the end of the study (Week 24), the treatment difference was substantial (16 %) and ranged throughout the rest of the study from 20 % to 30 %. At Week 24 LOCF, 42% of subjects in the ropinirole CR group compared to 14% of subjects in the placebo group were responders. The adjusted odds ratios, confidence intervals and p-values for the proportion of subjects with a score of much improved or very much improved on the CGI-I scale at Week 24LOCF in the ITT population is presented in Table 33.

Table 33 Analysis of Subjects with a Score of Much Improved or Very Much Improved on the CGI-I Scale at Week 24 LOCF (ITT Population: Study 169)

Treatment	Proportion of Responders, n/N (%)	Adjusted Odds Ratio[1]	95% CI for Odds Ratio[1]	P-value[1]
Ropinirole CR	83/200 (42%)	4.4	(2.63, 7.20)	<0.001
Placebo	27/189 (14%)			

Data Source: Section 13, Table 7.50.
1. Adjusted for country.

In the ITT population, the odds of a subject receiving ropinirole CR being a CGI-I responder was more than 4 times that of a subject receiving placebo. The adjusted odds ratio for ropinirole CR vs. placebo at Week 24 LOCF was 4.4 (95% CI: [2.63, 7.20], $p < 0.001$) indicating a statistically significant benefit of ropinirole CR over placebo.

Proportion of Subjects Requiring Reinstatement of L-Dopa Following Reduction in Dose

Guidelines for the planned reduction in L-dopa dose, and reinstatement due to loss of symptom control were described earlier in the section on the study design. A total of 26 subjects (ropinirole CR: 10 subjects; placebo: 16 subjects) violated the protocol and did not reduce their dose of L-dopa at any stage during the study. Thirteen of these 26 subjects (ropinirole CR: 5 subjects; placebo: 8 subjects) were not titrated to dose level 4 (level at which L-dopa reduction was required) of study medication, thus the mandatory reduction of L-dopa medication would not have applied. For the remaining 13 subjects (ropinirole CR: 5 subjects: placebo: 8 subjects), up-titration to dose level 4 or higher was achieved, without reducing the L-dopa dose as specified in the protocol. Eleven of these 13 subjects (ropinirole CR: 4 subjects: placebo: 7 subjects) were flagged as protocol violators for this reason, including subject 5329 in the ropinirole CR group who did not have an L-dopa dose recorded at baseline and who was also flagged as a protocol violator for increasing L-dopa above baseline levels. One of the subjects in the ropinirole CR group (subject 5181) did not have an L-dopa dose recorded at baseline and was flagged as a protocol violator for increasing L-dopa above baseline levels. One of the subjects in the placebo group (subject 4858) was titrated to dose level 4 and then withdrawn from the study due to a protocol violation.

Among the vast majority of subjects who underwent L-dopa dose reduction, reinstatement of L-dopa was required for 7% (14/191 subjects) in the ropinirole CR group and 28% (49/174 subjects) in the placebo group; conversely the reduction in dose was sustained in 93% of patients who received ropinirole CR and in 72% of subjects who received placebo. The results from the logistic regression for the proportion of subjects requiring reinstatement of L-dopa following a reduction in dose are provided in Table 34 for the ITT population.

Table 34 Analysis of Subjects Requiring Reinstatement of L-Dopa Following a Reduction in Dose (ITT Population: Study 169)

Treatment	Proportion of Subjects Requiring Reinstatement[1]	Adjusted Odds Ratio[2]	95% CI for Odds Ratio[2]	P-value[2]
Ropinirole CR	14/191 (7%)	0.2	(0.09, 0.34)	<0.001
Placebo	49/174 (28%)			

Data Source: Section 13, Table 7.56 and Table 7.57.

1. Subject defined as requiring reinstatement with L-Dopa if, at any time during the trial excluding the 7-day down-titration period, their dose of L-Dopa was reinstated up to, or above, their baseline level.
2. Adjusted for country.

For the ITT population the adjusted odds ratio for ropinirole CR vs. placebo was 0.2 (95% CI: [0.09, 0.34], $p<0.001$), indicating a statistically significant benefit of ropinirole CR over placebo. The odds of a subject receiving placebo requiring reinstatement with L-dopa was 5 times that of a subject receiving ropinirole CR.

Summary statistics for the change from baseline in the dose of L-dopa at Week 24 LOCF are presented in Table 35.

Table 35 Summary Statistics for Change From Baseline in Daily Dose of L-Dopa (mg/day) at Week 24 LOCF (ITT Population: Study 169)

Dose of L-dopa Medication (mg/day)	Ropinirole CR N=201	Placebo N=190
Baseline Dose	**n=199**	**n=190**
Mean (SD)	824 (424.4)	776 (357.3)
Median (Min, Max)	800 (150, 3000)	700 (150, 2000)
Week 24 LOCF Dose	**n=201**	**n=190**
Mean (SD)	546 (378.0)	613 (349.3)
Median (Min, Max)	500 (50, 2750)	556 (100, 1800)
Change from Baseline to Week 24 LOCF	**n=199**	**n=190**
Mean (SD)	-278 (192.6)	-164 (163.9)
Median (Min, Max)	-250 (-1000, 0)	-125 (-688, 100)

Data Source: Section 13, Table 7.54 and Table 7.55.

At baseline, the mean daily dose of L-dopa was slightly higher in the ropinirole CR group than in the placebo group (mean: 824 mg/day vs. 776 mg/day). Over the course of the study there was a larger decrease in the daily dose of L-dopa in the ropinirole CR group than in the placebo group. At Week 24 LOCF the mean dose of L-dopa had decreased by 278 mg/day in the ropinirole CR group compared to 164 mg/day in the placebo group. A formal statistical analysis of the treatment difference for the change from baseline in daily dose of L-dopa was not conducted by the sponsor.

Reviewer Comment

- Interestingly, the % reduction of L-dopa dose from baseline to the end of the study (LOCF) was approximately 34 % for ropinirole CR and 21 % for placebo. Although the sponsor noted that a "formal statistical analysis of the treatment difference" was not conducted, I wonder if the sponsor conducted some "informal" statistical analysis and did not present this analysis because it was not statistically "positive" and consistent with the suggestion that ropinirole CR was exerting an effect substituting for the amount of L-dopa dosage that had been decreased.

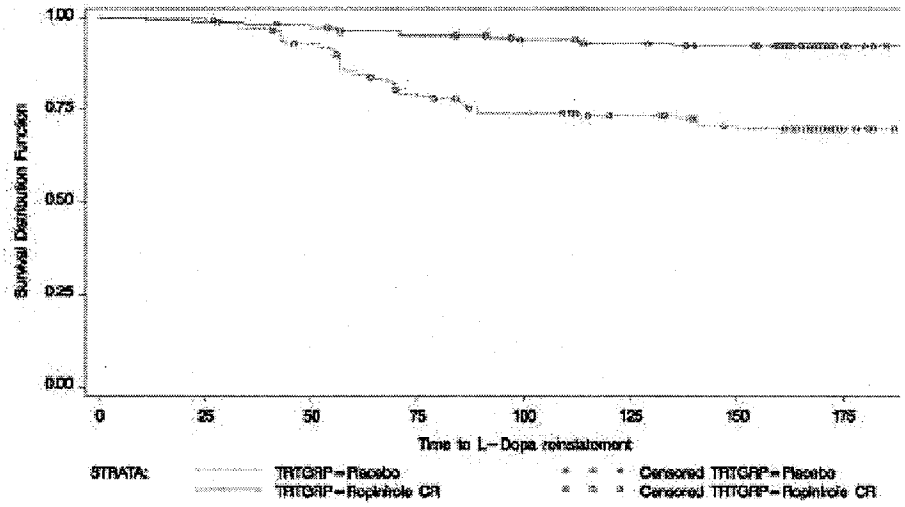
- The mean absolute reduction in daily L-dopa dose in the ER ropinirole group was greater than that in the placebo group (
- Table **35**). In addition, proportion of patients requiring reinstatement of L-dopa following L-dopa dose reduction was much higher (4 fold) for placebo (28 %) than for ER ropinirole (7 %) and the odd ratio for this action was statistically significant (Table 34). These results are consistent with the expected effect that would occur with the addition of therapeutically beneficial treatment such as might occur with ER ropinirole.

Time to Reinstatement of L-Dopa Following Reduction in Dose

The Kaplan Meier plot for the time to reinstatement of L-dopa following a reduction in dose for the ITT population is provided in Figure 7. A total of 26 subjects are excluded

from both this plot and the corresponding analysis (ropinirole CR: 10 subjects; placebo: 16 subjects) as they did not reduce their dose of L-dopa at any stage during the study.

Figure 7 Kaplan Meier Plot of Time to Reinstatement of L-Dopa following Reduction in Dose (ITT Population: Study 169)



Data Source: Section 13, Figure 7.3.
Time to L-dopa reinstatement is shown in days.

The median time to reinstatement of L-dopa could not be estimated for either treatment group as insufficient numbers of subjects required reinstatement of L-dopa. The assumption of proportional hazards was not violated therefore a Cox's proportional hazards model was fitted to the data. The results from the model for the time to reinstatement of L-dopa following a reduction in dose are provided in Table 36 for the ITT population.

Table 36 Adjusted Hazard Ratio and 95% Confidence Interval for the Time to Reinstatement of L-dopa Following a Reduction in Dose (Days) (ITT Population: Study 169)

Treatment Comparison	Adjusted Hazard Ratio[1]	95% CI for Hazard Ratio[1]	P-value[1]
Ropinirole CR vs. Placebo	0.2	(0.11, 0.37)	<0.0001

Data Source: Attachment 2.
1. Adjusted for country.

There was a statistically significant benefit of ropinirole CR over placebo for time to reinstatement of L-dopa following a reduction in dose. At any time point, subjects who received placebo were approximately 5 times more likely to require reinstatement with L-dopa than subjects who received ropinirole CR.

Other Efficacy Results

Change from Baseline in Total Mentation, Behavior and Mood Score of the UPDRS

In the ITT population, at baseline the mean total mentation, behavior and mood score of the UPDRS was approximately 2 points in each treatment group (the total score ranged from 0 to 16, where 0 represented normal/no symptoms and 16 represented worst possible case). At Week 24 LOCF, the mean total score had improved slightly by 0.6 points in the ropinirole CR group and 0.4 points in the placebo group indicating no treatment effect of ropinirole CR. A formal, adjusted analysis of change from baseline in total mentation, behavior and mood score of the UPDRS was not planned or conducted.

Questions 32, 33 and 34 of the UPDRS – Dyskinesia

Questions 32, 33 and 34 of the UPDRS asked subjects "What proportion of the waking day are dyskinesias present?", "How disabling are the dyskinesias?" and "How painful are the dyskinesias?" For each of these questions responses could range from 0 to 4. The responses to questions 32-34 were summed to give a total score for dyskinesia; the total score could range from 0 to 12. The scores were summed for the total score only if all questions 32-34 were answered.

Summary statistics for UPDRS questions relating to dyskinesias, and change from baseline is shown in
Table 37. This summary of data was retrospectively defined. At baseline the mean total score for questions 32, 33 and 34 of the UPDRS was similarly low in each treatment group (ropinirole CR: 1.0; placebo 1.2). At Week 24 LOCF the mean total score was 1.0 in each group. Overall, there was no meaningful change in the score over the course of the study.

Table 37 Summary Statistics for UPDRS Questions 32, 33 and 34 - Dyskinesias (ITT Population: Study 169)

UPDRS Question 32-34 Total Score[1]	Ropinirole CR N=201	Placebo N=190
Baseline Score	n=201	n=189
Mean (SD)	1.0 (1.58)	1.2 (1.64)
Median (Min, Max)	0.0 (0, 10)	0.0 (0, 9)
Week 24 LOCF Score	n=198	n=185
Mean (SD)	1.0 (1.33)	1.0 (1.56)
Median (Min, Max)	0.0 (0, 6)	0.0 (0, 9)
Change from Baseline to Week 24 LOCF[2]	n=198	n=184
Mean (SD)	-0.1 (1.39)	-0.2 (1.28)
Median (Min, Max)	0.0 (-10, 4)	0.0 (-6, 6)

Data Source: Section 13, Table 7.110 and Table 7.111.

1. For question 32 of the UPDRS subjects were asked "What proportion of the waking day are dyskinesias present?" and responses could range from 0 to 4. For question 33 of the UPDRS subjects were asked "How disabling are the dyskinesias?" and responses could range from 0 to 4. For question 34 of the UPDRS subjects were asked "How painful are the dyskinesias?" and responses could range from 0 to 4. Thus, the total score for questions 32-34 ranged from 0 (minimum) to 12 (maximum). The scores were summed for the total score only if all questions 32-34 were answered.
2. A decrease from baseline indicates an improvement.

Change From Baseline in Total UPDRS Score

In the ITT population, at baseline the mean total UPDRS score was 46.8 points in the placebo group and 45.5 points in the ropinirole CR group (the total UPDRS score ranges

from 0 to 176, where 0 represents normal/no symptoms and 176 represents worst possible case). At Week 24 LOCF, the mean total score had improved by 11.9 points in the ropinirole CR group and by 5.2 points in the placebo group. A formal, adjusted analysis of change from baseline in total UPDRS score was not planned or conducted.

Efficacy by Dose

Summary statistics for the change from baseline in the total awake time spent "off" at Week 24 LOCF, by dose at Week 24 LOCF, are shown in Table 38.

Table 38 Summary Statistics for Change from Baseline in Total Awake Time Spent "Off" at Week 24 LOCF by Dose (ITT Population: Study 169)

Change From Baseline in Total Awake Time Spent "Off" (Hours)[1]	Ropinirole CR N=201	Placebo N=190
2 mg	n=2	n=1
Mean (SD)	0.25 (0.707)	0.38 (NA[2])
Median (Min, Max)	0.25 (-0.3, 0.8)	0.38 (NA[2])
4 mg	n=2	n=3
Mean (SD)	1.38 (0.707)	1.92 (0.813)
Median (Min, Max)	1.38 (0.9, 1.9)	1.88 (1.1, 2.8)
6 mg	n=2	n=5
Mean (SD)	-2.25 (5.303)	-1.15 (3.358)
Median (Min, Max)	-2.25 (-6.0, 1.5)	-0.13 (-5.9, 2.3)
8 mg	n=19	n=6
Mean (SD)	-1.59 (3.236)	0.46 (2.980)
Median (Min, Max)	-1.50 (-7.8, 4.6)	0.56 (-3.8, 4.3)
12 mg	n=25	n=14
Mean (SD)	-3.03 (2.374)	-0.34 (3.597)
Median (Min, Max)	-3.38 (-6.0, 2.9)	0.44 (-11.4, 3.0)
16 mg	n=27	n=30
Mean (SD)	-2.26 (2.717)	-0.21 (3.892)
Median (Min, Max)	-2.38 (-7.5, 4.5)	0.00 (-13.4, 10.4)
20 mg	n=25	n=24
Mean (SD)	-1.56 (3.962)	-0.79 (2.137)
Median (Min, Max)	-1.38 (-9.9, 9.3)	-0.75 (-5.8, 4.0)
24 mg	n=99	n=107
Mean (SD)	-2.19 (3.291)	-0.45 (3.320)
Median (Min, Max)	-2.50 (-13.9, 11.5)	-0.63 (-12.0, 11.6)

Data Source: Section 13, Table 7.108.
1. A decrease from baseline indicates an improvement.
2. Not applicable (NA) as only one subject in the dosage group.

Reviewer Comment

- I will comment on the dose-related effect of ropinirole CR treatment (vs placebo) being well cognizant that dose-dependent effects are best generated from randomized, double-blind, placebo-controlled studies in which patients are randomized to one of several, fixed doses. In this study design, patients randomized to ropinirole CR were titrated to an optimal dose based upon the combined impression/assessment of efficacy and tolerability/safety/toxicity.

  Among the lowest doses, of ropinirole CR or placebo (i.e. 2,4,6, or 8 mg), there were relatively small numbers of patients at these dose levels in each group. If

one assesses the treatment effect (ropinirole CR – Placebo) at levels consisting of at least 10 patients/treatment, the mean treatment effect/difference for reduction of total "off" hours ranged from 0.8 to 2.8. **There was no clear suggestion of a dose-dependent benefit of ropinirole CR at a daily dose ≥ 8 mg.** Although the number of patients was quite small (N < 10) in either or both treatment groups at dose levels 6 and 8 mg/day, there was a question that ropinirole CR might be exerting a benefit at these relatively low levels such as 8 mg. At daily doses ranging from 8-24 mg, the mean treatment effect/difference (for decrease of "off" hours) was **generally relatively similar** and approaching approximately a 2 hour reduction in "off" hours. Interestingly, analyses of these data further raise the question that patients are being treated with excessive doses of ER ropinirole that are above the maximal therapeutic effect/benefit and would likely appear to expose these patients to excessive toxicity.

The sponsor did not make any comment or interpretation about these dose-related data.

- I raise the question about whether the sponsor should conduct a phase 4 study as post-marketing commitment to assess dose response for ER ropinirole. I am not aware that the sponsor has conducted any appropriate studies to characterize the dose-response curves for efficacy and safety as could be accomplished by conducing a randomized, double-blinded, placebo-controlled study in which parallel groups patients were randomized to one of several fixed doses of ER ropinirole and compared to placebo. Neither I am aware that the sponsor has ever conducted such appropriate studies to characterize the dose-response of IR ropinirole appropriately in a randomized, parallel group fixed dose study (vs placebo). **I think that making such a phase 4 post-marketing commitment with an approval for ER ropinirole would be highly desirable.**

  If a fixed dose study for ER ropinirole was requested as a phase 4 post-marketing commitment, I believe that such as study should be conducted in advanced Parkinson's Disease at the least, with consideration also given to the desirability of a similar study in early Parkinson's Disease.

  If a lower maximal recommended dose of ER ropinirole was suggest in these studies for patients with advanced and/or early Parkinson's Disease, the question would be raised about what to do for dosing patients with IR ropinirole.

Subgroup Analyses

Summary statistics for the change from baseline to Week 24 LOCF in total awake time spent "off" were submitted and presented by gender, by age group, by race, by country, by medication taken with or without food, by whether the subject entered the study pre or post amendment 1 and by prior exposure to dopamine agonists. A summary of the adjusted analysis for change from baseline in total awake time spent "off" for subjects who did and did not have prior exposure to ropinirole was presented earlier (Table 20).

For subgroups in which the numbers of subjects were sufficient to allow a meaningful interpretation of summary statistics, results for the change from baseline to Week 24 LOCF in total awake time spent "off" were similar to those observed for the total Population, with improvements observed in the ropinirole CR group compared to the placebo group. A summary of results for the subgroups of age, gender, pre- and post-amendment 1, and prior or no prior exposure to dopamine agonists, is shown in Table 39.

The sponsor noted that for the following subgroups, the number of subjects in at least one of the treatment groups was ≤ 10, and suggested that summary statistics should be interpreted with caution: race (subgroups of American/Hispanic, Arabic/North African, Black, East and South East Asian, Other); country (subgroups of Belgium, France, Italy, Spain); investigational
product taken without food; prior exposure to ropinirole. Thus, data for the subgroups of race, country, investigational product taken with/without food and prior exposure/no prior exposure to ropinirole are not presented in Table 39.

Table 39 Summary Statistics for Change from Baseline to Week 24 LOCF in Total Awake Time Spent "Off" (Hours) by Subgroup: (ITT Population: Study 169)

	Ropinirole CR N=201	Placebo N=190
All Subjects Mean (SD)	n=201 -2.1 (3.20)	n=190 -0.4 (3.25)
Gender		
Male Mean (SD)	n=117 -2.2 (3.36)	n=129 -0.4 (3.39)
Female Mean (SD)	n=84 -2.0 (2.99)	n=61 -0.3 (2.97)
Age Group		
18-64 years Mean (SD)	n=73 -2.0 (3.34)	n=78 -0.3 (3.05)
65-74 years Mean (SD)	n=93 -2.3 (3.31)	n=69 -0.3 (3.09)
≥75 years Mean (SD)	n=35 -1.8 (2.60)	n=43 -0.6 (3.89)
Pre- or Post-Amendment 1		
Pre-amendment 1 Mean (SD)	n=91 -2.1 (3.14)	n=82 0.1 (2.91)
Post-amendment 1 Mean (SD)	n=110 -2.2 (3.27)	n=108 -0.8 (3.46)
Prior exposure to Dopamine Agonists		
No prior exposure Mean (SD)	n=141 -2.1 (3.40)	n=129 -0.2 (3.19)
Prior exposure Mean (SD)	n=60 -2.1 (2.72)	n=61 -0.8 (3.37)

Section 13, Table 7.3, Table 7.4, Table 7.8 and Table 7.9.

Table 40 Effect of Treatment on Change of "OFF" Hours by Country

Country: Belgium

Visit		Placebo (N=9)	Ropinirole CR (N=7)
Week 24 LOCF	n	9	7
	Mean	-3.07	-1.88
	SD	5.862	3.771
	Median	-1.00	-2.50
	Min.	-13.4	-6.0
	Max.	4.3	4.5

Country: Czech Republic

Visit		Placebo (N=29)	Ropinirole CR (N=30)
Week 24 LOCF	n	28	30
	Mean	-0.92	-2.24
	SD	3.557	3.043
	Median	-0.63	-2.75
	Min.	-11.4	-7.5
	Max.	6.6	4.6

Country: France

Visit		Placebo (N=5)	Ropinirole CR (N=4)
Week 24 LOCF	n	5	4
	Mean	1.50	-3.84
	SD	3.160	2.953
	Median	0.63	-3.13
	Min.	-1.1	-7.8
	Max.	7.0	-1.4

Country: Hungary

Visit		Placebo (N=16)	Ropinirole CR (N=17)
Week 24 LOCF	n	16	17
	Mean	-1.02	-1.80
	SD	2.491	3.226
	Median	-0.94	-2.63
	Min.	-5.9	-7.0
	Max.	3.4	6.3

Country: Italy

Visit		Placebo (N=10)	Ropinirole CR (N=10)
Week 24 LOCF	n	10	10
	Mean	-1.71	-1.38
	SD	3.360	3.056
	Median	-2.69	-1.81
	Min.	-5.8	-5.3
	Max.	4.6	3.6

Country: Poland

Visit		Placebo (N=90)	Ropinirole CR (N=82)
Week 24 LOCF	n	80	82
	Mean	0.11	-2.09
	SD	2.539	2.475
	Median	-0.38	-2.00
	Min.	-5.4	-9.0
	Max.	11.6	2.5

Country: Spain

Visit		Placebo (N=2)	Ropinirole CR (N=3)
Week 24 LOCF	n	2	3
	Mean	3.19	-2.63
	SD	10.165	5.349
	Median	3.19	-5.00
	Min.	-4.0	-6.4
	Max.	10.4	3.5

Country: United States

Visit		Placebo (N=40)	Ropinirole CR (N=48)
Week 24 LOCF	n	40	48
	Mean	-0.27	-2.17
	SD	3.113	4.250
	Median	0.13	-2.56
	Min.	-9.4	-13.9
	Max.	6.9	11.5

Reviewer Comment

- The subgroup analyses shown in Table 39 suggest generally similar effects in all the respective subgroups and do not suggest any significant effect of any of these subgroup variables in the primary efficacy endpoint.

- Dr. Yam, the primary statistical reviewer, conducted independent analyses (see Statistical Review by Dr. Yam for additional details) for the primary efficacy endpoint for subgroups based upon gender and age and found similar results as shown in the analyses conducted by the sponsor (Table 39).

- Table 40 shows the effect of treatment in all countries on the primary efficacy endpoint. Ropinirole CR appeared to be show a "substantial" numerical benefit (e.g. $\geq$ mean 0.8 hrs reduction in "off" hours from baseline) in most countries (Czech Republic, France, Hungary, Poland, Spain, U.S.) but did not show an apparent treatment benefit in patients treated in Belgium or Italy. Although the number of patients in each treatment group was relatively small (i.e. N $\leq$ 10) in Belgium and Italy, the number of patients was even smaller in each treatment group (i.e. N $\leq$ 5) in France and Spain that showed a treatment difference/benefit of > 5.3 hours reduction in "off" hours compared to baseline. There is no readily apparent explanation for these observations.

  Of significance and relevance to our review of NDA 22008, the mean treatment difference/benefit in the U.S. was – 1.9 hours, a value similar to that of the primary ITT analysis (- 1.7 hours) for all relevant patients in all countries. Of additional relevance, relatively large numbers of patients were enrolled in each treatment group (N = 48 ropinirole CR; N = 40 Placebo) in the U.S. Overall, patients treated in the U.S. accounted for ~ 23 % of all patients included in the primary ITT analysis of the primary efficacy endpoint. This clear therapeutic benefit of ER ropinirole in a substantial percentage of all randomized and treated patients treated in the U.S. is clearly a desirable result that contributes significantly toward considering an approval of ER ropinirole in the U.S.

6.1.4.2 Study 168 Efficacy Findings

The disposition of all randomized subjects is summarized in Table 41.

Table 41 Summary of Subject Disposition (All Subjects: Protocol SK&F-101468/168)

Study Stage / Population	Total	
	n	(%)
Randomised	161	(100)
Completed Week 36	123	(76)
Received at least one dose of investigational product (Safety population)	161	(100)
Received at least one dose of investigational product and attended at least one post-baseline assessment (ITT population)	161	(100)

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

A total of 161 subjects were randomized to the study and received at least one dose of investigational product. A total of 128 subjects received both ropinirole IR and ropinirole CR, 12 subjects received ropinirole CR only and 21 subjects received ropinirole IR only. Thus, overall 140 subjects were exposed to ropinirole CR and 149 subjects were exposed to ropinirole IR.

Subjects in the Safety population (i.e. those who received at least one dose of investigational product) who discontinued from the study prematurely are summarized in Table 42, by reason for withdrawal.

Table 42 Summary of Study Discontinuation (Safety Population: Protocol SK&F-101468/168)

	Total N=161	
	n	(%)
Completion Status		
Completed	123	(76)
Prematurely Discontinued	38	(24)
Primary Reason for Premature Discontinuation [1]		
Adverse Event	14	(9)
Subject Decided to Withdraw	10	(6)
Lack of Efficacy	5	(3)
Lost to Follow-up	1	(<1)
Other [2]	8	(5)

Data Source: Section 12, Table 6.2.

1. Primary reason, as documented by the investigator on the end of study record.
2. Other reasons for discontinuation included: (i) subject not having a stable UPDRS score at the end of the 12-week up-titration period (6 subjects); (ii) Week 12 UPDRS score (1 subject); (ii) decided by clinician (1 subject).

Of the 161 subjects in the Safety population, 38 (24%) were discontinued from the study

prematurely. The most common reason for premature discontinuation was adverse event, which was cited as the *primary* reason for discontinuation on the end of study record for 14 subjects (9%).

Protocol Deviations Leading to Exclusion from PP Population

Subjects with one or more major protocol deviations (defined in protocol) were excluded from the PP population and analysis. The number (%) of subjects in the ITT population with major protocol deviations leading to exclusion from the PP population are summarized in

Table 43 Number of Subjects with Protocol Deviations Leading to Exclusion From the PP Population (ITT Population: Protocol SK&F101468/168)

	Total N=161	
	n	(%)
Subjects with at Least One Protocol Deviation Leading to Exclusion[1]	47	(29)
Hoehn & Yahr criteria not stage I-III at screening	2	(1)
Not 80-120% investigational product compliant during maintenance period 1	7	(4)
Not 80-120% investigational product compliant during maintenance period 2	7	(4)
Not 80-120% investigational product compliant during maintenance period 3	6	(4)
Missed >3 consecutive days of investigational product	14	(9)
Took significant amount of prohibited concomitant medication	11	(7)
Did not achieve stable UPDRS score during up-titration [2]	20	(12)

Data Source: Section 12, Table 6.4.

1. Subjects may have had more than one protocol deviation leading to exclusion.
2. Of the 20 subjects who did not achieve a stable UPDRS score during up-titration, 10 were subsequently withdrawn from the study, although all of these subjects entered maintenance period 1 for at least a short period of time. The primary reasons for withdrawal for these 10 subjects were as follows: non-stable UPDRS score: 6 subjects; lack of efficacy: 1 subject; lost to follow-up: 1 subject; subject decided to withdraw: 2 subjects.

The most common protocol deviation leading to exclusion from the PP population was that subjects did not achieve a stable UPDRS score during up-titration (20 subjects, 12%). No subject had a minor protocol deviation, defined as a deviation that did not lead to exclusion from the PP population.

Demographics and Other Baseline Characteristics

Demographic characteristics for the PP population are summarized in As this is a cross-over study, subjects act as their own controls and hence, comparisons between treatment groups are not necessary.

Table 44 Summary of Demographic Characteristics (PP Population: Protocol SK&F-101468/168)

	Total N=114	
Age (years)		
Mean (SD)	60.3 (9.83)	
Median (Range)	62.0 (37 – 84)	
Age Group	**n**	**(%)**
18-64	77	(68)
65-74	29	(25)
≥ 75	8	(7)
Sex	**n**	**(%)**
Female	52	(46)
Male	62	(54)
Race	**n**	**(%)**
White/Caucasian	111	(97)
Black	1	(<1)
Arabic/North African	1	(<1)
American Hispanic	1	(<1)

Data Source: Section 12, Table 6.7.

The demographic characteristics of all three populations (Safety, ITT, PP; as defined in study 169) were similar.

Baseline Characteristics

Parkinson's Disease History

A summary of subjects' Parkinson's disease history at screening for the PP population is shown in Table 45.

Table 45 Summary of Parkinson's Disease History at Screening (PP Population: Protocol SK&F-101468/168)

	Total N=114	
Age of Onset of PD (years) [1]		
Mean (SD)	57.5 (10.21)	
Median (Range)	58.0 (33 – 81)	
Disease Duration (years) [1]		
Mean (SD)	2.70 (2.442)	
Median (Range)	2.00 (0.0 – 12.0)	
Hoehn & Yahr	**n**	**(%)**
Stage I	23	(20)
Stage I.5	29	(25)
Stage II	46	(40)
Stage II.5	10	(9)
Stage III	6	(5)
Stage IV	0	
Stage V	0	

Data Source: Section 12, Table 6.18.

1. Reported values for age at onset and disease duration were rounded to one decimal place.

The Parkinson's disease history for all three populations (PP, ITT and Safety) were similar, with the exception that in that ITT and Safety populations, one subject met the Hoehn & Yahr criteria for Stage IV disease and one subject met the Hoehn & Yahr criteria for Stage V disease; these 2 subjects were excluded from the PP population as they were major protocol violators.

Prior Pharmacotherapy for Parkinson's Disease

Prior medications for Parkinson's disease that were taken up to 30 days prior to the start date of investigational product were received by 52% of subjects in the Safety population. A summary of the number (%) of subjects who received the most common (≥ 5%) prior medications for Parkinson's disease is presented in Table 46.

Table 46 Number (%) of Subjects Who Received the Most Common (Greater Than or Equal to 5%) Prior Medications for Parkinson's Disease (Safety Population: Protocol SK&F-101468/168)

	Total N=161	
Ingredient	n	(%)
Any Prior Parkinson's Disease Medication	**84**	**(52)**
Selegiline hydrochloride	24	(15)
Selegiline	23	(14)
Amantadine sulphate	20	(12)
Pramipexole	14	(9)
Biperiden hydrochloride	11	(7)
Amantadine hydrochloride	8	(5)
Levodopa+carbidopa	8	(5)

Data Source: Section 12, Table 6.16.

Ongoing treatment with certain Parkinson's disease medications (e.g. selegiline, amantadine, and anti-cholinergics such as biperiden hydrochloride) was permitted, provided the dose was stable for at least 4 weeks prior to screening and throughout the study. Subjects previously treated with moderate to low doses of any L-dopa preparation (for up to 3 months in total) or with a dopamine agonist (for up to 6 months in total) must have discontinued such treatment a minimum of two weeks prior to screening. No prior exposure to ropinirole (marketed by GlaxoSmithKline as REQUIP) was permitted.

Prior Dopamine Agonist Medications

Prior dopamine agonists were received by 14% of subjects in the Safety population. Any dopamine agonist treatment within 2 weeks of study start was not permitted. A summary of the number (%) of subjects who received prior dopamine agonists is presented in Table 47.

Table 47 Number (%) of Subjects Who Received Prior Dopamine Agonist Medications (Safety Population: Protocol SK&F-101468/168)

	Total N=161	
Ingredient	n	(%)
Any Dopamine Agonist	**23**	**(14%)**
Pramipexole	14	(9)
Piribedil	5	(3)
Cabergoline	2	(1)
Bromocriptine	1	(<1)
Pergolide	1	(<1)

Data Source: Section 12, Table 6.15.

On-Treatment Concomitant Medications

On-treatment concomitant medications were received by 87% of subjects in the Safety population. The most frequently used classes of concomitant medications were those for the nervous system, used by 70% of subjects and those for the cardiovascular system, used by 58% of subjects. Individual on-treatment concomitant medications received by ≥ 10% of subjects are summarized in Table 48 shows the most common concomitant medications used during the study.

Table 48 Number (%) of Subjects Who Received the Most Common (Greater Than or Equal to 10%) On-Treatment Concomitant Medications (Safety Population: Protocol SK&F-101468/168)

	Total N=161	
Ingredient	n	(%)
Any On-Treatment Medication	**140**	**(87)**
Acetylsalicylic acid	35	(22)
Selegiline hydrochloride	25	(16)
Selegiline	22	(14)
Amantadine sulphate	20	(12)
Paracetamol	16	(10)

Data Source: Section 14, Table 8.29.

Subjects who took significant amounts of prohibited concomitant medications were excluded from the PP population (a list of prohibited medications had been specified). A total of 11 subjects (7%) were excluded from the PP population for this reason.

Treatment Compliance

To be overall compliant for a particular maintenance period, the subject must have a tablet compliance of ≥ 80% and ≤120% for ropinirole CR (or matching placebo) and ropinirole IR (or matching placebo), and must not have missed > 3 consecutive days of investigational product.

In the ITT population, overall compliance was higher for subjects receiving ropinirole CR compared to ropinirole IR for each maintenance period. For maintenance period 1, overall compliance was achieved for 97% of subjects for ropinirole CR and 92% of subjects for ropinirole IR. For maintenance period 2, overall compliance was achieved for 97% of subjects for ropinirole CR and 88% of subjects for ropinirole IR. For maintenance period 3, overall compliance was achieved for 97% of subjects for ropinirole CR and 90% of subjects for ropinirole IR. In the PP population, all subjects met the definition for overall compliance in each maintenance period (non-compliant subjects were excluded from the PP population).

Timing of Dosing In Relation to Food

No instructions were given in the protocol regarding the timing of dosing with regard to food. However, at study conclusion, investigators asked subjects if they generally took investigational product within 2 hours of a meal, or not. Overall, 154 subjects (96%) reported that they took their investigational product within 2 hours of a meal.

Titration of Dose

Summary statistics for the dose of each ropinirole treatment at the end of each study period, by sequence, are shown in Table 49.

Table 49 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.

During the 12-week up-titration period, subjects randomized to receive ropinirole CR were able to titrate to a higher dose more quickly than subjects randomized to receive ropinirole IR (Table 49). The increased speed of up-titration for ropinirole CR was due to the faster titration schedule for this formulation and the tolerability of ropinirole CR. Thus, at the end of the up-titration period, subjects receiving ropinirole CR achieved a mean dose of approximately 18 mg/day overall, compared to a mean of approximately 7 mg/day for subjects receiving ropinirole IR. At the end of the 12-week titration phase subjects who had achieved a stable UPDRS motor score began the first 8-week flexible

dose maintenance period with the same formulation that they received during the up-titration phase. At the end of maintenance period 1 the mean dose of ropinirole CR was very similar to that observed at the end of the up-titration period (18.0 mg/day at Week 12 and 18.6 mg/day at Week 20 LOCF), whereas for ropinirole IR, there had been a slight increase in the mean dose (from 7.0 mg/day at Week 12 to 8.9 mg/day at Week 20 LOCF). The changes in the average dose at the end of each of the maintenance period can be explained by the different treatment sequences that subjects received and the fact that when subjects switched between formulations, as far as practically possible, the total daily dose of ropinirole remained constant. At the end of maintenance period 1 at Week 20, 50% of patients switched formulation for the first time. Thus, for subjects who had been receiving the CR formulation up to the end of maintenance period 1, half of these continued with a relatively high dose of CR, but half were replaced by subjects switched from a relatively low dose of IR to an equivalent low dose of CR (see Table 49). Thus, the overall mean CR dose at the end of maintenance period 2 (14.0 mg/day) moderately lower than at the end of maintenance period 1 (18.6 mg/day). Similarly, at the end of maintenance period 2, the remaining CR subjects switched formulation. Thus, the remaining 50% of subjects receiving a relatively high dose of CR were now replaced by subjects switched from a relatively low dose of IR to an equivalent low dose of CR. Thus the overall mean dose for the CR formulation at the end of maintenance period 3 (9.6 mg/day) was lower than at the end of maintenance period 2 (14.0 mg/day). For the IR group the reverse happened, thus the overall mean dose for the IR formulation increased from the end of maintenance period 1 (8.9 mg/day) to period 2 (13.9 mg/day) to period 3 (18.8 mg/day).

Reviewer Comment

- It is interesting and noteworthy was that CR dose at end of titration much higher than IR. If these formulations that show a similar PK profile at steady state exerted a similar therapeutic benefit and toxicity, one would expect that ultimately the titrated doses of ropinirole would be similar for each formulation if this was conducted under blinded conditions, as it supposedly was. Regardless that the titration rate was greater for CR vs IR, if the pharmacodynamic actions at PK steady state were similar for efficacy and safety/toxicity, I would expect that patients should have ultimately ended up at similar doses for each formulation. I think that this observation raises the question/specter that the IR formulation could more effective on a mg per mg basis comparison.

EFFICACY RESULTS

Change from Period Baseline in UPDRS Total Motor Score

Non-Inferiority Assessment (Per Protocol Population)
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 Table 50. A plot of the mean UPDRS total motor score at each time point is shown in Figure 8.

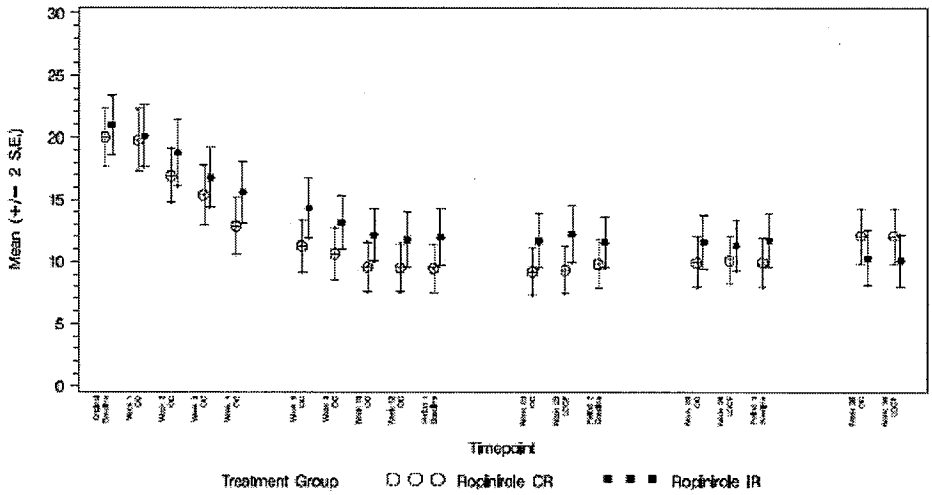
Table 50 Summary Statistics for Change from Period Baseline in UPDRS Total Motor Score at Each Time point (PP Population: Protocol SK&F-101468/168)

	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.

Figure 8 Mean (± 2 Standard Error Bars) UPDRS Total Motor Score at Each Time point (PP Population: Protocol SK&F-101468/168)



Data Source: Section 13, Figure 7.1.
Note: spacing between weeks is not evenly distributed.

During the initial 12-week up-titration period, there was an improvement in the UPDRS total motor score for both for formulations. The pattern (Figure 8) of the changes in the UPDRS motor score appeared similar and the changes in each formulation appeared to be parallel to each other. The sponsor noted that the magnitude of this improvement was greater for subjects receiving ropinirole CR compared to ropinirole IR; at the end of the up-titration period (Week 12 OC) because the mean UPDRS total motor score had improved by 10.4 points for subjects receiving ropinirole CR and by 8.9 points for subjects receiving ropinirole IR. The sponsor suggested that efficacy in terms of the UPDRS total motor score appears to be dose related rather than formulation related considering that there were supposedly greater improvements observed with higher total daily doses and lesser improvements observed with lower total daily doses, irrespective of formulation.

Summary statistics for the change from period baseline in UPDRS total motor score at the end of each period (Titration, Maintenance 1, Maintenance 2, Maintenance 3) in the PP and ITT populations and for observed case (OC) and LOCF data analyses were very similar to the changes reflected in
Table **50**. There was little difference for OC vs LOCF analyses and for the ITT vs PP populations.

Analysis of Covariance
The overall adjusted mean change from period baseline, treatment difference, confidence interval (CI) and p-value for the UPDRS total motor score are shown in Table 51. A total of 276 observations were included in this analysis.

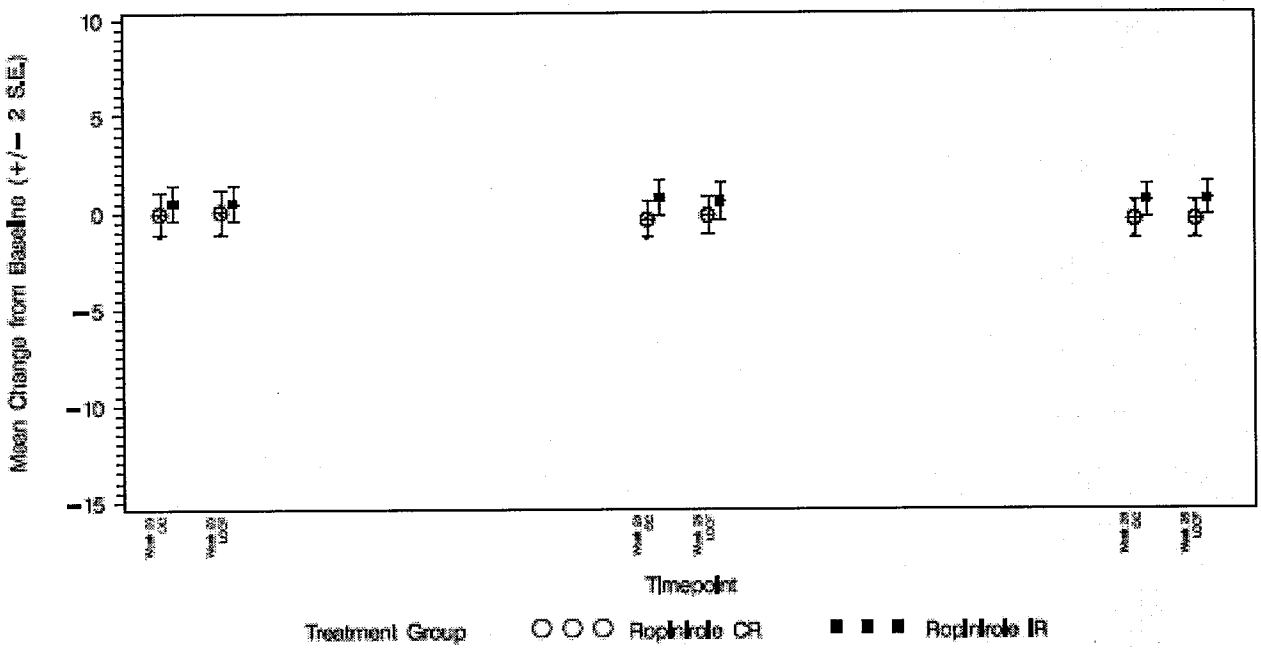
Table 51 Adjusted Analysis of Change from Period Baseline in UPDRS Total Motor Score (PP Population: Protocol SK&F-101468/168

	Adjusted[1] Mean (SE) Change from Period Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Ropinirole CR	-0.1 (0.28)	-0.7	(-1.51, 0.10)	0.0842
Ropinirole IR	0.6 (0.30)			

Data Source: Section 13, Table 7.3.
1. Adjusted for period, carry over effect and period baseline score. Subject was fitted as a random term.
2. A decrease from period baseline indicates an improvement.

The 95% CI for the treatment difference was (-1.51, 0.10). As the upper limit of the 95% CI was less than the pre-defined threshold of 3 points, ropinirole CR was demonstrated to be non-inferior to ropinirole IR.

Figure 9 **Mean Change from Baseline (± 2 SE) in Total Motor Score of UPDRS for IR and ER Ropinirole for Observed Case vs LOCF Analyses (Maintenance Periods 1, 2, and 3 Only)**



Robustness of the Primary Analysis

Fixed Effects Model

In order to assess the sensitivity of the primary analysis to the effects of missing data, a fixed effects model was fitted to the data. For this model, subject was included as a covariate (a fixed effect) instead of as a random term. A total of 276 observations were included in this analysis. The results from this analysis supported those obtained from the primary analysis (treatment difference: -0.5; 95% CI: (-1.16, 0.21); p-value: 0.1728), i.e. ropinirole CR was demonstrated to be non-inferior to ropinirole IR. To further support the results of the primary analysis utilizing the LOCF data, the mixed model was refitted using the OC data. A total of 264 observations were included in this analysis. The results from this analysis using OC data were similar as the above analysis utilizing LOCF data and supported results obtained from the primary analysis (treatment difference: -0.9; 95% CI: (-1.69, -0.07); p-value: 0.0331), i.e. ropinirole CR was demonstrated to be non-inferior to ropinirole IR.

Superiority Assessment (Intent-to-Treat Population)

As non-inferiority for the primary endpoint was demonstrated in the PP population, the superiority of ropinirole CR to ropinirole IR could be assessed. Primary inference with regards to the superiority of ropinirole CR compared to ropinirole IR is based on the LOCF dataset for the ITT population. The results from the analysis of covariance for the change from period baseline in the UPDRS total motor score are provided in **Table 54 for** the ITT population. A total of 371observations were included in this analysis. By this

analysis CR showed a -0.6 difference but this difference vs not statistically significant and did not suggest that CR was superior to IR ropinirole.

Table 52 Adjusted Analysis of Change from Period Baseline in UPDRS Total Motor Score at Each Time point (ITT Population: Protocol SK&F-101468/168)

	Adjusted[1] Mean (SE) Change from Period Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Ropinirole CR	-0.2 (0.24)	-0.6	(-1.28, 0.12)	0.1053
Ropinirole IR	0.4 (0.25)			

Data Source: Section 13, Table 7.6.
1. Adjusted for period, carry over effect and period baseline score. Subject was fitted as a random term.
2. A decrease from period baseline indicates an improvement.

Change From Original Baseline in UPDRS Total Motor Score at Week 20 LOCF

In order to further investigate the improvement from original baseline in the UPDRS total motor score for each formulation, **a retrospectively defined analysis** of covariance was conducted for data collected at Week 20 LOCF (i.e. up to the time of the first switch in ropinirole formulations). Up to this time point, subjects had been receiving only ropinirole CR or ropinirole IR. The results from the analysis of covariance for the change from original baseline in the UPDRS total motor score at Week 20 LOCF are provided in Table 53 for the ITT population. The 95% CI for the treatment difference between ropinirole CR and ropinirole IR at Week 20 LOCF was (-3.77, 0.05) (p=0.0565). Although in favor of ropinirole CR, this treatment difference was not statistically significant.

Table 53 Adjusted Analysis of Change from Original Baseline in UPDRS Total Motor Score at Week 20 LOCF (ITT Population: Protocol SK&F-101468/168)

	Adjusted[1] Mean (SE) Change from Period Baseline[2]	Adjusted[1] Treatment Difference	95% CI for Treatment Difference	P-Value
Ropinirole CR	-10.6 (0.71)	-1.9	(-3.77, 0.05)	0.0565
Ropinirole IR	-8.8 (0.69)			

Data Source: Section 13, Table 7.37.
1. Adjusted for original baseline and country.
2. A decrease from period baseline indicates an improvement.

Reviewer Comment

- Although the sponsor attempted to make a comparison of ER ropinirole vs IR, primarily to show that ER is not inferior to IR, I think that it is difficult to make this comparison given the marked difference in the "optimal" dose of ropinirole achieved under blinded conditions with each formulation. Table 49 shows that the daily dose of ER ropinirole (~ 18 mg) was typically approximately twice that for IR ropinirole (~ 9 mg). I consider the study design utilized as not ideal for showing non-inferiority of the new ER ropinirole formulation. Clearly, a better way to compare the efficacy of these formulations would have been to conduct a

randomized, double-blind, controlled study in which patients were randomized to several, identical fixed doses of each formulation.

- **Overall, I consider that study 168 showed that the efficacy produced by ER ropinirole vs IR (without consideration of dose) was quite similar with respect to improving the UPDRS motor score in early Parkinson's Disease.** However, given the fact that the dose of ER ropinirole was approximately twice that of IR for the titration period and maintenance period 1, these data suggest some interesting possibilities. First, IR is more potent that ER ropinirole on a mg per mg basis. Second, the "optimal" titrated dose of ER ropinirole achieved was excessive because a lower dose similar to that achieved for the IR formulation may have produced the same efficacy. Third, the rate of titration ultimately affects the "optimal" dose achieved/selected considering that patients who underwent a slower titration rate with IR "selected" a much lower than the much higher dose of patients treated with ER ropinirole and who underwent a more rapid/aggressive titration.

  However, there was relatively little change in the UPDRS motor score for either formulation as the study progressed and the mean dose for ER ropinirole progressively decreased through the subsequent, maintenance phases (titration-18.0 mg, maintenance period #1-18.8 mg, maintenance period #2-14.0 mg, maintenance period #3-9.6mg) and the mean dose of IR ropinirole progressively increased through the subsequent, maintenance phases (titration-7.0 mg, maintenance period #1-8.9 mg, maintenance period #2-13.9 mg, maintenance period #3-18.8 mg). I interpret these data as arguing against a difference potency of each formulation but rather supporting the second and third possibilities outlined above here. Thus, I think that there is evidence suggesting the reasonably good possibility of excessive dosing occurring with both formulations by recommending daily dosing up to 24 mg. I also think that the more aggressive titration scheme utilized for ER ropinirole increases the chance of titrating to higher than necessary dose that could potentially be associated with excess toxicity and no additional clinical/therapeutic benefit than might be experienced by following the slower titration recommended for IR ropinirole.
- Table **50** showed the primary efficacy endpoint data for CR vs IR but did not show these results according to each of the 4 specific dosing schemes for the maintenance periods as shown in Table 49. I have asked the sponsor to submit results of the 4 dosing schemes showing similar columns as in Table 49 for the efficacy data (for observed case and LOCF data for both the PP and ITT populations) shown in Table 50.

- Although the data in Table 53 shows the change of the UPDRS motor score for each formulation over 20 weeks using a 12 week titration phase and 8 week maintenance phase. This analysis would be more comparable to results of a simple, conventional Parkinson's Disease study of 3-6 months study duration. It also relevant to note that the adjusted mean change from baseline of 10.6 and 8.8

for ER and IR ropinirole, respectively does not have a placebo group to indicate the true magnitude of the treatment effect/difference.

- I am not sure that the margin (i.e. 3) selected for showing non-inferiority was appropriate. I question whether this margin was too large and where a smaller margin may have been more appropriate. Two recently approved drugs (rotigotoine, rasagiline) for early Parkinson's Disease showed treatment effects difference/ (drug – placebo) that were < 3. The treatment effect/difference for the UPDRS motor score change from baseline for the lowest recommended dose of rotigotine was -2.3 after approximately 3 months treatment. The treatment effect/difference for the UPDRS motor score change from baseline for 1 mg rasagiline was -2.3 after approximately 6 months treatment.

- Given the results described and discussed above, I raise the question that the dosing regimen of any "optimal" daily dose of ER ropinirole up to 24 mg may be facilitating excessive dosing whereby patients may be receiving excessive doses that do not provide any additional benefit over a lower dose but are only be exposed to increased risk of toxicity. **I think that the DNP should require that the sponsor make a phase 4 commitment to characterize the dose-response curve for efficacy and safety for at least ER ropinirole.** Ideally, this could be accomplished by conducting a randomized, double-blind, placebo-controlled, parallel group study in which patients are randomized to one of several, fixed daily doses of ER ropinirole (ideally 6, 12, 18, 24 mg; but at least 8, 16, 24 mg) or placebo. Such a study could also include similar daily dosing arms for IR ropinirole. If, so, such a study would not only characterize the dose-response curve for efficacy and safety for each formulation but would also permit an appropriate comparison of the efficacy and safety of each formulation. Although formal sample size estimates would be necessary to assess the appropriate sample size for each arm, I would not be surprised if such a 9 arm (placebo, 6, 12, 18, 24 mg for ER ropinirole , and 6,12,18, and 24 mg for IR ropinirole might be feasible with ~50-60 patients/arm.

- Ideally, it would be desirable to know the dose-response curves for efficacy and safety for both early and advanced Parkinson's Disease with each formulation. Considering that the 3 pivotal studies supporting approval of IR ropinirole were all flexible, titration studies, it is also possible the ideal, appropriate dosing is not known for the IR formulation and a dedicated study characterizing dose-response might suggest a different dosing range than is different from the tremendously wide (e.g., 32 fold difference from lowest to highest dose), recommended daily dose range from 0.75 mg to 24 mg for the IR formulation. All that seems to be known is that pivotal studies showed that patients treated with this dose range experienced efficacy relative to placebo. If a dose-response data derived from a fixed dose study characterize the appropriate dosing (lowest effective dose and maximally recommended dose) in a specific population (e.g. advanced Parkinson's Disease) for a specific formulation, it would not necessarily be

appropriate to extrapolate that dosing to a different formulation or population other than to the formulation and to the population studied.

Other Efficacy Endpoints

Total UPDRS Score

The total UPDRS score scale ranged from 0 to 176 points, where 0 represented normal/no symptoms and 176 represented the worst possible case. The mean (SD) UPDRS score at original baseline was 29.2 (13.38) for ropinirole CR and 29.8 (12.20) for ropinirole IR.

The change from baseline for the titration phase and for each maintenance period (using the beginning of the maintenance period as the new "baseline" for CR and IR ropinirole is shown in Table 54. At the end of the up-titration period, at Week 12 OC, there was an improvement in the total UPDRS score for both formulations. The mean improvement in total score was 13.7 points for ropinirole CR and 12.4 points for ropinirole, quite similar effects, despite using nearly twice the mean dose or ropinirole for the CR formulation as for the IR formulation. There was then little further change in scores on this scale over maintenance periods 1, 2 or 3. The total UPDRS score and change from baseline for this score are driven largely by the UPDRS total motor score and to a lesser extend by the UPDRS ADL score.

Table 54 Summary Statistics for the Change from Period Baseline in the Total UPDRS Score

Period	Visit		Ropinirole CR (N=140)	Ropinirole IR (N=149)
Up-Titration	Week 1 OC	n	71	79
		Mean	-0.5	-1.7
		SD	4.19	4.02
		Median	0.0	-0.1
		Min.	-10	-17
		Max.	12	10
	Week 2 OC	n	71	79
		Mean	-3.4	-3.5
		SD	5.08	4.21
		Median	-2.0	-3.0
		Min.	-15	-16
		Max.	10	5
	Week 3 OC	n	71	79
		Mean	-6.5	-5.7
		SD	7.09	5.37
		Median	-5.8	-5.0
		Min.	-25	-19
		Max.	9	9
	Week 4 OC	n	71	79
		Mean	-9.4	-7.2
		SD	8.54	5.69
		Median	-9.0	-7.0
		Min.	-42	-20
		Max.	10	5
	Week 6 OC	n	71	77
		Mean	-11.0	-8.8
		SD	8.64	7.71
Up-Titration	Week 6 OC	Median	-10.0	-8.0
		Min.	-47	-26
		Max.	1	15
	Week 8 OC	n	72	78
		Mean	-12.3	-10.4
		SD	8.91	7.68
		Median	-11.6	-10.0
		Min.	-48	-29
		Max.	0	8
	Week 10 OC	n	72	77
		Mean	-13.4	-12.1
		SD	9.05	8.59
		Median	-13.0	-11.0
		Min.	-48	-34
		Max.	0	8
	Week 12 OC	n	70	78
		Mean	-13.7	-12.4
		SD	9.33	8.49
		Median	-13.0	-11.0
		Min.	-48	-34
		Max.	2	8
Maintenance Period 1	Week 20 OC	n	63	63
		Mean	-0.2	0.3
		SD	4.79	4.32
		Median	0.0	0.0
		Min.	-10	-8
		Max.	18	26
Maintenance Period 1	Week 20 LOCF	n	66	70
		Mean	-0.1	0.5
		SD	4.78	4.22
		Median	0.0	0.0
		Min.	-10	-8
		Max.	18	26
Maintenance Period 2	Week 28 OC	n	64	50
		Mean	-0.2	0.5
		SD	5.49	3.53
		Median	0.0	0.0
		Min.	-22	-8
		Max.	15	12
	Week 28 LOCF	n	67	53
		Mean	0.3	0.4
		SD	6.41	3.56
		Median	0.0	0.0
		Min.	-22	-8
		Max.	26	12
Maintenance Period 3	Week 36 OC	n	55	45
		Mean	-0.1	0.4
		SD	4.89	3.40
		Median	0.0	0.0
		Min.	-11	-6
		Max.	15	9
	Week 36 LOCF	n	56	49
		Mean	-0.1	0.5
		SD	4.95	3.36

Efficacy by Dose

UPDRS Total Motor Score and Dose at the End of Each Maintenance Period

The relationship between UPDRS total motor score and dose at the end of each maintenance period is shown in Table 55.

Table 55 Mean UPDRS Total Motor Score and Dose at the End of Each Maintenance Period (Protocol SK&F-101468/168)

	Ropinirole CR [1]		Ropinirole IR [1]	
	UPDRS Total Motor Score [2]	Mean Daily Dose	UPDRS Total Motor Score [2]	Mean Daily Dose
Week 20 LOCF	n=67 10.5	n=71 18.6 mg	n=73 12.9	n=79 8.9 mg
Week 28 LOCF	n=72 11.1	n=74 14.0 mg	n=56 11.3	n=60 13.9 mg
Week 36 LOCF	n=58 12.3	n=64 9.6 mg	n=50 11.3	n=62 18.8 mg

Data Source: Section 12, Table 6.12 and Section 13, Table 7.4.

1. The mean daily dose was calculated for the Safety population. The mean UPDRS total score was calculated for the ITT population. It should be noted that the numbers of subjects (n) used to calculate the UPDRS total motor score at each timepoint are lower than the numbers used to calculate the mean daily dose, despite the overall number of subjects in each population being the same. This is due to the fact that fewer subjects had a UPDRS total motor score available during each period, than a mean daily dose.
2. The total motor score of the UPDRS ranges from 0 to 108, where 0=normal/no symptoms and 108=worst possible case.

A similar UPDRS motor score was observed when subjects were treated with a comparable lower dose of either formulation (12.3 points at a mean CR dose of 9.6 mg/day; 12.9 points at a mean IR dose of 8.9 mg/day), a comparable higher dose of either formulation (10.5 points at a mean CR dose of 18.6 mg/day; 11.3 points at a mean IR dose of 18.8 mg/day) or a comparable intermediate dose of either formulation (11.1 points at a mean CR dose of 14.0 mg/day; 11.3 points at a mean IR dose of 13.9 mg/day).

The sponsor noted that efficacy in terms of the UPDRS total motor score appears to be dose related rather than formulation related. Greater improvements were observed with higher total daily doses and lesser improvements were observed with lower total daily doses, irrespective of formulation.

Reviewer Comment

- Technically, the sponsor is correct in noting that greater changes in motor score were associated with higher doses of each formulation suggesting a direct relationship between efficacy and dose. **However, from a larger perspective, of considering the relatively minimal magnitude of these changes compared to the relatively large changes in mean dose, I argue that there is little evidence for meaningful dose-response additional clinical benefit of using much larger doses. I also strongly suggest that essentially the same efficacy was experienced with lowest doses that were approximately half that of the highest mean doses.** See my earlier discussion of dose-response considerations and my suggestion that the best way to characterize dose-response is in a fixed dose, parallel group study.

Review of results in Table 50 for the primary efficacy endpoint (change of motor score) showed that there was no substantial change in the motor scores throughout maintenance periods 1-3 as the study progressed and the mean dose for ER ropinirole progressively decreased through the subsequent, maintenance phases (titration-18.0 mg, maintenance period #1-18.8 mg, maintenance period #2-14.0 mg, maintenance period #3-9.6mg) and the mean dose of IR ropinirole progressively increased through the subsequent, maintenance phases (titration-7.0 mg, maintenance period #1-8.9 mg, maintenance period #2-13.9 mg, maintenance period #3-18.8 mg). I suggest that if mean ropinirole doses > 9 mg daily for either formulation were providing much additional therapeutic benefit that the motor scores would progressive increase (e.g. suggesting clinical deterioration) as ER ropinirole dose progressively decreased and that motor scores would progressive decrease (e.g. suggesting clinical improvement) as IR ropinirole dose progressively increased.

6.1.4.3 Study 228 Efficacy Findings

Disposition of Subjects

The disposition of randomized subjects is summarized in Table 56.

Table 56 Summary of Subject Disposition (All Subjects: Protocol SK&F-101468/228)

Population	Number (%) Subjects		
	Ropinirole CR	Sinemet	Total
Randomized population	105 (100)	104 (100)	209 (100)
Safety population	104 (>99)	104 (100)	208 (>99)
ITT population	104 (>99)	104 (100)	208 (>99)
Study completer	0	1[1] (<1)	1 (<1)
Early withdrawal	105[2] (100)	103 (>99)	208 (>99)

1. One subject in the Sinemet group who was withdrawn because of early termination of the study was erroneously recorded as a Study Completer on the End of Study CRF page. No subjects completed the study.
2. One subject randomized to treatment with ropinirole CR did not receive study medication and is not included in the safety or ITT populations.

Data Source: Section 14, Table 6.1

Subjects in the Safety/ITT population who were withdrawn prematurely are summarized in Table 57.

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Table 57 Summary of Subject Discontinuation (Safety Population: Protocol SK&F-101468/228)

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

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

Data Source: Section 14, Table 6.2

Demographics and Other Baseline Characteristics

Demographic characteristics are summarized by treatment group in Table 58.

Table 58 Demographic Characteristics (Safety Population: Protocol SK&F-101468/228)

Characteristic	Ropinirole CR (N=104)	Sinemet (N=104)	Total (N=208)
Age (years)			
n	104	104	208
Mean (SD)	61.4 (7.00)	62.1 (7.20)	61.8 (7.09)
Median (Range)	63 (39-70)	64 (34-71)	63 (34-71)
Age group, years			
n	104	104	208
30-64, n (%)	60 (58)	53 (51)	113 (54)
≥65, n (%)	44 (42)	51 (49)	95 (46)
Sex, n (%)			
n	104	104	208
Female	44 (42)	30 (29)	74 (36)
Male	60 (58)	74 (71)	134 (64)
Race, n (%)			
n	104	104	208
American Hispanic	3 (3)	7 (7)	10 (5)
Arabic/North African	0	1 (<1)	1 (<1)
Black	2 (2)	6 (6)	8 (4)
East & South East Asian	4 (4)	2 (2)	6 (3)
White/Caucasian	95 (91)	87 (84)	182 (88)
Other	0	1 (<1)	1 (<1)
Height (cm)			
n	102	103	205
Mean (SD)	169.6 (12.3)	172.0 (10.7)	170.8 (11.5)
Median (Range)	170 (117-196)	173 (150-196)	173 (117-196)
Weight (kg)			
n	103	103	206
Mean (SD)	86.4 (18.0)	85.7 (17.0)	86.0 (17.5)
Median (Range)	87.2 (48-142)	85.0 (46-142)	85.5 (46-142)
Body mass index (kg/m²)			
n	102	103	205
Mean (SD)	30.2 (6.77)	28.9 (4.98)	29.6 (5.96)
Median (Range)	29.05 (20-64)	27.85 (19-47)	28.41 (19-64)

Data Source: Section 14, Table 6.3

The trial population was predominantly male (64%) and predominantly Caucasian (88%). No important between-group differences occurred in the distributions of age, weight, height, BMI, sex, or race.

Baseline Characteristics for Parkinson's Disease

Parkinson's disease history at Screening is summarized by treatment group in Table 59.

Table 59 Summary of Parkinson's Disease History at Screening (Safety Population: Protocol SK&F-101468/228)

Characteristic	Ropinirole CR (N=104)	Sinemet (N=104)	Total (N=208)
Duration of PD (yrs)			
N	100	102	202
Mean (SD)	2.7 (2.07)	2.7 (2.41)	2.7 (2.25)
Median (Range)	2.3 (0-11)	2.1 (0-13)	2.3 (0-13)
Age at Onset of PD (yrs)			
N	100	102	202
Mean (SD)	58.69 (8.071)	59.28 (7.833)	58.99 (7.938)
Median (Range)	60.00 (31-70)	61.00 (30-69)	61.00 (30-70)
Duration of L-dopa (yrs)			
N	104	103	207
Mean (SD)	0.79 (0.806)	0.83 (1.034)	0.81 (0.924)
Median (Range)	0.50 (0.1-3.4)	0.30 (0.1-6.3)	0.40 (0.1-6.3)
Hoehn & Yahr Stage, n (%)			
N	104	104	208
Stage I	15 (14)	25 (24)	40 (19)
Stage I.5	25 (24)	19 (18)	44 (21)
Stage II	31 (30)	32 (31)	63 (30)
Stage II.5	20 (19)	16 (15)	36 (17)
Stage III	12 (12)	11 (11)	23 (11)
Stage IV	0	1 (<1)	1 (<1)
Stage V	1 (<1)	0	1 (<1)

PD = Parkinson's disease
Data Source: Section 14, Table 6.4

The distributions of disease duration, age at onset, duration of L-dopa treatment, and disease severity (Hoehn and Yahr stage) were similar for the 2 treatment groups. Both groups included subjects with L-dopa exposure longer than 3 years (2 in the ropinirole CR group and 3 in the Sinemet group.

All but one subject were recorded as prematurely withdrawn, the majority (73%) because of the premature closure of the study by the sponsor. The most common reasons for early withdrawal, other than premature closure of the study, included AEs (23 subjects total, 15 [14%] in the ropinirole CR group and 8 [8%] in the Sinemet group) and dyskinesia (14 subjects total, 2 [2%] in the ropinirole group and 12 [12%] in the Sinemet group).

Protocol Deviations

Because of the early study closure, no subjects completed the trial and no formal evaluations of major or minor protocol deviations were undertaken. However the following deviations were noted.

Because of the potentially important effect on the primary endpoint, the Baseline UPDRS Part IV scores were reviewed to determine if any subjects deviated from the protocol

exclusion of subjects with dyskinesia. Although dyskinesia was not detected or reported during the Screening period, 8 subjects, 4 in each treatment group, reported some degree of dyskinesia on the UPDRS obtained at Baseline.

There were deviations in 4 other subjects related to the Inclusion and Exclusion criteria. In addition, after database freeze (and during the production of this report), a dispensing error was discovered for down titration of ropinirole CR. This affected those subjects (23 subjects in total) who down titrated on Dose Level 5 (a total daily dose of 12mg) and Dose Level 8 (a total daily dose of 24mg). Dose level 5 subjects (n=19) should have been taking a total of 8mg for 4 days and 4mg for 3 days during the Down Titration phase. However, due to the error, these subjects received 4mg for 4 days, and 2mg for 3 days. Dose level 8 subjects (n=4) should have been taking at a total of 16mg for 4 days and 8mg for 3 days. Instead, these subjects received 8mg for 4 days and 4mg for 3 days. An evaluation of the AE data for the subjects who down titrated with a greater reduction than planned for the first 4 days and a comparison to the AE data for those subjects who down titrated as per protocol was performed and no safety concerns were identified.

Prior Pharmacotherapy for Parkinson's Disease

All subjects had received prior treatment with L-dopa. In addition to the L-dopa-containing medications, the data for a few subjects listed selegiline and entacapone in this category of prior medications. Between-group differences in prior medical treatment (non-dopaminergic agonists0 of Parkinson's disease with selegiline, amantadine, and trihexyphenidyl hydrochloride were small (Table 60). Table 61 shows the prior Parkinson's Disease treatment recorded as prior L-dopa medications. Some responses included medications described in Table 60.

Table 60 Number (%) of Subjects Who Received the Most Common (≥ 2% in Either Treatment Group) Prior Medications for Parkinson's Disease (Excluding L-dopa) (Safety Population: Protocol SK&F-101468/228)

	Number (%) of Subjects	
Ingredient	Ropinirole CR N=104	Sinemet N=104
Any Prior Parkinson's Disease Medication	21 (20)	26 (25)
Selegiline	5 (5)	3 (3)
Entacapone	4 (4)	8 (8)
Amantadine	4 (4)	2 (2)
Trihexyphenidyl hydrochloride	2 (2)	4 (4)
Selegiline hydrochloride	2 (2)	1 (<1)

Data Source: Section 14, Table 6.8

Table 61 Number (%) of Subjects Who Received Prior L-dopa Medications (Safety Population: Protocol SK&F-101468/228)

Ingredient	Number (%) of Subjects	
	Ropinirole CR N=104	Sinemet N=104
Any Prior L-dopa Medication	104 (100)	104 (100)
Levodopa	104 (100)	103 (>99)
Carbidopa	103 (>99)	100 (96)
Entacapone	14 (13)	14 (13)
Selegiline	0	1 (<1)

Data Source: Section 14, Table 6.9

Prior Dopamine Agonist Treatment

Prior dopamine agonist medications for Parkinson's disease as reported and characterized by the investigators, are summarized by treatment group in Table 62.

Table 62 Number (%) of Subjects Who Received Prior Dopamine Agonist Treatment (Safety Population: Protocol SK&F-101468/228)

Ingredient	Number (%) of Subjects	
	Ropinirole CR N=104	Sinemet N=104
Any Prior Dopamine Agonist	31 (30)	23 (22)
Pramipexole	17 (16)	14 (13)
Investigational drug (NOS)	10 (10)	2 (2)
Ropinirole	8 (8)	9 (9)
Pergolide	3 (3)	2 (2)

NOS = not otherwise specified.
Data Source: Section 14, Table 6.12

Concomitant Medications

Concomitant medications (On-treatment, Down-titration, Post-treatment) were defined using the start and stop dates relative to the first and last dose dates of study medication. If a medication was started or stopped on the same day the first or last dose of On-treatment/Down-titration randomized study medication was taken, then this was considered a concomitant (On-treatment, Down-titration) medication. A medication could be counted in more than 1 phase. Baseline L-dopa use was tabulated separately from other concomitant medications.

Baseline L-dopa Medications

The majority of subjects (75%) enrolled were receiving less than or equal to 400mg L-dopa; the remaining subjects (25%) were receiving greater than 400mg L-dopa at enrollment. The use and mean daily dose of medications containing L-dopa at Baseline is summarized by treatment group in Table 63. The number of subjects and range of L-dopa doses were similar for the 2 groups.

Table 63 Summary of Total Daily Dose of L-dopa Medications at Baseline (Safety Population: Protocol SK&F-101468/228)

L-dopa Medication	Number (%) of Subjects	
	Ropinirole CR N=104	Sinemet N=104
ALL	n=102	n=102
Mean (SD), mg	368.9 (168.23)	363.7 (212.38)
Median (Range)	300.0 (100-1400)	300.0 (100-2000)
Carbidopa	n=0	n=1
Mean (SD), mg	--	300.0
Median (Range)	--	300.0 (NA)
Levodopa	n=1	n=4
Mean (SD), mg	200.0	275.0 (50.00)
Median (Range)	200.0 (NA)	300.0 (200-300)
Levodopa + Carbidopa	n=87	n=84
Mean (SD), mg	375.1 (172.29)	375.0 (230.05)
Median (Range)	300.0 (100-1400)	300.0 (100-2000)
Levodopa + Carbidopa + Entacapone	n=14	n=14
Mean (SD), mg	342.9 (142.58)	300.0 (103.77)
Median (Range)	300.0 (150-600)	300.0 (150-450)

Note: Four subjects (2 in each treatment group) were missing information and could not be included in the calculations. One subject in the Sinemet group reported both levadopa+carbidopa and levadopa+carbidopa+entacapone, and therefore, the N's add up to 103.
Data Source: Section 14, Table 6.15

On-treatment L-Dopa Medications

The use of On-treatment L-dopa medications is summarized by treatment group in Table 64.

Table 64 Number (%) of Subjects Who Received On-treatment L-dopa Medications (Safety Population: Protocol SK&F-101468/228)

Ingredient	Number (%) of Subjects	
	Ropinirole CR N=104	Sinemet N=104
Any On-treatment L-dopa Medication	**104 (100)**	**104 (100)**
Levodopa	104 (100)	103 (>99)
Carbidopa	103 (>99)	100 (96)
Entacapone	14 (13)	15 (14)
Selegiline	0	1 (<1)

Data Source: Section 14, Table 6.10

EFFICACY RESULTS

Twenty-one (21) subjects experienced dyskinesia, as recorded on the CRF page designated to capture the primary endpoint, 3 in the ropinirole CR group and 18 in the

Sinemet group. These results were examined in a Kaplan-Meier analysis with log rank tests, as shown in Table 65 and Figure 10.

Table 65 Kaplan-Meier Analysis of Time to Onset of Dyskinesia for the ITT Population (Protocol SK&F- 101468/228)

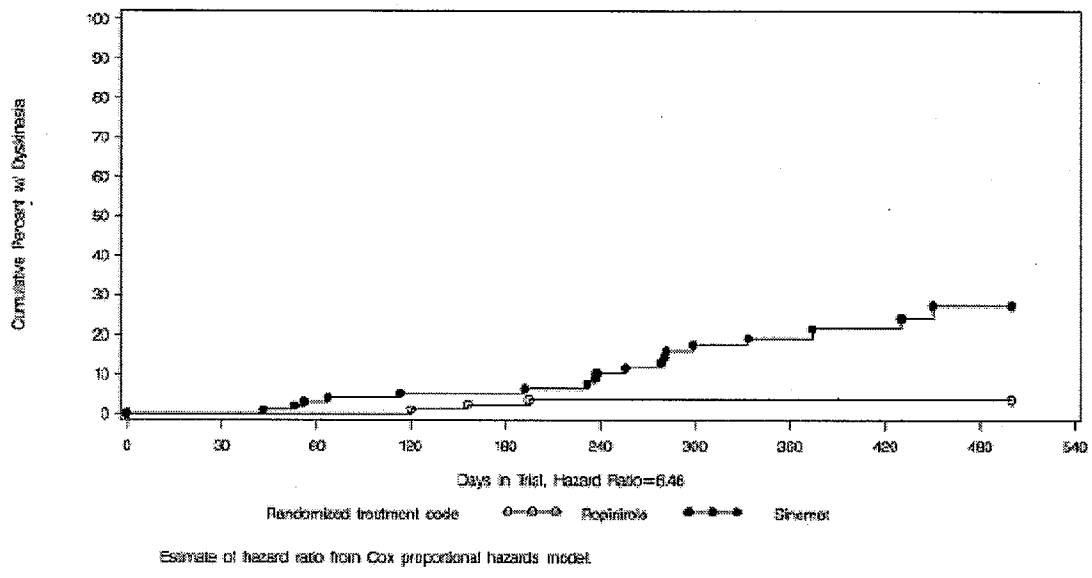
	Ropinirole CR N = 104		Sinemet N = 104	
Subjects with dyskinesia	n=3		n=18	
Subjects with dyskinesia up to Time t-postdose				
Subjects in Analysis	n=104		n=104	
Time	N at Risk	n (%)	N at Risk	n (%)
30 days	95	0	101	0
60 days	95	0	96	3 (3)
120 days	87	1 (1)	83	5 (5)
180 days	80	2 (2)	80	5 (5)
240 days	73	3 (4)	68	9 (10)
300 days	62	3 (4)	53	14 (18)
360 days	50	3 (4)	41	15 (19)
420 days	39	3 (4)	31	16 (21)
540 days	16	3 (4)	14	18 (27)
Median Time to Dyskinesia[1]		N/A		N/A
p-value[2,3]		-		<0.001**

1. Median time to dyskinesia cannot be estimated by Kaplan-Meier methods because of the small number of events.
2. P-values from log-rank test.
3. Note: * significant at 0.05; ** significant at 0.01.

Data Source: Section 14, Table 7.2

There was a statistically significant delay in the time to onset of dyskinesia for the ropinirole CR-treated subjects ($p < 0.001$).

Figure 10 Kaplan-Meier Plot of Time to Onset of Dyskinesia (ITT Population: Protocol SK&F- 101468/228)



Data Source: Section 14, Figure 7.1

Because Investigators were informed of GSK's decision to terminate the trial on 28 September 2005, a second Kaplan Meier analysis was performed post-hoc with censoring of observations after 28 September 2005 to evaluate any possible impact of termination on the primary endpoint as summarized in Table 66 and shown graphically in Figure 11.

Table 66 **Kaplan-Meier Analysis of Time to Onset of Dyskinesia for the ITT Population (Censored at Time of Decision to Terminate Study Protocol SK&F-101468/228)**

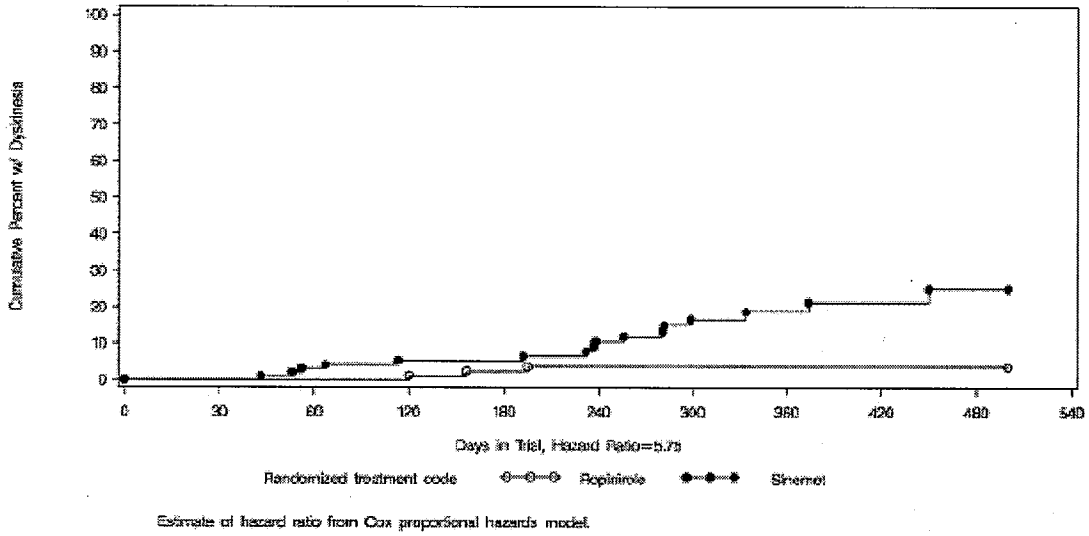
	Ropinirole CR N = 104		Sinemet N = 104	
Subjects with dyskinesia[1]	3		16	
Subjects with dyskinesia up to Time t postdose				
Subjects in Analysis	n=104		n=104	
Time	N at Risk	n (%)	N at Risk	n (%)
30 days	95	0	99	0
60 days	93	0	95	3 (3)
120 days	84	1 (1)	83	5 (5)
180 days	79	2 (2)	76	5 (5)
240 days	69	3 (4)	66	9 (11)
300 days	59	3 (4)	50	13 (17)
360 days	44	3 (4)	35	14 (19)
420 days	36	3 (4)	29	15 (21)
540 days	13	3 (4)	12	16 (25)
Median Time to Dyskinesia[2]		N/A		N/A
p-value[3,4]		-		0.002**

1. Investigators were informed of Sponsor's decision to terminate the trial on 28 September 2005. Observations after 28 September 2005 are censored. Dates with a missing day are set to the beginning of the month.
2. Median time to dyskinesia cannot be estimated by Kaplan-Meier methods because of the small number of events.
3. P-values from log-rank test.
4. Note: * significant at 0.05; ** significant at 0.01.

Data Source: Section 14, Table 7.3

The results of this post-hoc analysis show a similar delay in time to onset of dyskinesia for ropinirole CR-treated subjects (p=0.002) to that of the primary analysis above.

Figure 11 Kaplan-Meier Plot of Time to Dyskinesia Censored at Time of Decision to Terminated Study (ITT Population: Protocol SK&F-10468/228)



Data Source: Section 14, Figure 7.2

The results of this post-hoc analysis show a similar delay in time to onset of dyskinesia for ropinirole CR-treated subjects (p=0.002) to that of the primary analysis above.

Further, post-hoc examination revealed that 8 subjects, 4 in each treatment group, reported some degree of dyskinesia on the UPDRS Part IV obtained at Baseline. Two of these 8 subjects also had a subsequent dyskinesia event prior to study termination. Therefore, a third Kaplan-Meier analysis of time to onset of dyskinesia was conducted with censoring at study termination (as above) plus removal of the 8 subjects with evidence of dyskinesia per UPDRS assessment at Baseline to determine if these subjects had an impact on the primary endpoint. These results are summarized in Table 67 and shown graphically in Figure 12.

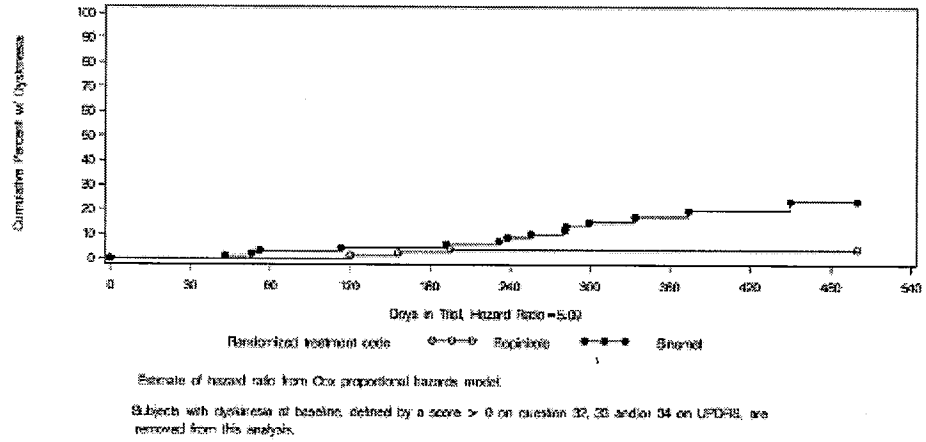
Table 67 Kaplan-Meier Analysis of Time to Onset of for the ITT Population (Removal of Subjects with Baseline Dyskinesia, Censored at Time of Decision to Terminate Study: Protocol SK&F-101468/228)

	Ropinirole CR N = 104		Sinemet N = 104	
Subjects with dyskinesia[1,2]	3		14	
Subjects with dyskinesia up to Time t postdose				
Subjects in Analysis	n=100		n=100	
Time	N at Risk	n (%)	N at Risk	n (%)
30 days	91	0	95	0
60 days	90	0	91	3 (3)
120 days	82	1 (1)	80	4 (4)
180 days	77	2 (2)	73	4 (4)
240 days	68	3 (4)	64	7 (9)
300 days	58	3 (4)	49	11 (15)
360 days	43	3 (4)	34	12 (17)
420 days	35	3 (4)	29	13 (20)
540 days	12	3 (4)	12	14 (24)
Median Time to Dyskinesia[3]		N/A		N/A
p-value[4, 5]		-		0.004**

1. Subjects with dyskinesia at Baseline were removed from the analysis. Dyskinesia at Baseline was defined by a score greater than zero at Baseline on questions 32, 33, and/or 34 on the UPDRS.
2. Investigators were informed of Sponsor's decision to terminate the trial on 28 September 2005. Observations after 28 September 2005 are censored. Dates with a missing day are set to the beginning of the month.
3. Median time to dyskinesia cannot be estimated by Kaplan-Meier methods because of the small number of events.
4. P-values from log-range test.
5. Note: * significant at 0.05; ** significant at 0.01.

Data Source: Section 14, Table 7.4

Figure 12 Kaplan-Meier Plot of Time to Dyskinesia Censored at Time of Decision to Terminate Study and Removing Patients with UPDRS Defined Dyskinesia at Baseline (ITT Population: Protocol SK&F-101468/228)



Data Source: Section 14, Figure 7.3

The results of this post-hoc analysis also show a similar delay in time to onset of dyskinesia for ropinirole CR-treated subjects (p=0.004) to that of the primary analysis.

Reviewer Comment

- It is interesting that the secondary, post-hoc analyses of the primary efficacy endpoint did not alter the number of patients (N=3) who had developed dyskinesia in the ER ropinirole group after randomization. Only patients in the Sinemet group (initially N=18 developed dyskinesia in the original ITT analysis) were excluded from the analysis of those developing (N=2) when the analysis was limited until the time that the planned study termination was announced, and four patients were excluded from those who developed post-randomization dyskinesia when all patients with any dyskinesia at baseline were censored from the analysis. It is not clear if the number of patients developing post-randomization dyskinesia would be decreased to 12 if an analysis was conducted in which the development of dyskinesia was assessed until the time study termination was announced and those with any baseline dyskinesia were also censored from the analysis.

- It does not appear that this study result was related to fact that there was inadequate control of efficacy because the change from baseline for UPDRS ADL and motor score appeared to be reasonably similar for both ER ropinirole and Sinemet. The sponsor did not collect diary data to be able to assess how each treatment controlled "off" episodes, a common primary efficacy endpoint for advanced Parkinson's Disease.

- It is not clear that the sponsor discussed this design and analysis of this study with the DNP. Considering that the End of Phase 2 meeting was held in 2/03 and this study was initiated in 10/03, it seems likely that the sponsor had plans to conduct this study at the time of the End of Phase 2 meeting.

- [redacted] b(4)

- This study was terminated prematurely and the number of events was relatively small. These observations further support the perspective that it is not necessarily appropriate [redacted] b(4)

b(4)

Secondary Efficacy Endpoints

I have presented selected secondary efficacy endpoints, particularly those that impact on showing a comparison of the efficacy of ER ropinirole vs that of Sinemet.

Incidence of Dyskinesia

The incidence of dyskinesia at each time point was not formally summarized. Overall, 3 of 104 ropinirole CR-treated subjects (3%) and 18 of 104 Sinemet-treated subjects (17%) experienced the onset of dyskinesia as assessed by the primary endpoint dyskinesia page of the CRF. Four of these 21 subjects, all in the Sinemet group, had positive responses to dyskinesia-related items on the Baseline UPDRS Part IV, although all subjects were recorded as meeting Exclusion Criteria 1 (excluding subjects with dyskinesia).

The ropinirole CR subjects with Baseline positive UPDRS responses related to dyskinesia included 3 with reports of disability and 2 with reports of non-zero duration of dyskinesia. These 4 subjects had no positive responses to dyskinesia related items during treatment with ropinirole CR. One of the 4 subjects had a positive response to duration of dyskinesia at Post-treatment. The 4 Sinemet subjects with Baseline positive UPDRS responses related to dyskinesia included 2 with reports of disability, 1 with a positive duration of dyskinesia (Subject 103), and 3 with painful dyskinesia.

Two subjects had positive responses to dyskinesia items during treatment with Sinemet. Two Subjects had positive responses to dyskinesia items at Post-treatment.

UPDRS Activities of Daily Living (ADL) score (UPDRS Part II)
UPDRS ADL scores (irrespective of "off" or "on") at Week 28 OC and at the end of the study (Week 104 LOCF) and change from Baseline to Week 28 OC and to end of study are summarized by treatment group in Table 68. UPDRS ADL scores from the ON state and OFF state evaluations at baseline and at different time points after randomization/treatment throughout the study were relatively similar for ER ropinirole and Sinemet groups.

Table 68 Mean Change from Baseline at Week 28 (OC) and End of Study (Week 104 LOCF) in Average Total Activities of Daily Living (ADL) Score (without regard to "Off" or "On" state)of the UPDRS (ITT Population: Protocol SK&F-101468/228)

Visit	Ropinirole CR N=104	Sinemet N=104
Baseline Score[1]		
n	**102**	**104**
Mean (SD)	8.6 (4.83)	8.2 (5.72)
Median (Range)	8.0 (1-22)	7.0 (1-41)
Week 28 Score (OC)		
n	**83**	**83**
Mean (SD)	6.9 (5.02)	6.5 (5.32)
Median (Range)	6.0 (0-21)	4.0 (0-24)
Change from Baseline to Week 28 (OC)		
n	**82**	**83**
Mean (SD)	-1.5 (3.83)	-1.2 (3.92)
Median (Range)	-1.5 (-17-9)	-1.0 (-14-15)
End of Study (Week 104 LOCF)		
n	**101**	**104**
Mean (SD)	7.5 (5.83)	7.3 (6.72)
Median (Range)	6.5 (0-31)	5.0 (0-49)
Change from Baseline to End of Study		
n	**100**	**104**
Mean (SD)	-1.0 (4.35)	-0.9 (3.62)
Median (Range)	-1.0 (-22-13)	-1.0 (-11-12)

LOCF=last observation carried forward, OC=observed cases
1. Note: The Total ADL Score of the UPDRS ranges from 0 to 52, where 0 = normal/no symptoms and 52 = worst possible case.
Data Source: Section 14, Table 7.5 and Table 7.6

Mean changes at all time points in both treatment groups were small, whether evaluated using OC or LOCF methods. No clinically important between-group differences were observed.

UPDRS Motor Score (UPDRS Part III)

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" or "off" states and summaries of the UPDRS motor score at each visit were produced separately for each state. Summaries of the UPDRS motor score at each visit, and change from Baseline, were also produced regardless of state. These analyses showed that the baseline score was similar for each treatment group and similar changes occurred in each group throughout treatment. The last On-treatment value was carried forward regardless of the state. UPDRS Part III (motor) scores at Week 28 (OC) and End of Study (Week 104 [LOCF]) are summarized by treatment group in Table 69 for all evaluations whether conducted during the "on" or "off" state. For both treatment groups, the mean motor score baseline in the "On" state was similar as were the

changes from baseline throughout treatment in the "On" state. Although the baseline motor score in the "Off" state was higher in the ER ropinirole group (~ 27) vs the Sinemet group (~ 23), and the change after treatment appear to be generally greater in the ER ropinirole group, the number of patients in each of these group was relatively small at baseline (ER ropinirole, N=12; Sinemet, N=11), and at many post-treatment time points, there were no "observed case" post-treatment time points in which both treatment groups had ≥ 10 patients. Table 70 and Table 71 provide additional perspective on these effects.

Table 69 Mean Change from Baseline at Week 28 (OC) and End of Study (Week 104 LOCF) in Total Motor Score of the UPDRS (without regard to "Off" or "On" state) (ITT Population: Study 228)

Visit	Ropinirole CR N=104	Sinemet N=104
Baseline Score[1]		
n	102	104
Mean (SD)	19.6 (10.51)	19.4 (12.43)
Median (Range)	19.0 (1-47)	18.0 (1-86)
Week 28 Score (OC)		
n	83	81
Mean (SD)	15.6 (10.91)	15.3 (9.80)
Median (Range)	14.0 (0-56)	13.0 (0-40)
Change from Baseline (Week 28 OC)		
n	83	81
Mean (SD)	-3.7 (9.32)	-3.5 (6.99)
Median (Range)	-3.0 (-43-18)	-3.0 (-26-12)
End of Study Score (Week 104 LOCF)		
n	99	102
Mean (SD)	15.9 (11.03)	16.0 (13.45)
Median (Range)	14.0 (0-53)	13.0 (0-98)
Change from Baseline (Week 104 LOCF)		
n	98	102
Mean (SD)	-3.6 (9.16)	-3.3 (7.82)
Median (Range)	-3.0 (-36-30)	-3.0 (-25-20)

LOCF=last observation carried forward, OC=observed cases
1. The Total Motor Score of the UPDRS ranges from 0-108, where 0=normal/no symptoms and 108=worst possible case.
Data Source: Section 14, Table 7.9 and Table 7.10

Mean and median changes at all time points in both treatment groups were small and, in general, showed improvements from Baseline. No clinically important between-group differences were observed. UPDRS Motor Scores in the "on" state and "off" state are summarized in Table 70 and Table 71.

Table 70 Summary Statistics for the UPDRS Total Motor Score with Subjects in the "On" State at Week 28 OC and Week 104 LOCF (ITT Population: Protocol SK&F-101468/228)

Visit	Ropinirole CR N=104	Sinemet N=104
Baseline	n=90	n=92
Mean (SD)	18.6 (10.06)	18.9 (12.15)
Median (Range[1])	18.0 (1-43)	18.0 (1-86)
Week 28 OC[2]	n=71	n=74
Mean (SD)	15.2 (11.29)	14.8 (9.58)
Median (Range)	13.0 (0-56)	13.0 (0-40)
End of Study (Week 104 LOCF)[2]	n=89	n=90
Mean (SD)	14.9 (10.74)	15.3 (13.71)
Median (Range)	13.0 (0-53)	12.5 (0-98)

1. LOCF = last observation carried forward; OC = observed cases; UPDRS = Unified Parkinson's Disease Rating Scale.
2. The UPDRS Total Motor Score ranges from 0 to 108, where 0=normal/no symptoms and 108=worst possible case.
3. Changes from Baseline to Week 28 OC and Week 104 LOCF were not calculated.
Data Source: Section 14, Table 7.11

Table 71 Summary Statistics for the UPDRS Total Motor Score with Subjects in the "Off" State at Week 28 OC and Week 104 LOCF (ITT Population: Protocol SK&F-101468/228)

Visit	Ropinirole CR N=104	Sinemet N=104
Baseline	n=12	n=11
Mean (SD)	26.8 (11.47)	22.9 (14.91)
Median (Range[1])	25.0 (8-47)	25.0 (1-47)
Week 28 OC[2]	n=11	n=7
Mean (SD)	18.5 (8.54)	20.6 (11.31)
Median (Range)	21.0 (7-32)	15.0 (10-40)
End of Study (Week 104 LOCF)[2]	n=9	n=11
Mean (SD)	25.1 (10.78)	21.0 (10.59)
Median (Range)	20.0 (13-44)	22.0 (8-41)

1. LOCF = last observation carried forward; OC = observed cases; UPDRS = Unified Parkinson's Disease Rating Scale.
2. The UPDRS Total Motor Score ranges from 0 to 108, where 0=normal/no symptoms and 108=worst possible case.
3. Changes from Baseline to Week 28 OC and Week 104 LOCF were not calculated.

Data Source: Section 14, Table 7.12

Clinical Global Impression of Improvement (CGI-I) and Severity (CGI-S)

The percentage of subjects reporting much or very much improvement is summarized in Table 72.

Table 72 Number (%) of Responders (Score of 1 or 2) on the Clinical Global Impression (CGI) Global Improvement Scale by Visit (ITT Population: Protocol SK&F-101468/228)

	Ropinirole CR N=104		Sinemet N=104	
CGI-I Responder[1]	n/N	(%)	n/N	(%)
Week 1	12/98	(12)	11/101	(11)
Week 4	21/100	(21)	21/102	(21)
Week 8	34/94	(36)	31/99	(31)
Week 16	41/93	(44)	32/91	(35)
Week 28	35/83	(42)	29/83	(35)
Week 40	37/73	(51)	27/68	(40)
Week 52	26/56	(46)	24/54	(44)
Week 64	8/13	(62)	7/11	(64)
Week 76	7/14	(50)	1/8	(13)
Week 88	0/8	–	5/10	(50)
Week 96	1/2	(50)	0/1	–
End of study (Week 104 LOCF[2])	35/101	(35)	35/104	(34)

1. Responder defined as CGI-I score of 1 (very much improved) or 2 (much improved).
2. LOCF = last observation carried forward; Week 1 through 96 are observed case (OC) analysis.

Data Source: Section 14, Table 7.17

At End of Study (Week 104 [LOCF]), 35% of ropinirole CR subjects and 34% of Sinemet subjects were reported to be "much improved" or "very much improved." The number and percentage of subjects with scores of 3 (improved), 4 (unchanged), 5

(worse), 6 (much worse), and 7 (very much worse) were similar for the 2 treatment groups.

Change from Baseline in the MMSE Score
Scores on the MMSE at Screening and Week 104 LOCF are summarized by treatment group in Table 73. At both Screening and End of Study (Week 104 [LOCF]), most subjects (≥ 90%) in each treatment group had MMSE scores in the normal range (27-30).

The percentage of subjects with MMSE scores of 26 or lower changed from 4% to 10% in the ropinirole CR group and was 4% at both time points in the Sinemet group.

Table 73 Summary of Mini Mental State Examination (MMSE) (ITT Population: Protocol SK&F-101468/228)

	Number (%) of Subjects	
Visit	Ropinirole CR (N=104)	Sinemet (N=104)
Screening		
n	103	104
Normal (Scores 27-30)	99 (96)	100 (96)
Scores 21-26	4 (4)	4 (4)
Scores 11-20	0	0
End of Study (Week 104 LOCF)		
n	90	92
Normal (Scores 27-30)	81 (90)	88 (96)
Scores 21-26	8 (9)	3 (3)
Scores 11-20	1 (1)	1 (1)

LOCF = last observation carried forward
Data Source: Section 14, Table 7.41

Other Efficacy Results

UPDRS Complications of Therapy
Complications of therapy (e.g. regarding various "Off" episodes) are summarized by treatment group at Baseline, at Week 28 (OC), and at Week 104 (LOCF) in Table 74. Overall, these complications at baseline and at post-randomization/treatment were relatively similar.

Table 74 Summary of UPDRS Complications of Therapy at Baseline and Week 28 and at End of Study at Week 104 (ITT Population: Study 228)

Item	Number (%) of Subjects	
	Ropinirole CR (N=104)	Sinemet (N=104)
CLINICAL FLUCTUATIONS		
Predictable 'Off' Periods		
Baseline, n	**97**	**100**
No	51 (53)	58 (58)
Yes	46 (47)	42 (42)
Week 28, n	**76**	**78**
No	44 (58)	44 (56)
Yes	32 (42)	34 (44)
End of Study (Week 104 LOCF), n	**101**	**104**
No	52 (51)	58 (56)
Yes	49 (49)	46 (44)
Unpredictable 'Off' Periods		
Baseline, n	**97**	**100**
No	70 (72)	79 (79)
Yes	27 (28)	21 (21)
Week 28, n	**76**	**78**
No	66 (87)	66 (85)
Yes	10 (13)	12 (15)
End of Study (Week 104 LOCF), n	**101**	**104**
No	86 (85)	89 (86)
Yes	15 (15)	15 (14)
Sudden 'Off' Periods		
Baseline, n	**97**	**99**
No	88 (91)	89 (90)
Yes	9 (9)	10 (10)
Week 28, n	**76**	**78**
No	72 (95)	73 (94)
Yes	4 (5)	5 (6)
End of Study (Week 104 LOCF), n	**101**	**104**
No	90 (89)	92 (88)
Yes	11 (11)	12 (12)
Duration of 'Off' Periods		
Baseline, n	**97**	**99**
None	34 (35)	44 (44)
1-25% of day	49 (51)	49 (49)
26-50% of day	12 (12)	4 (4)
51-75% of day	1 (1)	2 (2)
76-100% of day	1 (1)	0
Week 28, n	**76**	**78**
None	36 (47)	38 (49)
1-25% of day	30 (39)	34 (44)
26-50% of day	8 (11)	6 (8)
51-75% of day	2 (3)	0
76-100% of day	0	0
End of Study (Week 104 LOCF), n	**101**	**104**
None	46 (46)	45 (43)
1-25% of day	41 (41)	47 (45)
26-50% of day	11 (11)	10 (10)
51-75% of day	2 (2)	2 (2)
76-100% of day	1 (<1)	0

6.1.5 Efficacy Conclusions

Analysis, Summary and Conclusions of Statistical Reviewer (Dr. Sharon Yan) for Study 169 (For additional details, see Dr. Yan's Review)

Statistical Reviewer's Analysis

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

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

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

Statistical Issues and Collective Evidence

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

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

Statistical Reviewer Conclusions and Recommendations

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

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

Sponsor Efficacy Conclusions for Study 169

· Ropinirole CR was demonstrated to be superior to placebo as assessed by the primary endpoint, change from baseline in awake time spent "off" at Week 24 LOCF. At all visits from Week 2 OC onwards there was a clinically relevant and statistically significant benefit of ropinirole CR over placebo in the total awake time spent "off".

· When efficacy was evaluated in terms of the mean awake time spent "off" by dose at Week 24 LOCF, ropinirole CR was shown to be efficacious at doses from 8 mg to 24 mg.
· A statistically significant benefit of ropinirole CR when compared to placebo was observed for each of the following secondary efficacy variables:
  · change from baseline in awake time spent "on" without troublesome dyskinesias;
  · change from baseline in percent awake time spent "on" without troublesome dyskinesias;
  · change from baseline in the UPDRS motor score;
  · change from baseline in the UPDRS total ADL score;
  · proportion of subjects scoring much or very much improved on the CGI-I scale;
  · proportion of subjects requiring reinstatement of L-dopa following a reduction in dose;
  · time to reinstatement of L-dopa following a reduction in dose;
  · proportion of subjects achieving a 20% reduction from baseline in awake time spent 'off' and a 20% reduction from baseline in L-dopa dose.
· There was also a statistically significant benefit of ropinirole CR when compared to placebo for each of the following additional secondary efficacy variables:
  · change from baseline in the BDI-II total score;
  · change from baseline in the mobility, ADL, emotional well-being, stigma and communication domains of the PDQ-39;
  · change from baseline in the PDSS total score;
  · change from baseline in percent awake time spent "off";
  · change from baseline in awake time spent "on";
  · change from baseline in percent awake time spent "on".
· There was no statistically significant difference between ropinirole and placebo for change from baseline in the ESS total score, thus indicating that there was no statistical evidence that ropinirole CR altered the likelihood of dozing when compared to placebo.
· There was no statistically significant difference between ropinirole and placebo for the change from baseline in the social support, cognitive impairment and bodily discomfort domains of the PDQ-39 at Week 24 LOCF.
· For the subgroup analyses in which the numbers of subjects were sufficient to allow a meaningful interpretation of data (namely, race subgroup of White/Caucasian; country

subgroups of Czech Republic, Hungary, Poland, US; subgroup of investigational product taken with food; subgroup of subjects enrolled pre/post amendment 1; and subgroup of subjects with prior/no prior exposure to dopamine agonists), the results for the change from baseline to Week 24 LOCF in total awake time spent "off" were similar to those observed for the total population.

Reviewer Efficacy Conclusions for Study 169

- 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 (> mean 14 mg) 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 dose of 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.

Sponsor Efficacy Conclusions for Study 168

· Ropinirole CR was demonstrated to be non-inferior to ropinirole IR as assessed by the primary endpoint, change from period baseline in the UPDRS total motor score.
· No statistically significant differences between ropinirole CR and ropinirole IR were observed for any of the efficacy endpoints.
· Both ropinirole formulations were effective treatments for Parkinson's disease, as illustrated by the change from baseline in efficacy variables (e.g. UPDRS total motor score, CGI-I responders) over the first 12 weeks and 20 weeks of the study.
· Ropinirole CR doses could be increased more quickly than IR doses, resulting in an earlier efficacy response (e.g. UPDRS total motor score, CGI-I response) for this formulation.
· Although the study was not powered to show statistical significance for parallel group analyses, differences in favor of ropinirole CR over ropinirole IR for the first 20 weeks were apparent for a number of endpoints (CGI-I responders, UPDRS total motor score and time to maintained response).
· The efficacy results suggest that response is driven by dose and not by formulation, as evidenced by the efficacy response versus the ropinirole dose at the end of each maintenance phase (for UPDRS total motor score and CGI-I responders).
· The overnight dose switches, to a similar dose of the alternate formulation, used in this study were appropriate; few subjects required a dose adjustment following switching and the number of dose adjustments was similar for ropinirole CR and IR.
· During each of the three maintenance periods, compliance was slightly better for the CR formulation than for the IR formulation.

Reviewer Efficacy Conclusions for Study 168

- Overall, I conclude that ER ropinirole appears to show similar efficacy to IR ropinirole in patients with early Parkinson's Disease 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.

- 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 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.

Statistical Reviewer Conclusions for Study 228

Analysis of Primary Efficacy Variable

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

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

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

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

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

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

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

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

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

First, subjects who did not have dyskinesia were censored at their last randomized treatment. A p-value of 0.0006 was obtained from the log-rank test in the treatment comparison with this censoring scheme. When subjects were censored after 28 September 2005, including the 2 subjects who experienced dyskinesia after the date, a p-value of 0.0017 was obtained. Finally, when subjects were censored after 28 September 2005, and 8 subjects who reported some degree of dyskinesia at baseline were removed, the analysis

yielded a p-value of 0.0044. The analyses suggested that ropinirole CR may have an effect in delaying the onset of dyskinesia when compared to Sinemet.

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

Sponsor Efficacy Conclusions for Study 228

· Twenty-one subjects developed dyskinesia (as measured by the designated CRF page used to determine the primary endpoint), 3 in the ropinirole group (3%) and 18 in the Sinemet group (17%). Based on a Kaplan-Meier analysis, the addition of controlled-release ropinirole resulted in a statistically significant delay in onset of dyskinesia when compared with Sinemet ($p<0.001$).
· A post-hoc Kaplan-Meier analysis that employed censuring on the day sites were informed of the early study terminations showed a similar result favoring ropinirole CR ($p=0.002$).
· A post-hoc Kaplan-Meier analysis that excluded 8 subjects with positive dyskinesia-related responses on the Baseline UPDRS Part IV, 4 of whom were among the 21 subjects who developed dyskinesia during the study, showed a similar result favoring ropinirole CR ($p=0.004$).
· Other measures evaluating the status and progression of subjects' Parkinson's disease showed no clinically significant differences in the effects of ropinirole CR and Sinemet. These included:
    · Change from Baseline in UPDRS Part II, Part III, and Part IV scores
    · Change from Baseline in ESS scores
    · Change from Baseline in CGI assessments
    · Change from Baseline in BDI scores
    · Change from Baseline in PDQ-39 scores
    · Change from Baseline in PDSS scores
    · Change from Baseline in MMSE scores
    · Change from Baseline in PPRS scores
    · Change from Baseline in the Parkinson's disease Symptom Control questionnaire
· Although the study was terminated early and was based on a smaller number of subjects than originally planned, this study 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. Despite these

limitations, the data show a positive result for ropinirole CR versus Sinemet which was statistically significant.

· It should be noted that the primary endpoint was collected by a Yes/No question of whether or not dyskinesia was present rather than the more traditional measures such as UPDRS items or AE occurrence in order to enable measurement of onset. UPDRS evaluations in subjects who have had dyskinesia for some time would be expected to show different outcomes than in those with newer onset dyskinesia. Even with these caveats, the study has demonstrated that the stability of the UPDRS scores over the course of the study and the substantial number of subjects who continued in the study from the time of enrollment until the early termination, combined with the slow titration rate reported in Section 6, suggest that ropinirole CR provides a durable effect for subjects with treated Parkinson's disease experiencing early evidence of declining control with L-dopa.

Reviewer Efficacy Conclusions for Study 228

- I believe that results from study 228 support the possibility that ER ropinirole may increase the time to dyskinesia when added to levodopa as adjunctive treatment of patients with advanced Parkinson's Disease. However, I believe that these results are at the level of hypothesis testing [redacted] b(4)

7 INTEGRATED REVIEW OF SAFETY

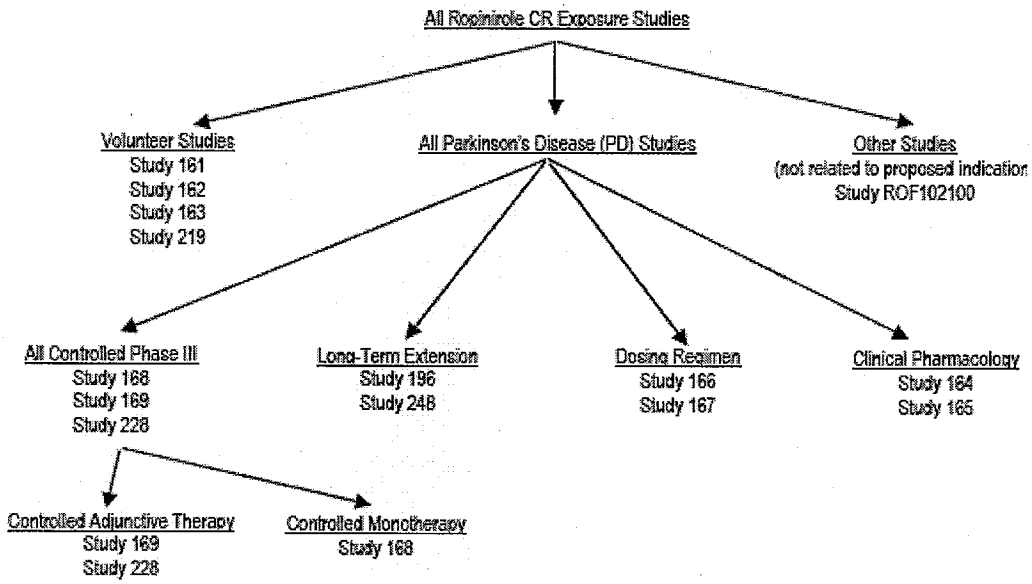
7.1 Methods and Findings

Organization and Analysis of Safety Data

Overview of the Ropinirole CR Parkinson's Disease Program
The ropinirole CR development program was designed to assess the efficacy and safety of ropinirole CR (ER ropinirole) in subjects with PD. The clinical program consisted of 14 studies; 6 clinical pharmacology studies and 8 clinical studies.

The grouping of studies for this ISS is presented in Figure 13.

Figure 13 Study Groupings for Ropinirole CR Clinical Development Program



The primary safety data are provided by the 3, controlled, Phase 3 studies, Studies 169, 228 and 168, which employed individual titration, and a maximum dose of 24mg/day. Treatment duration was 9 months in Study 168 (across both formulations in this cross-over study), 6 months in Study 169, and 107 weeks (2 years and 3 weeks) in Study 228. The proposed dosing regimen for the CR formulation of ropinirole was used in all 3 of these studies. Supporting evidence is provided from the 2 completed, clinical pharmacology studies with PD subjects (Studies 164 and 165), 2, completed, Phase 2 studies (Studies 166 and 167), and interim results from the 2, ongoing, long-term extension studies (Studies 196 and 248).

Interim, long-term safety data are provided primarily from the 2 ongoing, long-term extension studies, Study 196 (extension to Studies 164 and 167) and Study 248 (extension to Studies 165, 168 and 169) with exposure of up to 30 months; median of approximately 22 months). Additional long-term safety data are provided from Study 228 in which subjects were exposed for up to 107 weeks (2 years and 3 weeks).

Data Cut-off Dates

All studies in the clinical program are complete with the exception of the 2, long-term extension studies (Studies 196 and 248). Study 228, the time to onset of dyskinesia study was discontinued by the Sponsor on 07 December 2005 (date of last subject, last visit) for administrative reasons unrelated to safety considerations. Enrollment in the long-term extension studies, Studies 196 and 248 is complete, but treatment is ongoing. No new studies were initiated prior to the cutoff date.

Full safety data are provided for the 4 completed studies in healthy volunteers and 7 completed studies in PD subjects. The cut-off dates (all quality-assured clinical trial data received in-house at GSK) for inclusion of other data are as follows :

• 24 January 2006 for all safety data from ongoing studies with the exception of the data noted in the next 2 bullet points below.
• 31 May 2006 for SAEs (deaths and nonfatal events) and pregnancy data from the ongoing, long-term extension studies and post-marketing surveillance data from the OCEANS database.
• 31 May 2006 for the review of relevant published literature related to safety. A total of 946 unique subjects (110 healthy volunteers, 746 PD subjects, and 90 fibromyalgia subjects) received at least 1 dose of ropinirole CR in the clinical development program.

The sponsor noted that during the post-marketing experience, the safety of ropinirole IR has been reviewed on a regular basis and findings included in the 6-monthly Periodic Safety Update Reports (PSUR). These regular safety reviews have continued to show that ropinirole IR is a well-tolerated drug in the treatment of PD.

Regulatory Interactions

The sponsor submitted NDA 22008 in early 2006 but the sponsor withdrew the NDA when it was clear that the DNP was planning to refuse to file (RTF) the application because of the poor content and format of the NDA. The content and format of this ISS 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 requested many general and specific analyses particularly related to safety for individual study reports and pooled analyses to be included in the ISS. Some of these requests included, analyzing : 1) the data by dose; 2) by onset of adverse events in the titration or maintenance phase; 3) mean and outlier data over time.

7.1.1 Deaths

Clinical Pharmacology Studies

Healthy Subjects

No deaths reported in any of the clinical pharmacology studies.

Parkinson's Disease Subjects

There was 1 fatal SAE (myocardial infarction) during Study 164 in patient (Subject 101).

The following is a narrative summary description of this subject who died.

Study 101468/164 – Subject 00101 –Comprehensive Summary

This 75-year-old male subject was enrolled in an open-label, randomised, 2 part trial, in which the aim was to study the relative bioavailability of ropinirole CR and IR formulations and the effect of food on the pharmacokinetics of the ropinirole CR formulation in subjects with early stage Parkinson's disease. The subject's relevant medical history includes coronary artery bypass grafting and was taking low-dose aspirin, depression for which he received sertraline and memory problems for which he was treated with donepezil. He also took a cox-2 inhibitor. The subject was randomised to receive treatment sequence 1 (CR-CR-IR-CR); Note that there are inconsistencies between the SAE narrative and the study records as to the number of days to the start of the events.

HALLUCINATIONS: Fourteen days after the start of treatment he discontinued sertraline and donepizil for reasons which are not known. Sixteen days after the start of treatment he had a special interest serious AE of hallucination (confusion/hallucinations) (Study 101468/164 – Subject 00101 – Hallucination) of moderate intensity. Study medication was stopped as a result, and the subject was withdrawn from the study and hospitalised; the event was ongoing at time of follow-up. The hallucinations were accompanied with a serious AE of moderate confusional state (confusion/hallucinations), (Study 101468/164 – Subject 00101 – Confusional state). Zolpidem, sertraline and donepazil were restarted on day 21. The mental status changes were initially felt to be related to study medication but the investigator later changed the attribution to unlikely to be related.

MYOCARDIAL INFARCTION (SAE): Thirty-nine days after the start of study treatment and 18 days after last dose of study medication, the subject had an event of myocardial infarction (myocardial infarction) which resulted in death (Study 101468/164 – Subject 00101 – Myocardial infarction). The myocardial infarction was considered unlikely to be treatment–related.

GSK Medical Evaluation: A case of hallucinations and confusion while taking ropinirole CR 8mg. The hallucinations and confusion are most likely related to the discontinuation of antidepressant and cholinomimetic medications, rather than ropinirole. The relationship to the post-treatment myocardial infarction is unclear.

Clinical Studies

Table 75 summarizes deaths in the clinical studies.

Table 75 Summary of Deaths in Clinical Studies (Original NDA Data-Off (31 May 2006)

Study Number	Subject Number (Age/Gender)	Preferred Term	Treatment (Dose)	Treatment-Related (Y/N)[1]
Placebo				
169	5131 (70/F)	Hip fracture	Placebo(F/U)	N
169	6006 (72/M)	Pneumonia	Placebo(Post F/U)	N
Ropinirole On-Treatment				
169	5987 (75/M)	Pneumonia	Ropinirole CR (16mg/d)	N
196[2]	01103 (78/M)[4]	Intestinal infarction (mesenteric infarction) Cardiac arrest	Ropinirole CR (20mg/d)	N
196[2]	06106 (78/F)	Hemorrhage intracranial Fall	Ropinirole CR(10mg/d)	N
248[2]	653 (71/F)	Ovarian cancer Uterine cancer	Ropinirole CR (8mg/d)	N
248[2]	735 (76/M)	Colon cancer	Ropinirole CR (20mg/d)	N
248[2]	751(74/M)	Myocardial infarction	Ropinirole CR (8mg/d)	N
248[2]	881 (69/F)	Bronchopneumonia	Ropinirole CR (unspecified)	N
248[2]	1024 (79/F)	Pulmonary embolism	Ropinirole CR (8mg/d)	N
248[1]	1031 (68/M)	Atrial fibrillation Cardiovascular disorder Respiratory failure	Ropinirole CR (16mg/d)	N
Ropinirole Follow-up or Post Follow-Up				
164	00101(75/M)	Myocardial infarction	Ropinirole CR (8mg/d) and Ropinirole IR (7.5mg/d)	N
248[2]	183 (71/M)[3]	Sudden death	Ropinirole CR (16mg/d)	N

Data Source: Table A9.2 (m5.3.5.3, Tabulation of Case Narratives); m5.3.5.3; Study 164 Listing DS40; Study 169 Listing 8.2; Study 248 Listing 8.2; ISS Listing 3 (Study 196); OCEANS safety database

1. As judged by the investigator.
2. Study is ongoing.
3. OCEANS narrative for this subject classifies the event as on-treatment because of errors in reporting of dates. The clinical trial database narrative correctly assigns the event to post-treatment (Table A9.2 (m5.3.5.3, Tabulation of Case Narratives) and m5.3.5.3)
4. Subject 01103: intestinal infarction occurred on treatment but cardiac arrest occurred <1 day after last study medication, both TESAEs were marked as fatal. The death is also classified as a follow-up event in Table 5.176 and Table 5.179, see Table 468

Narrative summary descriptions of patients who were treated with ER ropinirole and died in the clinical studies are provided here.

• Study 169, Subject 5987, a 75-year-old male, received oral ropinirole CR and was up-titrated to 16mg daily. On day 148 after the start of investigational product, the subject fell into a lake while fishing, and was admitted to the hospital as he was wet and very cold. A chest x-ray showed basal pneumonia on both sides. Two days after admission the subject lost consciousness and died; an autopsy confirmed cause of death was due to pneumonia. The investigator considered there was no reasonable possibility that the pneumonia was caused by treatment with investigational product.

• Study 196, Subject 01103, a 78-year-old male, was on a stable daily dose of ropinirole CR 20mg daily. On day 367, the subject had an AE of severe intestinal infarction (mesenteric infarction), leading to cardiac arrest and death. He was hospitalized and diagnosed with multiple mesenteric infarcts. An aortogram and visceral arteriogram showed patency of the superior mesenteric and celiac arteries but severe diffuse narrowing of the superior mesenteric arterial branches suggesting diffuse spasm, possible hypovolemic state or possible diffuse inflammatory process.

The investigator reported these events to be unrelated to treatment with investigational product.

• Study 196, Subject 06106, a 76-year-old female, received ropinirole CR in an open-label extension study. 703 days after the start of treatment she had a serious AE of severe hemorrhage intracranial. While boarding a bus, the subject fell backwards, struck her head and lost consciousness for approximately 1 minute. She was awake, alert, and able to answer questions appropriately; however, she had no memory of the fall. A chest X-ray revealed bilateral non-displaced rib fractures. Computed tomography (CT) scan of the head revealed a contusion, a linear, non-displaced occipital skull fracture, and a subarachnoid and a subdural bleed bilaterally within the frontal lobes. She became unresponsive. A repeat CT scan of the head revealed extensive intraparenchymal, intraventricular and subarachnoid hemorrhage. The subject died one day after admission to the hospital. The investigator considered the serious fatal event of intracranial hemorrhage as not related to the investigational product.

• Study 248, Subject 183, a 71-year-old male, was enrolled in an open-label extension study. The subject received ropinirole CR; 228 days after the start of treatment, and 54 days after treatment had ended, during the follow-up phase, he had a special interest serious AE of sudden death (unexpected sudden death) which was not considered to be treatment-related. As the AE occurred post follow-up, no action relating to study medication was reported as a result of the event. It is noted that this AE occurred 54 days post-treatment and that the investigator attributed the fatal event to possible cardiac disease. The subject also had a history of renal failure.

• Study 248, Subject 653, a 71-year-old female subject, died five days after a uterine and ovarian tumor had been identified. At the time of diagnosis the patient was receiving ropinirole treatment at dose of 8mg daily. The cause of death was considered to be uterine and ovarian cancer. The investigator considered that there was no reasonable possibility that the uterine and ovarian cancers were related to treatment with ropinirole.

• Study 248, Subject 735, a 76-year-old male, received oral ropinirole in study 248 starting at 2mg/d and uptitrated to 24mg/d, and then stabilized at a dose of 20mg/d. 174 days after starting ropinirole at 20mg, the subject was hospitalized with a sudden onset of abdominal pain and vomiting. The subject was diagnosed with colon cancer with metastases of the liver and pancreas. Investigational product was discontinued. The subject died two days after diagnosis as a result of ileus caused by the colon cancer. The investigator considered there was no reasonable possibility that the colon cancer may have been caused by investigational product.

• Study 248, Subject 751, a 74-year-old male subject with ongoing medical conditions of hypertension and a history of smoking was found dead at home 426 days after the start of ropinirole treatment in study 248. At the time of the event the patient was taking 8mg ropinirole daily. An autopsy was not performed. The suspected cause of death was a myocardial infarction. The investigator considered that there was no reasonable possibility that the suspected myocardial infarction may have been caused by ropinirole

and that the event was possibly due to the subject's concurrent medical condition and the disease under study.

• Study 248, Subject 881, a 69-year-old female developed severe bronchopneumonia approximately four months after the first dose of ropinirole. Treatment with ropinirole was continued. The subject died 27 days later. Cause of death was bronchopneumonia. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the bronchopneumonia may have been caused by treatment with ropinirole and that the event was possibly due to disease under study (Parkinson's Disease).

• Study 248, Subject 1024, a 79-year-old female who had an ongoing complaint of reduced motor activity of the right leg, developed a severe pulmonary embolism 341 days after the start of ropinirole treatment. At the time of the event the patient was taking 8mg ropinirole daily. The subject was hospitalized. The patient's circulation was reported to have "stopped" and she stopped breathing. After resuscitation, she was hospitalized in an intensive care unit. Three days later the patient suffered a second pulmonary embolism and died the same day. An autopsy was not performed.

The investigator considered that there was no reasonable possibility that the pulmonary embolism may have been caused by ropinirole CR and that the event was possibly due to decreased motor activity of the right leg.

• Study 248, Subject 1031, a 68-year-old male subject had medical conditions at the time of the event which included coronary artery disease and smoking, developed severe paroxysmal atrial fibrillation (confirmed by ECG), severe acute circulatory insufficiency and severe acute respiratory insufficiency 417 days after the start of ropinirole treatment. At the time of the event the subject was receiving 16mg ropinirole daily. The subject died the same day. The cause of death was severe paroxysmal atrial fibrillation and severe acute circulatory insufficiency. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the paroxysmal fast atrial fibrillation, acute circulatory insufficiency and acute respiratory insufficiency may have been caused by treatment with ER ropinirole.

Reviewer Comment

- There was no strong suggestion that any of these deaths were related to treatment with ER ropinirole.

7.1.2 Other Serious Adverse Events (SAEs)

Clinical Pharmacology Studies

Healthy Subjects

One post-study SAE was reported in Study 162 in Subject 107 – "curettage of missed abortion" (preferred term abortion missed) in a subject with an unintended pregnancy, approximately 1 month after the last dose of study drug (ropinirole IR 0.25mg tid). This event was reported as suspected related to treatment.

Parkinson's Disease Patients

Table 76 shows the SAEs in Parkinson's Disease patients in the clinical pharmacology studies.

Table 76 Table of SAEs Reported as of Safety Cut-off Date of 31 May 2006

CLINICAL PHARMACOLOGY STUDIES IN PD SUBJECTS (Studies 164 and 165) (page 1 of 1)

Study Number	Subject Number (Age [years]/ Gender)	Preferred Term	Treatment (dose)	SAE	Withdrawal AE	AESI	AESI Likely[1]	AESI Possible[1]	AESI Unlikely[1]
164	101 (75/M)	Confusional state	Ropinirole CR (9mg)	√	√				
		Myocardial infarction	(Post FU)	√ (Fatal)					
		Hallucination	Ropinirole CR (8mg)	√	√	√	√		
165	50 (70/M)	Pain in extremity	Ropinirole CR (2mg)	√	√				

Abbreviations: SAE=serious adverse event; AE=adverse event; AESI=adverse event of special interest; M=male; CR=controlled-release; FU=follow-up

1. AESI are discussed in detail in Section 11 of the Integrated Summary of Safety (ISS) These events were identified through database searches using well-defined screening procedures for the following terms: gambling and hypersexuality; QTc prolongation and arrhythmia; fibrosis; melanoma; and retinal pathology. Potential events were filtered to determine if they met the pre-specified criteria for a "case" of special interest and were judged 'likely', 'possibly' or 'unlikely' to be of special interest following GSK medical review of the event narrative which included appropriate medical history and clinical and laboratory data.

Clinical Studies

Data sources for the pooled and individual study analyses of treatment-emergent (including down-titration) SAEs were presented. The sponsor emphasized that the pooled analyses are confounded by heterogeneity in study design and patient population, prior dopaminergic treatment, concurrent dopaminergic treatment, initiation vs. maintenance of treatment, and duration of study treatment. In particular, the pooled ropinirole CR treatment group is a combination of data from subjects receiving ropinirole CR both as monotherapy and adjunctive therapy whereas the ropinirole IR treatment group is data from subjects receiving ropinirole IR only as monotherapy.

All treatment-emergent SAEs (TESAEs) with onset during any study period (including down-titration) reported for the Pooled Safety Population from All Parkinson's. were presented for incidence and for number of events.

For *All PD Studies,* subjects in all treatment groups reported a TESAE with the highest incidence observed in the Sinemet group (14%), followed by the ropinirole CR (10%), placebo (4%), and ropinirole IR (1%) groups. The higher incidence among ropinirole CR and Sinemet subjects may be partially attributable to the longer duration of exposure to these treatments compared with placebo or ropinirole IR.

The most common SOCs (occurring in ≥ 2% of any treatment group) with TESAEs were :

- Nervous System Disorders
- General Disorders and Administration Site Conditions

- Infections and Infestations
- Cardiac Disorders
- Renal and Urinary Disorders
- Gastrointestinal (GI) Disorders
- Hepatobiliary Disorders

Generally, differences observed were not >2% among the treatment groups for any SOC.

For the placebo and ropinirole IR groups, no body system had a TESAE incidence >1%. The number of TESAEs reported was highest in the ropinirole CR group (129), followed by the Sinemet (27), placebo (10), and ropinirole IR (3) groups. Similarly, the number of TESAEs reported for each SOC was higher overall in the ropinirole CR group compared with the other treatment groups (except for GI Disorders).

Table 77 shows the most common SAEs in the pooled analyses of randomized, double-blind, controlled studies of ER ropinirole/CR ropinirole vs placebo in study 169, vs IR-ropinirole in study 168) and vs Sinemet in study 228. The pooled analyses of ER ropinirole/CR ropinirole includes patients with early (e.g. monotherapy) and advanced Parkinson's Disease (e.g. adjunctive treatment consisting of at least levodopa, and typically a dopa decarboxylase inhibitor (e.g. usually carbidopa or benserazide).

Table 77 Treatment-Emergent SAEs (Reported in ≥2 Subjects in Any Treatment Group) With Onset During Any Study Period by Preferred Term (Pooled Safety Population: All Parkinson's Disease Studies)

	All Parkinson's Disease Studies (164/165/166/167/168/169/196/228/248)							
	Placebo N=191		Ropinirole CR N=746		Ropinirole IR N=209		Sinemet N=104	
Preferred Term	E[1]	n (%)[2]	E	n (%)[2]	E	n (%)[2]	E	n (%)[2]
Any TESAE	10	8 (4)	129	76 (10)	3	3 (1)	27	15 (14)
Chest pain	0	0	10	8 (1)	0	0	0	0
Coronary artery disease	0	0	4	4 (<1)	0	0	0	0
Hallucination	0	0	4	4 (<1)	0	0	0	0
Chronic obstructive pulmonary disease	0	0	3	2 (<1)	0	0	0	0
Transient ischemic attack	0	0	2	2 (<1)	0	0	1	1 (<1)
Akinesia	0	0	2	2 (<1)	0	0	0	0
Enceshalopathy	0	0	2	2 (<1)	0	0	0	0
Acute coronary syndrome	0	0	2	2 (<1)	0	0	0	0
Non-cardiac chest pain	0	0	2	2 (<1)	0	0	0	0
Osteoarthritis	0	0	2	2 (<1)	0	0	0	0
Gastroenteritis	0	0	2	2 (<1)	0	0	0	0
Rib fracture	0	0	2	2 (<1)	0	0	0	0
Paranoia	0	0	2	2 (<1)	0	0	0	0
Psychotic disorder	0	0	2	2 (<1)	0	0	0	0
Renal failure	0	0	2	2 (<1)	0	0	0	0
Urinary retention	0	0	2	2 (<1)	0	0	0	0
Hypertensive crisis	0	0	2	2 (<1)	0	0	0	0
Cholelithiasis	0	0	2	2 (<1)	0	0	1	1 (<1)
Hyponatremia	0	0	2	2 (<1)	0	0	0	0
Nausea	0	0	0	0	0	0	2	2 (2)

Data Source: Table 5.267 (incidence)]; Table 5.268 (# events) [24 January 2006 clinical trial database cut-off date]
Abbreviations: PD = Parkinson's Disease; CR = controlled-release; IR = immediate-release; TESAE = treatment-emergent adverse event
TESAEs are ordered by decreasing frequency for the ropinirole CR group.
1. # events = the total number of times each event is reported.
2. Incidence = the number and percentage of subjects with TESAE.

Overall, the incidence of TE-SAEs reported at the Preferred Term (PT) level was low. The majority of events were reported in < 1% of subjects among all treatment groups. Only one TE-SAE (nausea in the Sinemet group) was reported with an incidence of ≥ 2%.

A number of events occurred only in the ropinirole CR group. The most common TE-SAEs in the ropinirole CR group were chest pain (1%, 10 events in 8 subjects), coronary artery disease (< 1%, 4 subjects with single events) and hallucination (< 1%, 4 subjects with single events).

Table 78 shows the incidence of TE-SAEs in the pooled controlled trials of patients with advanced Parkinson's Disease. The frequency of TE-SAEs was relatively rare/uncommon.

Table 78 Treatment-Emergent SAEs Occurring in >1 Subject with Onset During Any Study Period Reported at the PT Level (Pooled Safety Population: All Controlled Phase 3 Adjunctive Therapy Studies) [169, 228]

		Treatment and Study Drug Dose Groups for All Controlled Phase 3 Adjunctive Therapy Studies [169 and 228]											
		Placebo				Ropinirole CR				Sinemet			
Preferred Term		≤8 n=191	>8 to ≤16 n=177	>16 n=135	Any N=191	≤8 n=306	>8 to ≤16 n=233	>16 n=140	Any N=306	≤200 n=104	>200 to ≤800 n=36	>800 n=9	Any N=104
Any Event	n (%)	4 (2)	2 (1)	2 (1)	7 (4)	10 (3)	9 (4)	4 (3)	23 (8)	13 (13)	2 (6)	1 (11)	15 (14)
Acute coronary syndrome	n (%)	0	0	0	0	2 (<1)	0	0	2 (<1)	0	0	0	0
	# Events	0	0	0	0	2 [M]	0	0	2 [M]	0	0	0	0
Chest pain	n (%)	0	0	0	0	1 (<1)	0	1 (<1)	2 (<1)	0	0	0	0
	# Events	0	0	0	0	1 [M]	0	1 [M]	2 [M]	0	0	0	0
Gastroenteritis	n (%)	0	0	0	0	0	1 (<1)	1 (<1)	2 (<1)	0	0	0	0
	# Events	0	0	0	0	0	1 [M]	1 [M]	2 [M]	0	0	0	0
Hallucination	n (%)	0	0	0	0	0	1 (<1)	1 (<1)	2 (<1)	0	0	0	0
	# Events	0	0	0	0	0	1 [M]	1 [M]	2 [M]	0	0	0	0
Cellulitis	n (%)	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)	0	0	1 (<1)
	# Events	0	0	0	0	0	1 [M]	0	1 [M]	1 [M]	0	0	1 [M]
Transient ischemic attack	n (%)	0	0	0	0	1 (<1)	0	0	1 (<1)	1 (<1)	0	0	1 (<1)
	# Events	0	0	0	0	1 [T]	0	0	1 [T]	1 [M]	0	0	1 [M]
Nausea	n (%)	0	0	0	0	0	0	0	0	1 (<1)	1 (3)	0	2 (2)
	# Events	0	0	0	0	0	0	0	0	1 [M]	1 [M]	0	2 [M]

Data Source: Table 5.62 [n (%) - Any period, including down-titration; Table 5.99 [# events); Table 5.63 (titration); Table 5.64 (maintenance); Table 5.65 (persisting from titration phase through maintenance phase)

Abbreviations: CR=controlled-release; N(n) = number of subjects; TESAE = treatment-emergent serious adverse event; T=titration phase; M=maintenance phase; P=persisting from titration phase through maintenance phase.

TESAE data were analyzed for incidence (ie, percentage of total number of subjects reporting a given event [n [%]) and total number of events reported (# events) for a given TESAE.

TESAEs are ordered by decreasing incidence in the ropinirole CR any dose group.

TESAEs reported in single subjects are tabulated in Table A9.1(m5.3.5.3, Tabulation of Case Narratives).

Table 79 shows the incidence of TE-SAEs in all pivotal, controlled studies involving treatment with ER ropinirole in each of the pivotal, controlled studies vs the respective comparator.

Table 79 Treatment-Emergent SAEs Occurring in >1 Subject with Onset During Any Study Period Reported at the PT Level (Safety Population: Controlled Phase 3 Studies) [169, 228, 168]

	Treatment and Study Drug Dose Groups for Controlled Phase 3 [169, 228 and 168]											
	Study 169				Study 228				Study 168			
	Placebo N=191		Ropinirole CR N=202		Ropinirole CR N=104		Sinemet N=104		Ropinirole CR N=149		Ropinirole IR N=149	
Preferred Term	E[1]	n (%)[2]	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Any TESAE	--	7 (4)	--	8 (4)	--	15 (14)	--	15 (14)	--	3 (2)	--	3 (2)
Hallucination	0	0	2 [M]	2 (<1)	--	--	--	--	--	--	--	--
Transient ischemic attack	0	0	1 [T]	1 (<1)	0	0	1 [T]	1 (<1)	1 [T]	1 (<1)	0	0
Chest pain	0	0	1 [M]	1 (<1)	1 [M]	1 (<1)	0	0	--	--	--	--
Gastroenteritis	--	--	--	--	2 [M]	2 (2)	0	0	--	--	--	--
Acute coronary syndrome	--	--	--	--	2 [M]	2 (2)	0	0	--	--	--	--
Cellulitis	--	--	--	--	1 [M]	1 (<1)	1 [M]	1 (<1)	--	--	--	--
Lumbar spinal stenosis	--	--	--	--	1 [M]	1 (<1)	1 [M]	1 (<1)	--	--	--	--
Hyponatremia	--	--	--	--	1 [M]	1 (<1)	0	0	1 [M]	1 (<1)	0	0
Chronic sinusitis	--	--	--	--	0	0	2 [M]	1 (<1)	--	--	--	--
Angina pectoris	--	--	--	--	0	0	1 [M]	1 (<1)	0	0	1 [M]	1 (<1)
Nausea	--	--	--	--	0	0	2 [M]	2 (2)	--	--	--	--
Diarrhea	--	--	--	--	0	0	1 [M]	1 (<1)	--	--	--	--
Gastric ulcer	--	--	--	--	0	0	1 [M]	1 (<1)	0	0	1 [M]	1 (<1)
Asthma	--	--	--	--	0	0	2 [M]	1 (<1)	--	--	--	--

Data Source: Study 169: Any period – including down-titration - Table 5.30 (n [%]); Titration - Table 5.31(n[%]), Table 5.84 (# events); Maintenance - Table 5.32 (n [%]), Table 5.85 (# events); Persisting from Titration into Maintenance - Table 5.33 (n [%]); Table 5.86 (# events).

Study 228: Any period – including down-titration - Table 5.46 (n [%]); Titration - Table 5.47 (n [%]); Table 5.92 (# events); Maintenance - Table 5.48 (n [%]), Table 5.93 (# events); Persisting from Titration into Maintenance - Table 5.49 (n [%]); Table 5.94 (# events)

Study 168: Any period – including down-titration - Table 5.14 (n[%]); Titration - Table 5.15 (n [%]), Table 5.76 (# events); Maintenance - Table 5.16 (n [%]), Table 5.77 (# events); Persisting from Titration into Maintenance - Table 5.17 (n [%]), Table 5.78 (# events)

Abbreviations: CR=controlled-release; IR=immediate release; n=number of subjects; TESAE=treatment-emergent serious adverse event; T=titration period; M=maintenance period; P=persisting from titration period into maintenance period.

TESAEs are ordered by decreasing frequency for the ropinirole CR group in Study 228.

TESAEs reported in single subjects are tabulated in Table A9.1 (m5.3.5.3, Tabulation of Case Narratives).

1. # events = the total number of times each event is reported.
2. Incidence = the number and percentage of subjects with treatment-emergent events.

Table 80 shows the incidence of TE-SAEs in any period (e.g. at any time) in the randomized, double-blind, placebo-controlled study (169) of advanced Parkinson's Disease.

Table 80 Number (%) of Subjects with On-Treatment Serious Adverse Events (Fatal and Non-Fatal) (Safety Population: Protocol SK&F-101468/169)

	Ropinirole CR N=202		Placebo N=191	
Preferred Term	n	(%)	n	(%)
Subjects With At Least One SAE	**8**	**(4)**	**7**	**(4)**
Hallucination	2	(<1)	0	
Atrial fibrillation	1	(<1)	0	
Chest discomfort	1	(<1)	0	
Chest pain	1	(<1)	0	
Diabetes mellitus non-insulin-dependent	1	(<1)	0	
Pneumonia	1	(<1)	0	
Syncope	1	(<1)	0	
Transient ischaemic attack	1	(<1)	0	
Urinary retention	1	(<1)	0	
Anxiety	0		1	(<1)
Bronchitis chronic	0		1	(<1)
Cerebral circulatory failure	0		1	(<1)
Contusion	0		1	(<1)
Deep vein thrombosis	0		1	(<1)
Depression	0		1	(<1)
Dyspnoea	0		1	(<1)
Femur fracture	0		1	(<1)
Tremor	0		1	(<1)

Data Source: Section 14, Table 8.39.

Table 81 shows the incidence of TE-SAEs in any period (e.g. at any time) in study 169 when TE-SAE had its onset in the titration period, in the maintenance period, in the down-titration period, in the follow-up period, or persisted into the maintenance period after onset in the titration period. No specific TE-SAE based upon a PT appeared to stand

out as occurring relatively frequently or more frequently than other TE-SAEs for occurring at any time in this study or in a particular phase of the study.

Table 81 Treatment-Emergent SAEs with Onset by Study Period by PT for the Pivotal Placebo-Controlled Study (Adjunctive Therapy) [169] (Safety Population)

	Study 169									
	Titration		Maintenance		Persisting into Maint		Down-Titration		Follow-up	
Preferred Term	PBO	Ropin CR	PBO	Ropin CR	PBO	Ropin CR	PBO	Ropin CR	PBO	Ropin CR
n	191	202	160	188	160	--	178	190	191	202
Any TESAE	5 (3)	1 (<1)	2 (1)	8 (4)	1 (<1)	--	1 (<1)	1 (<1)	2 (1)	0
Cerebral circulatory failure	1 (<1)	0	--	--	1 (<1)	--	--	--	--	--
Transient ischemic attack	0	1 (<1)	--	--	--	--	--	--	--	--
Tremor	1 (<1)	0	--	--	--	--	--	--	--	--
Bronchitis chronic	1 (<1)	0	--	--	--	--	--	--	--	--
Confusion	1 (<1)	0	--	--	--	--	--	--	--	--
Dyspnea	1 (<1)	0	--	--	--	--	--	--	--	--
Deep vein thrombosis	1 (<1)	0	--	--	--	--	--	--	--	--
Hallucination	--	--	0	2 (1)	--	--	--	--	--	--
Anxiety	--	--	1 (<1)	0	--	--	--	--	--	--
Depression	--	--	1 (<1)	0	--	--	--	--	--	--
Chest discomfort	--	--	0	1 (<1)	--	--	--	--	--	--
Chest pain	--	--	0	1 (<1)	--	--	--	--	--	--
Atrial fibrillation	--	--	0	1 (<1)	--	--	--	--	--	--
Pneumonia	--	--	0	1 (<1)	--	--	--	--	--	--
Femur Fracture	--	--	1 (<1)	0	--	--	--	--	--	--
Diabetes mellitus	--	--	0	1 (<1)	--	--	--	--	--	--
Syncope	--	--	0	1 (<1)	--	--	--	--	--	--
Urinary Retention	--	--	0	1 (<1)	--	--	--	--	--	--
Inguinal hernia	--	--	--	--	--	--	1 (<1)	0	--	--
Akinesia	--	--	--	--	--	--	0	1 (<1)	--	--
Pneumonia	--	--	--	--	--	--	--	--	1 (<1)	0
Radius fracture	--	--	--	--	--	--	--	--	1 (<1)	0
Respiratory failure	--	--	--	--	--	--	--	--	1 (<1)	0

Data Source: Table 5.31, Table 5.32, Table 5.33, Table 5.149, Table 5.168
Abbreviations: PBO=Placebo; Ropin CR = Ropinirole CR; Maint = Maintenance

Open-Label Extension Studies [196, 248]

Study 196 and Study 248 are on-going, long term extension studies. Information reported in the clinical database reflects only subjects who either completed or were withdrawn from these studies as of 24 January 2006.

TESAEs captured in the clinical database as of 24 January 2006 for the *Open-Label Extension Studies [196, 248]* are presented summarized at the Preferred Term (PT) level in Table 82. TESAEs are ordered by decreasing incidence in the Monotherapy group. At the PT level, most TESAEs were reported in only 1 subject. Overall, the number and type of TESAEs were similar between the 2 treatment groups.

Table 82 Summary of Treatment-Emergent Serious Adverse Events (Reported in ≥2 Subjects) in Open-Label Extension Studies by Preferred Term *(Safety Population: Open-Label Extension Studies)*

	Open-Label Extension Studies (196/248)	
	Ropinirole CR	
	Monotherapy N=194	Adjunctive Therapy N=326
Preferred Term	n (%)	n (%)
Any Event	26 (13)	24 (7)
Chest pain	4 (2)	2 (<1)
Osteoarthritis	2 (1)	0
Renal failure	2 (1)	0
Coronary artery disease	1 (<1)	2 (<1)
Psychotic disorder	0	2 (<1)
Cholelithiasis	0	2 (<1)
Hypertensive crisis	0	2 (<1)

Data Source: Table 5.123, Table 5.124 [24 January 2006 clinical trial database cut-off date]
TESAEs are ordered by decreasing incidence in the Monotherapy group.

Safety Data (OCEANS)

The information for the TESAEs presented in Table 83 is taken solely from the OCEANS safety database maintained by GSK staff in the department of Global Clinical Safety and Pharmacovigilance. As studies are ongoing at the time of this report, these events have not all been reconciled with the clinical database, so discrepancies between the 2 databases are possible.

From study initiation up to the safety cut-off date 31 May 2006, 93 subjects in studies 196 and 248 experienced 165 SAEs. Fourteen reports were fatal and 151 were non-fatal. The most commonly occurring events were: chest pain (9 reports), coronary artery disease (5 reports), osteoarthritis (4 reports), angina pectoris (3 reports), and back pain (3 reports). There were 6 reports of worsening of Parkinson's disease. The remaining events were diverse in nature with no event reported more than twice. TESAEs reported in ≥ 2 subjects in the long term extension studies 196 and 248 are summarized in Table 83.

Table 83 Summary of SAEs Reported by ≥2 Subjects for Studies 196 and 248 as of 31 May 2006 by SOC and PT(Long-Term Extension Studies 196 and 248)

System Organ Class	Preferred Term	No Subjects	Study Number	Subject ID
Cardiac Disorders	Atrial flutter	2	Study 196 Study 248	06-105 105
	Angina pectoris	3	Study 248	433; 37; 966
	Coronary artery disease	5	Study 196 Study 248	10-102; 02-108 290; 485; 382
General disorders and administration site conditions	Chest pain	8	Study 196 Study 248	10-102; 02-105; 02-102; 14-101; 23-102 290; 409; 1001
Hepatobiliary disorders	Cholelithiasis	2	Study 248	485; 314
Infections and infestations	Pneumonia	2	Study 248	369; 923
	Urinary tract infection	2	Study 196 Study 248	19-102 978
Injury, poisoning and procedural complications	Femur fracture	2	Study 196 Study 248	42-103 78
	Femoral neck fracture	2	Study 196 Study 248	42-103 90
	Fall	2	Study 196 Study 248	06-106 21
Musculoskeletal and connective tissue disorders	Osteoarthritis	4	Study 196 Study 248	11-110; 03-105; 04-101 484
	Back pain	3	Study 248	944; 254; 234
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Colon cancer	2	Study 196 Study 248	01-106 735
Nervous system disorders	Hypokinesia	2	Study 248	251; 874
	Parkinson's disease	6	Study 248	419; 671; 914; 911; 912; 913
	Syncope	2	Study 196 Study 248	25-103 365
Psychiatric disorders	Delirium	2	Study 196 Study 248	02-108 923
	Hallucination, auditory	2	Study 248	369; 191
	Hallucination	2	Study 248	484; 1024
	Paranoia	2	Study 196 Study 248	11-112 369
	Psychotic disorder	2	Study 248	315; 17
Renal and urinary disorders	Renal failure	2	Study 196	42-103; 43-101
	Urinary retention	2	Study 248	372; 446
Reproductive system and breast disorders	Benign prostatic hyperplasia	2	Study 248	446; 726
Respiratory, thoracic and mediastinal disorders	Respiratory failure	2	Study 248	72; 1031
Vascular disorders	Hypertensive crisis	2	Study 248	355; 751

Data Source: Studies 196 and 248

Reviewer Comment

- No SAE stood out as being unusual or worthy of mention.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The reason for study discontinuation for all phase 3, controlled studies is shown according to treatment group in Table 84. The % of patients discontinuing from the study for TEAE is somewhat higher (8 %) for ER ropinirole than for IR ropinirole treatment.

Table 84 Subject Disposition (All Randomized Subjects: All Controlled Phase 3 Studies)

Analysis Population / Category	Treatment Groups for *All Controlled Phase 3 Studies* (Studies 169, 228 and 168)				
	Placebo n=191	Pooled Ropinirole CR n=447	Ropinirole IR n=149	Sinemet n=104	Total[1] N=763
Randomized, N	191	447	149	104	763
Pooled Safety[1], n (%)	191 (100)	446 (>99)	149 (100)	104 (100)	762 (>99)
Completed, n (%)	134 (70)	291 (65)	123 (83)	1 (<1)	426 (56)
Prematurely discontinued, n (%)	57 (30)	155 (35)	26 (17)	103 (>99)	336 (44)
Primary Reason for Premature Discontinuation, n (%)					
Sponsor-terminated study	1 (<1)	79 (18)	0	73 (70)	153 (20)
AE	10 (5)	34 (8)	7 (5)	8 (8)	59 (8)
Subject decided to withdraw	13 (7)	15 (3)	8 (5)	4 (4)	40 (5)
Lack of efficacy	27 (14)	8 (2)	4 (3)	2 (2)	41 (5)
Other[2]	3 (2)	9 (2)	6 (4)	15 (14)	33 (4)
Lost to follow-up	0	2 (<1)	0	0	2 (<1)
Protocol violation	2 (1)	2 (<1)	0	1 (<1)	5 (<1)
Non-compliance	1 (<1)	2 (<1)	0	0	3 (<1)

Data Sources: Table 1.1 [populations]; Table 1.3 [disposition] CSR 168, Listing 6.1, CSR 169, Listing 6.1, CSR 228, Listing 6.1

Abbreviations: CR=controlled-release; IR=immediate-release; N(n)=total (number of subjects); AE=adverse event

Notes: Subjects who received both ropinirole CR and IR in Study 168 were counted once in each treatment group and once in the total column. For this reason, the total number of subjects is less than the number of subjects in each treatment group.

Subjects in the placebo group were all enrolled in Study 169, subjects in the pooled ropinirole CR group were enrolled in all studies indicated, subjects in the ropinirole IR group were enrolled in Study 168, subjects in the Sinemet group were all enrolled in Study 228.

Primary reasons for premature discontinuation are ordered by decreasing incidence for the total group.

1. The Safety Population included subjects who were randomized/enrolled and took at least one study drug dose.
2. 'Other' reasons for discontinuation included the following: for Study 169, Sponsor requested withdrawal of subject due to study conduct violation (3 subjects), necessary to increase dose of L-dopa above baseline level (1 subject), subject enrolled in Study 248 after completing 12 weeks of double-blind treatment (1 subject), subject leaving for winter (1 subject), and safety of subject (1 subject); for Study 228, 14 subjects for dyskinesia, 3 subjects who should have been captured in sponsor-terminated category, 1 subject was incarcerated; and for Study 168, subject did not have a stable Unified Parkinson's Disease Rating Scale (UPDRS) score at the end of the 12-week, Up-Titration Phase (6 subjects), Week 12 UPDRS score (1 subject), and decided by clinician (1 subject).

Additional analyses for reason for study discontinuation are presented for the 2 advanced Parkinson's Disease studies. Table 10 shows that the most common reason for placebo

was lack of efficacy and the most common reason for ER ropinirole was TEAE (although this incidence -6 % was only slightly higher than that for placebo - 5 %).

Table 57 shows that the most common reason for study discontinuation in study 228 comparing ER ropinirole with Sinemet was TEAE for ER ropinirole (14 %) vs only 8 % for Sinemet. Of interest, dyskinesia was the reason for study discontinuation in 12 % of patients treated with Sinemet but only 2 % of patients treated with ER ropinirole.

7.1.3.2 Adverse events associated with dropouts

Pooled analyses of all controlled Parkinson's Disease studies in Table 85 shows that hallucination was the most frequent TEAE (based upon preferred term - PT) and that the frequency for ER ropinirole (2 %) was higher than for placebo (1 %).

Table 85 TEAEs Leading to Discontinuation from Study Drug with Onset by PT During Any Study Period (Including Down-Titration) Reported by > 1 Subject in Any Treatment Group *(Pooled Safety Population: All Parkinson's* Disease Studies)

	All Parkinson's Disease Studies (104/105/108/107/108/109/198/228/248)							
	Placebo N=101		Ropinirole CR N=746		Ropinirole IR N=209		Sinemet N=104	
Preferred Term	E[1]	n (%)[2]	E	n (%)	E	n (%)	E	n (%)
Any TEAE	16	12 (6)	123	79 (11)	14	9 (4)	15	10 (10)
Hallucination	2	2 (1)	15	15 (2)	0	0	0	0
Nausea	1	1 (<1)	8	8 (1)	1	1 (<1)	1	1 (<1)
Somnolence	0	0	6	6 (<1)	0	0	0	0
Dyskinesia	0	0	4	4 (<1)	0	0	2	2 (2)
Paranoia	0	0	4	4 (<1)	0	0	0	0
Vomiting	0	0	4	4 (<1)	1	1 (<1)	0	0
Confusional state	0	0	3	3 (<1)	1	1 (<1)	0	0
Delusion	0	0	3	3 (<1)	0	0	0	0
Hallucination, visual	0	0	3	3 (<1)	0	0	0	0
Amnesia	0	0	2	2 (<1)	0	0	0	0
Dizziness	0	0	2	2 (<1)	0	0	0	0
Insomnia	1	1 (<1)	2	2 (<1)	0	0	1	1 (<1)
Depression	0	0	2	2 (<1)	1	1 (<1)	0	0
Anxiety	0	0	2	2 (<1)	0	0	0	0
Dyspepsia	0	0	2	2 (<1)	1	1 (<1)	0	0
Abdominal pain	0	0	3	2 (<1)	0	0	0	0
Dry mouth	0	0	2	2 (<1)	0	0	0	0
Gait disturbance	0	0	2	2 (<1)	0	0	0	0
Edema peripheral	0	0	2	2 (<1)	0	0	0	0
Hypotension	0	0	2	2 (<1)	0	0	0	0
Tremor	1	1 (<1)	1	1 (<1)	1	1 (<1)	2	2 (2)
Parkinson's Disease	2	2 (1)	1	1 (<1)	0	0	0	0
Parkinsonism	3	3 (2)	0	0	0	0	0	0
Hypoaesthesia	0	0	0	0	2	2 (<1)	0	0
Fatigue	0	0	0	0	1	1 (<1)	2	2 (2)

Data Source: Table 5.269 (incidence); Table 5.270 (# events);
TEAEs are ordered by decreasing frequency for the pooled ropinirole CR group.
Abbreviations: CR = controlled-release; IR = immediate-release; TEAE = treatment-emergent adverse events
1. E = the total number of times each event is reported
2. Incidence = the number and percentage of subjects with treatment-emergent adverse events.

A more focused pooled analysis (Table 86) of TEAEs in both controlled, phase 3 studies of patients with advanced Parkinson's Disease did not suggest a relatively common TEAE associated with study discontinuation.

Table 86 TEAEs Leading to Discontinuation Reported in > 1 Subject in Any Treatment Group with Onset During Any Study Period (Including Down-Titration) by PT *(Pooled Safety* Population: Controlled Phase 3 Adjunctive Therapy Studies) [169/228]

Any Study Period	n (%) of Subjects		
	Controlled Phase 3 Adjunctive Therapy Studies (169/228)		
Preferred Term	Placebo N=191	Ropinirole CR N=306	Sinemet N=104
Any TEAE	12 (6)	24 (8)	10 (10)
Hallucination	2 (1) [T,M]	4 (1) [T,M,P]	0
Nausea	1 (<1) [T]	4 (1) [T,P]	1 (<1) [M]
Dyskinesia	0	2 (<1) [T,M]	2 (2) [M]
Depression	0	2 (<1) [T,M]	0
Dry mouth	0	2 (<1) [T,M]	0
Edema peripheral	0	2 (<1) [M]	0
Somnolence	0	2 (<1) [M]	0
Tremor	1 (<1) [T]	1 (<1) [M]	2 (2) [T,M]
Parkinson's disease	2 (1) [T]	1 (<1) [M]	0
Chest pain	0	1 (<1) [M]	1 (<1) [M]
Feeling jittery	0	1 (<1) [M]	1 (<1) [T]
Parkinsonism	3 (2) [T,M,P]	0	0
Insomnia	1 (<1) [T]	0	1 (<1) [T]
Fatigue	0	0	2 (2) [T, M, P]

Data Source: Table 5.66 - Any period; Table 5.67 (titration); Table 5.68 (maintenance); Table 5.69 (persisting from titration phase into the maintenance phase); Table 5.158 (down-titration)
Abbreviations: CR=controlled-release; N(n) = number of subjects; TEAE=treatment-emergent adverse event ; T=titration phase; M=maintenance phase; P=persisting from titration phase into the maintenance phase.
TEAEs are ordered by decreasing incidence in the ropinirole CR any dose group.
No TEAEs were reported during the down-titration period.

Table 87 shows the frequency of specific TEAEs leading to study discontinuation in each of the phase 3 controlled studies. TEAEs occurring in ~ 2 % of patients treated with ER ropinirole were hallucination, nausea, somnolence, peripheral edema, and depression. The frequency of any TEAE leading to study discontinuation in any study phase was too low to be able to see any differences for these TEAEs developing in the titration or maintenance phase or how frequent these TEAEs that developed in the titration phase persisted into the maintenance phase. Although TEAEs shown in Table 87 were supposed to be presented only if occurring in > 2 patients in any phase 3 study, there are some error in that several TEAEs (e.g. dizziness, dry mouth, feeling jittery, dyspepsia, vomiting, syncope, anxiety, insomnia, chest pain, confusional state, hypoesthesia) are presented but only appeared to occur in 1 patient in a treatment group.

Table 87 TEAEs Leading to Discontinuation from Study Drug with Onset Reported in > 1 Subject in Any Treatment Group During Any Study Period (Including Down-titration) by PT *(Safety Populations: Controlled Phase 3 Studies) [169, 228, 168]*

	n (%) of Subjects					
	Study 169		Study 228		Study 168	
Preferred Term	Placebo N=191	Ropinirole CR N=202	Ropinirole CR N=104	Sinemet n=104	Ropinirole CR n=140	Ropinirole IR n=149
Any event	12 (6)	9 (4)	15 (14)	10 (10)	6 (4)	8 (5)
Hallucination	2 (1) [T,M]	4 (2) [T,M,P]	1 (<1) [M]	0	3 (2) [T,M]	0
Nausea	1 (<1) [T]	2 (<1) [T,P]	2 (2) [T]	1 (<1) [M]	1 (<1) [T]	1 (<1) [M]
Somnolence	--	--	2 (2) [M]	0	--	--
Edema peripheral	--	--	2 (2) [M]	0	--	--
Depression	--	--	2 (2) [T,M]	0	0	1 (<1) [T]
Dyskinesia	0	1 (<1) [T]	1 (<1) [M]	2 (2) [M]	--	--
Parkinson's disease	2 (1) [T]	0	1 (<1) [M]	0	--	--
Dizziness	--	--	1 (<1) [M]	0	--	--
Tremor	1 (<1) [T]	0	1 (<1) [M]	2 (2) [T,M]	0	1 (<1) [M]
Dry mouth	0	1 (<1) [T]	1 (<1) [M]	0	--	--
Feeling jittery	--	--	1 (<1) [M]	1 (<1) [T]	--	--
Dyspepsia	--	--	1 (<1) [T,P]	0	1 (<1) [T]	1 (<1) [M]
Vomiting	--	--	1 (<1) [T]	0	0	1 (<1) [M]
Parkinsonism	3 (2) [M,P]	0	--	--	--	--
Syncope	0	1 (<1) [M]	--	--	0	1 (<1) [T]
Anxiety	0	1 (<1) [M]	--	--	1 (<1) [M]	0
Hallucination, visual	0	1 (<1) [T]	--	--	1 (<1) [T]	0
Insomnia	1 (<1) [T]	0	0	1 (<1) [T]	--	--
Chest pain	0	1 (<1) [M]	0	1 (<1) [M]	--	--
Fatigue	--	--	0	2 (2) [T,M]	0	1 (<1) [T]
Confusional state	--	--	--	--	1 (<1) [M]	1 (<1) [M]
Hypoaesthesia	--	--	--	--	0	2 (1) [T,M]

Data Source: Study 169: Any period – Table 5.34 (n [%]); Titration – Table 5.35; Maintenance –Table 5.36; Persisting from Titration into Maintenance – Table 5.37; Down-titration –Table 5.150.

Study 228: Any period – Table 5.50 (n [%]); Titration – Table 5.51; Maintenance – Table 5.52; Persisting from Titration into Maintenance – Table 5.53; Table 5.154 – Down-titration.

Study 168: Any period – Table 5.18 (n[%]); Titration – Table 5.19; Maintenance – Table 5.20 – Persisting from Titration into Maintenance. Table 5.21; Down-titration –Table 5.146.

Abbreviations: CR=controlled-release; IR-immediate release; TEAE=treatment-emergent adverse event; T=titration phase; M=maintenance phase; P=persisting from titration phase into the maintenance phase.

TEAEs are ordered by decreasing frequency for the ropinirole CR group in study 228.

No TEAEs were reported during the Down-titration Period in any of the controlled phase 3 studies.

Table 88 shows the frequency of any TEAE leading to study discontinuation according to treatment group in the only randomized, double-blind, placebo-controlled phase 3 study. Hallucination was slightly more common with ER ropinirole than with placebo. If one combines "hallucination visual" with "hallucination" (and the patient with "hallucination visual" was not counted as discontinuing because of "hallucination"), then the frequency for hallucination is 2 % and twice the frequency for the placebo group. The frequency that nausea led to study discontinuation was also approximately twice as frequent for ER ropinirole (~ 1 %) than for placebo (~ 0.5 %)

Table 88 Number (%) of Subjects with Adverse Events Leading to Withdrawal During the On-Treatment Phase (Safety Population: Protocol SK&F-101468/169)

	Ropinirole CR N=202		Placebo N=191	
Preferred Term	n	(%)	n	(%)
Subjects With At Least One AE Leading to Withdrawal [1]	11	(5)	10	(5)
Hallucination	3	(1)	2	(1)
Nausea	2	(<1)	1	(<1)
Abdominal discomfort	1	(<1)	0	
Anxiety	1	(<1)	0	
Chest pain	1	(<1)	0	
Diplopia	1	(<1)	0	
Dry mouth	1	(<1)	0	
Dyskinesia	1	(<1)	0	
Hallucination, visual	1	(<1)	0	
Hypertension	1	(<1)	0	
Pneumonia	1	(<1)	0	
Syncope	1	(<1)	0	
Tachycardia	1	(<1)	0	
Vertigo	1	(<1)	0	
Parkinsonism	0		2	(1)
Akathisia	0		1	(<1)
Bradykinesia	0		1	(<1)
Dyspnoea	0		1	(<1)
Insomnia	0		1	(<1)
Mobility decreased	0		1	(<1)
Muscle spasms	0		1	(<1)
Parkinson's disease	0		1	(<1)
Swelling	0		1	(<1)
Tremor	0		1	(<1)

Data Source: Section 14, Table 8.50.

1. It should be noted that these numbers are based on the data recorded on the AE pages of the CRF, rather than on the 'End of Study Record' (the End of Study Record shows the *primary* reason for withdrawal). One of the subjects in the placebo group with an on-treatment AE leading to withdrawal had 'subject decided to withdraw from the study', rather than 'adverse event' cited as the primary reason for premature discontinuation on the end of study record (see subject disposition in Section 6.1).

Open-Label Extension Studies [196, 248]

All TEAEs leading to study drug discontinuation reported for the ongoing *Open-Label Extension Studies [196, 248]* are presented in Table 89. A higher incidence of subjects in the monotherapy group (11%) discontinued from study drug compared with the adjunctive therapy group (7%). As with the other study groupings, the most common SOC classes associated with discontinuation were Nervous System, Psychiatric, Gastrointestinal Disorders, and General Disorders and Administration Site Conditions. Overall the number and type of TEAEs were similar between the groups. The incidence of Nervous System Disorders was higher in the monotherapy group (4%) compared with the adjunctive therapy group (1%).

Table 89 TEAEs Leading to Study drug Discontinuation in Open-Label Extension Studies (196, 248)

	Open-Label Extension Studies (196/248)	
	Ropinirole CR (N=495))	
	Monotherapy N=194	Adjunctive Therapy N=326
Preferred Term	n (%)	n (%)
Any Event	22 (11)	24 (7)
Somnolence	3 (2)	1 (<1)
Paranoia	2 (1)	1 (<1)
Amnesia	1 (<1)	0
Dizziness	1 (<1)	0
Multiple sclerosis	1 (<1)	0
Nervous system disorder	1 (<1)	0
Apathy	1 (<1)	0
Confusional state	1 (<1)	0
Delusion	1 (<1)	1 (<1)
Hallucination	1 (<1)	7 (2)
Mania	1 (<1)	0
Sleep attacks	1 (<1)	0
Abdominal distension	1 (<1)	0
Abdominal pain	1 (<1)	0
Intestinal infarction	1 (<1)	0
Nausea	1 (<1)	1 (<1)
Gait disturbance	1 (<1)	1 (<1)
Edema	1 (<1)	0
Joint swelling	1 (<1)	0
Osteoarthritis	1 (<1)	0
Aortic aneurysm rupture	1 (<1)	0
Orthostatic hypotension	1 (<1)	0
Urinary tract infection	1 (<1)	0
Breast cancer	1 (<1)	0
Renal failure	1 (<1)	0
Psychotic disorder	0	1 (<1)
Dyskinesia	0	2 (<1)
Brain mass	0	1 (<1)
Disorientation	0	1 (<1)
Hallucination, auditory	0	1 (<1)
Hallucination, visual	0	1 (<1)
Insomnia	0	1 (<1)
Vomiting	0	2 (<1)
Difficulty walking	0	1 (<1)
[illegible]	[illegible]	[illegible]
Influenza-like illness	0	1 (<1)
Pain	0	1 (<1)
Hypertensive crisis	0	1 (<1)
Hypotension	0	1 (<1)
Vascular pseudoaneurysm	0	1 (<1)
Colon cancer	0	1 (<1)
Non-small cell lung cancer	0	1 (<1)
Bradycardia	0	1 (<1)
Post-procedural hematoma	0	1 (<1)

Data Source: Table 5.125; Table 5.126
Abbreviations: CR=controlled-release

Generally, the type and frequency of TEAEs leading to study drug withdrawal were similar between the monotherapy and adjunctive therapy groups. Hallucination was reported in 7 subjects (2%) in the adjunctive therapy group compared with 1 subject (<1%) in the monotherapy group. Auditory and visual hallucination are also noted

separately from "hallucination." Assuming these hallucinatory TEAEs occurred in different subjects, the frequency for hallucination leading to study drug discontinuation increases further.

Reviewer Comment

- Hallucination and nausea appear to be the most common TEAEs leading to study and drug discontinuation. Considering that the development of hallucination and nausea are associated with an increased risk in the titration period, and that these TEAEs can prompt study treatment discontinuation, the titration rate for ER ropinirole should be conservative and not excessively rapid to increase the chances that patients will tolerate ER ropinirole, particularly during up-titration.

7.1.3.3 Other significant adverse events

Analyses of TEAEs of "special interest" are presented in the following section (7.1.4 Other Search Strategies).

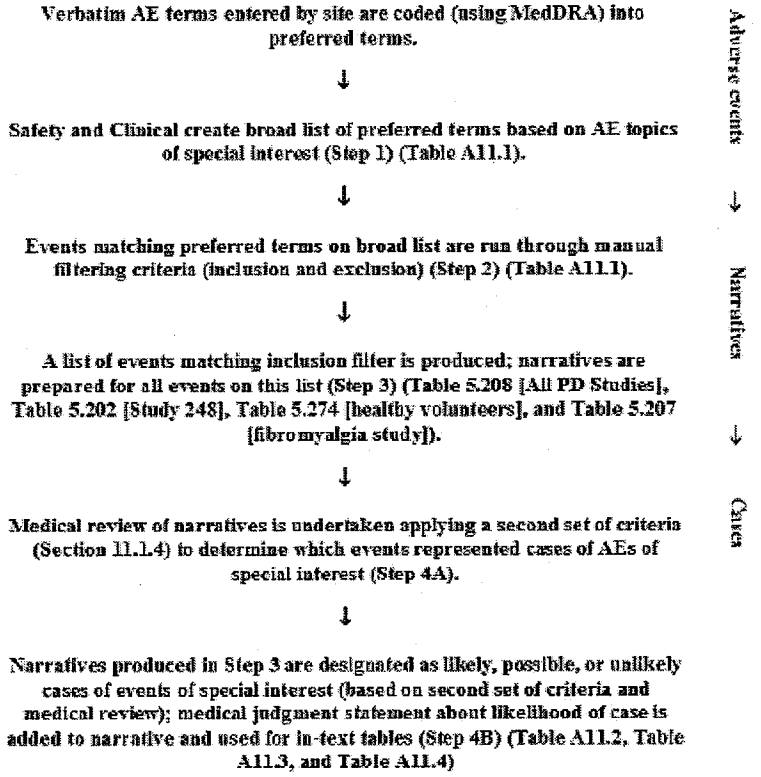
7.1.4 Other Search Strategies

AE topics of special interest (AESI) are based on known effects of ropinirole's pharmacologic class (dopaminergic agonist) such as **hypotension, hallucination, syncope, sudden onset of sleep, and withdrawal-emergent confusion and hyperpyrexia [neuroleptic malignant syndrome], preclinical findings (retinal pathology), and other relevant interests (QTc prolongation, clinically significant arrhythmia, relevant fibrotic complications, compulsive behaviors consisting of pathological gambling or of hypersexuality, fall/injury, or melanoma).** Evaluation of the special interest topics is best considered by review of multiple MedDRA® preferred terms. In order to best describe the proportion of subjects that experienced an event of special interest, a comprehensive screening and review process was applied for selection of subjects that experienced events of special interest.

This section and Figure 14 summarize the screening process by which AEs are determined. Narratives for each potential event were submitted.

Evaluation of the special interest topics was determined through a review of multiple MedDRA® preferred terms. A comprehensive screening and review process was then applied for selection of subjects that experienced events of special interest. The potential events were filtered to determine if the event is one that is a potential "case" of special interest. Cases were defined as events which satisfied the pre-specified criteria for the special interest topic and were judged likely or possibly an event of special interest following GSK medical review of the event narrative, including consideration of appropriate medical history and clinical and laboratory data.

Figure 14 Flow Diagram Describing Process of Defining Cases of TEAEs of Special Interest



Methodology for Selection of Cases and Narratives for Adverse Events of Special Interest

The sponsor's 4-step process for determining Events and Cases for AESIs is described below :

Step 1: Generation of a Broad Screen

A computerized search strategy was developed for identifying TEAEs/AEs requiring review in order to determine if the event was to be classified in a special interest category (potential cases that might represent a special interest AE). The GSK clinical development team and the Global Clinical Safety and Pharmacovigilance (GCSP) team collaborated to create a broad list of MedDRA preferred terms to be reviewed for each topic of special interest. This list is consistent with the approach used to survey the post marketing surveillance database and is applied to all clinical trials in which ropinirole CR is studied. Tabular summaries of all AEs identified during this broad screen search process were provided for all studies of ropinirole CR. ***These tabulated events were not all considered to be cases of AEs of potential interest. Rather, they are a comprehensive list of all events requiring further information/evaluation in order to determine whether or not they are judged AEs of potential interest.***

Step 2: Filtering to Potential AEs of Special Interest

A subset of these events was selected following manual application in a blinded fashion of a set of pre-specified filtering criteria developed by a medical reviewer based on relevant clinical data collected in the CRFs. Some of these filtering criteria were based upon the terms themselves, if they generated a clear reason that the potential event from the screen was not an event of interest (e.g., congenital fibrosis, for the topic of fibrosis).

Other criteria are based upon application of additional information (e.g. blood pressures for the topic of hypotension). A list of filtering criteria was used to generate a list of events requiring a narrative, if they satisfied the following criteria :

- Hallucinations: any event with a preferred term including "hallucination", "illusion", or "delusion."
- Withdrawal-emergent confusion and hyperpyrexia – Neuroleptic Malignant Syndrome (NMS): any event that occurs following drug withdrawal, and that also includes any one of a variety of preferred terms such as "hyperpyrexia", "confusional state", "muscle rigidity" or many others.
- Retinal pathology: any event with either: 1) the term "retina" AND a verbatim term suggesting degeneration or decline; OR 2) the term "scotoma" or "blindness."
- Fall / injury: any of a number of terms such as "fall", "fracture", "wound", AND no verbatim terms suggesting that the event occurred in some manner other than a fall (e.g. scratch due to animal).
- QTc abnormality, and arrhythmia: any term including any type of arrhythmia, or any term that can be used to describe cases with QT prolongation (e.g. torsade de pointes, sudden cardiac death, etc.).
- Syncope: any term including "syncope", or "loss of consciousness" or "collapse", unless verbatim term states consciousness is preserved.
- Hypotension: 1) any term including "hypotension" or "blood pressure decreased", OR 2) any term including "vertigo" or "dizziness" or "blood pressure immeasurable" AND a blood pressure (BP) within 2 weeks of the event that indicates a severe drop in systolic or diastolic BP.
- Melanoma: any term of "melanoma" or "spitz" or "skin neoplasm malignant."
- Compulsive behavior consisting of pathological gambling and hypersexuality : 1) any term including "gambling" or "high risk sexual behavior" or "libido increased", OR 2) any term including "obsess" or "compulsive" or "libido", AND verbatim term suggests gambling, or sexual behavior; OR 3) a host of personality or psychiatric disorders (e.g. mania) AND verbatim suggests compulsion.
- Sudden Onset of Sleep: 1) any term including "sleep attack" or "sudden onset of sleep", OR 2) any term including "somnolence" or "impaired driving" AND verbatim term suggesting sudden onset or attack; OR 3) "road traffic accident" unless the verbatim term rules out somnolence or a sudden onset of sleep.
- Fibrosis: any of a host of terms including "fibro" or "pleural effusion" or "pericardial effusion" or other terms that describe cardiac valve abnormalities (excluding events by medical judgment, such as cystic fibrosis or injection site fibrosis).

Step 3: Narratives for Potential AEs of Special Interest

The sponsor summarized the potential AESIs for the Clinical Pharmacology and Phase III clinical studies, respectively. Separate narratives for all potential AESIs based on the filtering search strategy were provided.

Step 4: Identification of Cases of AEs of Special Interest

The narrative descriptions of potential special interest events were submitted for medical review and a second final set of criteria were applied to determine which of these events represented cases, as follows:

- Hallucinations: medical judgment for any event descriptions not containing the word "hallucinations".
- Withdrawal-emergent confusion and hyperpyrexia, NMS: must have onset within 30 days of drug withdrawal, AND must include any 2 of the following: fever; confusion; motor symptoms; elevated creatine phosphokinase (CPK) – provided medical judgment does not suggest an alternate etiology (e.g. urinary tract infection with fever and confusion during the withdrawal period).
- Retinal pathology: all, provided medical judgment does not suggest an alternate etiology (e.g. blindness secondary to old injury).
- Falls / injury: all falls; and all injuries, provided nature of the injury suggests an alternate etiology (non-fall) for the injury (e.g., wound due to knife injury), AND provided that blood pressures recorded within 2 weeks of the event support a hypotensive etiology.
- QTc prolongation and cardiac arrhythmia: 1) any QT AE, provided medical judgment does not contravene (e.g. congenital QT prolongation), OR 2) any arrhythmia unless medical judgment suggests the arrhythmia is not clinically meaningful (e.g. U-wave abnormality).
- Syncope: 1) any event with loss of consciousness described within narrative; OR 2) any event in which no other information is available.
- Hypotension: 1) any event with the term of "hypotension" or "blood pressure decreased"; OR 2) any event in this category meeting blood pressure criteria within 2 weeks of the event, with appropriate time course subject to medical judgment.
- Melanoma: any preferred or verbatim term including "melanoma", or description consistent with melanoma.
- Compulsive behaviors consisting of pathological gambling or hypersexuality. Pathological gambling: any description containing gambling, unless medical judgment suggests non-pathological. Hypersexuality: 1) any description of increased libido, provided this is not a return to normal; OR 2) any description of changed sexual behavior that suggests compulsion or obsession.
- Sudden onset of sleep: 1) any description of any sudden onset or attack of sleep, OR 2) any sudden impairment of driving ability, OR 3) any road traffic accident in which there is no exculpatory information.
- Fibrosis: any event in this category for which the totality of information suggests a fibrosis-related etiology.

Following application of the above criteria and medical review, the GSK medical opinion about each event regarding its likelihood as a case was provided at the end of each narrative, in a section entitled "GSK medical judgment about the narrative".

All events of interest were identified as cases, using "likely", "possible", or "unlikely" tags. Likely cases meet the criteria in every way; possible cases may meet some criteria but other key criteria cannot be ascertained, or can be ascertained but may not be present at the exact time of the event (e.g. blood pressure criteria within 2 weeks of the event); and unlikely cases do not appear to meet the criteria. Events that were judged to be "likely" or "possible" were considered to be cases and were subject to further analysis. Details for identified events of special interest were provided. A listing of subjects identified as having "unlikely" cases and the reasons for the judgment of "unlikely" were also presented.

General Considerations for Analyses

Tabulation of AEs Meeting Screening Criteria for Narratives

Tables displaying TEAEs/AEs that met the broad screening criteria for AESI topics were provided. It should be noted that, in order to provide the most comprehensive set of events for review, the set of AEs considered for this screening were broader than the "treatment emergent" for the remainder of this integrated summary. In addition to the standard TEAEs, the following
events were also generally considered:

- AEs from extension studies that were not classified as emergent because they were present during the parent study at the same or at higher severity.
- AEs from Study 196 that could not be assigned to a study phase due to incomplete exposure data.
- Post treatment AEs
- AE present pre-treatment at the same or at higher intensity, and so not treatment emergent.

This combined set of AEs, hereafter called the "All AESI Set," includes TEAEs, AEs during down titration, AEs from ongoing studies that could not be assigned to a treatment period, and 34 AEs meeting the criteria outlined above that were selected as events for which a narrative was required. For the AESI topic "Withdrawal emergent confusion and hyperpyrexia, NMS," these analyses included AEs during the down titration and follow-up phases. The majority of the analyses in this AESI section were based on this AESI set and, therefore, reflect the number of subjects for which narratives were produced. There were 393 events in 234 subjects in the All AESI Set for the All Parkinson's Disease Studies pool.

In addition, a second set of data was used to analyze AESI data, hereafter referred to as the "Modified AESI Set." This set includes TEAEs, AEs during down-titration, and AEs from ongoing studies that could not be assigned to a treatment period. For the AESI topic "Withdrawal emergent confusion and hyperpyrexia, NMS," these analyses included AEs during the down-titration and follow-up phases. Modified AESI Set tables were prepared for the All PD Studies pool, and for individual Studies 168, 169, and 228. There are 359 events in 225 subjects in the Modified AESI Set for the All PD Studies pool.

I have focused on presenting analyses of this "Modified AESI set" because the they seem more appropriate and more likely to be treatment-emergent.

AEs requiring a narrative for AE topics of special interest for All PD Studies are summarized by treatment group in Table 90. Differences between the Modified AESI Set and the All AESI Set are noted in bold font. Overall, the profile of AEs requiring a narrative for AE topics of special interest for All Parkinson's Disease Studies from the Modified AESI Set was not substantially different from the results observed for this pool in the All AESI Set.

Table 90 **AEs Requiring a Narrative for Special Interest Topics, by Treatment Group (Pooled Safety Populations: All PD Studies [164, 165, 166, 167, 168, 169, 196, 228] – Modified AESI Set)**

	Number of Subjects with Events by Treatment Group							
	Placebo N= 191		Ropinirole CR N=613		Ropinirole IR N=209		Sinemet N=104	
AESI Topic	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
Sudden onset of sleep	1	1 (<1)	6	5 (<1)	1	1 (<1)	0	0
Syncope	0	0	7	7 (1)	6	5 (2)	0	0
Hypotension	9	5 (3)	63	49 (8)	25	17 (8)	2	2 (2)
Fall/Injury	11	10 (5)	90	54 (9)	11	6 (3)	17	7 (7)
Hallucinations[1]	6	5 (3)	59	45 (7)	3	3 (1)	1	1 (<1)
Withdrawal emergent confusion and hyperpyrexia, NMS	1	1 (<1)	4	3 (<1)	2	2 (<1)	0	0
Compulsive behaviors consisting of pathological gambling and hypersexuality[2]	0	0	9	6 (<1)	1	1 (<1)	0	0
QTc prolongation and arrhythmia	3	2 (1)	18	14 (2)	0	0	1	1 (<1)
Fibrosis	0	0	2	2 (<1)	0	0	0	0
Melanoma[3]	0	0	1	1 (<1)	0	0	1	1 (<1)
Retinal pathology	0	0	2	2 (<1)	1	1 (<1)	0	0

Data Source: Table 5.278 (n %) and Table 5.290 (# events); Listing 5.6
Abbreviations: AESI=adverse event of special interest; CR=controlled release; IR=immediate release; NMS=Neuroleptic Malignant Syndrome

1. Subject 62 (Study 228, ropinirole CR), had an AE reported as "auditory hallucinations" that is not reflected in Table 5.278, and Table 5.290; the subject was already included in these tables because she also had an olfactory hallucination that was counted. The auditory hallucination event has been added here for completeness.
2. Subject 3102 (Study 196, ropinirole CR) had an AE reported as "increase in compulsive gambling" that is not reflected in Table 5.278. The event has been added here for completeness.
3. Subject 6103 (Study 196, ropinirole CR) had an AE reported as "melanoma removal right ear," but actual pathology was "basal cell carcinoma" and this is not counted as a case of melanoma.

Note: This table summarizes events requiring narratives. Not all events requiring narratives comprise a "case" of an AE topic of special interest. Cases of AE topics of special interest were determined by another procedure that followed generation of this narrative list. Subjects could report more than one AESI.
Note: Differences between the Modified AESI Set and the All AESI Set are noted in bold font.

Table 91 presents potential cases with their identification as likely, possible, or unlikely cases of AESI following GSK medical review. Differences between the Modified AESI Set and the All AESI Set are noted in bold font. However, there was no suggestion of a substantial /major difference between these datasets.

Table 91 **Identification of AEs Requiring a Narrative for Special Interest Topics as Likely, Possible, or Unlikely Cases *(Pooled Safety Populations: All PD Studies [164, 165, 166, 167, 168, 169, 196, 228]* –Modified AESI Set)**

	Number of Subjects with Events by Treatment Group											
	Placebo N= 191			Ropinirole CR N=613			Ropinirole IR N=209			Sinemet N=104		
AESI Topic	L	P	U	L	P	U	L	P	U	L	P	U
Sudden onset of sleep	0	1	0	2	3	0	0	1	0	0	0	0
Syncope	0	0	0	6	1	0	5	0	0	0	0	0
Hypotension	3	0	2	38	6	7	10	7	0	1	1	0
Fall/Injury	10	0	0	48	3	4	6	0	0	7	0	0
Hallucinations	5	0	0	44	1	1	3	0	0	0	1	0
Withdrawal emergent confusion and hyperpyrexia, NMS	0	0	1	0	0	3	0	0	2	0	0	0
Compulsive behaviors consisting of pathological gambling and hypersexuality	0	0	0	6	0	0	1	0	0	0	0	0
QTc prolongation and arrhythmia	1	0	1	13	0	1	0	0	0	0	1	0
Fibrosis	0	0	0	0	0	2	0	0	0	0	0	0
Melanoma	0	0	0	0	0	1	0	0	0	1	0	0
Retinal pathology	0	0	0	1	1	0	0	0	1	0	0	0

Data Source: Table A11.2 (m5.3.5.3, Tabulation of Case Narratives); Listing 5.6
Abbreviations: CR=controlled release; IR=immediate release; L=likely case; NMS= Neuroleptic Malignant Syndrome; P=possible case; U=unlikely case
Note : A single subject can potentially count in each of the L, P, and U columns within a single special interest category, therefore, the totals in this table may not match the totals in tables that count subjects as cases (the sum of likely and possible events), in which such a subject count only once.
Note: Differences between the Modified AESI Set and the All AESI Set are noted in bold font.

In the All PD Studies pool (Table 92), there were differences of 1 to 3 subjects (no change in %) between the All AESI Set and Modified AESI Set for syncope; hypotension; fall/injury; hallucinations; withdrawal-emergent confusion and hyperpyrexia, NMS; and QTc prolongation and arrhythmia. There were relatively minimal differences observed between the All AESI Set and Modified AESI Set.

Table 92 **AEs Requiring a Narrative for Special Interest Topics, by Treatment Group *(Safety Populations: Study 169, Study 228, Study 168; Pooled Safety Population: All Controlled Phase 3 Adjunctive Therapy Studies [169 and 228]*,All PD Studies – Modified AESI Set)**

	Treatment Group															
	Placebo		Ropinirole IR		Sinemet		Ropinirole CR									
	Study 169 N=191		Study 168 N=149		Study 228 N=104		Study 169 N=202		Study 228 N=104		Study 168 N=149		All Controlled Phase 3 Adjunctive Studies [169, 228] N=306		All PD Studies N=613	
AESI Topic	# Events	n (%)	# Events	n (%)	# Events	n (%)	# Events	n (%)	# Events	n (%)	# Events	n (%)	# Events	n (%)	# Events	n (%)
Sudden onset of sleep	1	1 (<1)	1	1 (<1)	0	0	3	2 (<1)	0	0	0	0	3	2 (<1)	6	5 (<1)
Syncope	0	0	6	5 (3)	0	0	2	2 (<1)	2	2 (2)	2	2 (1)	4	4 (1)	7	7 (1)
Hypotension	9	5 (3)	14	10 (7)	2	2 (2)	19	14 (7)	3	3 (3)	3	3 (2)	22	17 (6)	63	49 (8)
Fall/Injury	11	10 (5)	10	5 (3)	17	7 (7)	17	13 (6)	21	12 (12)	11	7 (5)	38	25 (8)	96	54 (9)
Hallucinations[1]	6	5 (3)	3	3 (2)	1	1 (<1)	21	16 (8)	7	6 (6)	10	5 (4)	28	22 (7)	59	45 (7)
Withdrawal emergent confusion and hyperpyrexia, NMS	1	1 (<1)	0	0	0	0	2	2 (<1)	0	0	0	0	2	2 (<1)	4	3 (<1)
Compulsive behaviors consisting of pathological gambling and hypersexuality[2]	0	0	1	1 (<1)	0	0	3	2 (<1)	2	1 (<1)	0	0	5	3 (<1)	9	6 (<1)
QTc prolongation and arrhythmia	3	2 (1)	0	0	1	1 (<1)	4	4 (2)	1	1 (<1)	2	2 (1)	5	5 (2)	18	14 (2)
Fibrosis	0	0	0	0	0	0	0	0	1	1 (<1)	0	0	1	1 (<1)	2	2 (<1)
Melanoma[3]	0	0	0	0	1	1 (<1)	0	0	0	0	0	0	0	0	1	1 (<1)
Retinal pathology	0	0	0	0	0	0	1	1 (<1)	1	1 (<1)	0	0	2	2 (<1)	2	2 (<1)

Data source: Table 5.276 (169: n, %), Table 5.288 (164; # events), Table 5.277 (228: n, %), Table 5.289 (228; # events), Table 5.275 (168: n, %), Table 5.287 (168; # events), Table 5.278 (All PD Studies: n, %), Table 5.290 (All PD Studies, # events); Listing 5.6
Abbreviations: AESI=adverse event of special interest; CR=ropinirole controlled release; IR=ropinirole immediate release; NMS=Neuroleptic Malignant Syndrome
1. Subject 62 (Study 228, ropinirole CR), had an AE reported as "auditory hallucinations" that is not reflected in Table 5.277, Table 5.289, Table 5.278, and Table 5.290; the subject was already included in these tables because she also had an olfactory hallucination that was counted. The auditory hallucination event has been added here for completeness.
2. Subject 3102 (Study 196, ropinirole CR) had an AE reported as "increase in compulsive gambling" that is not reflected in Table 5.278. The event has been added here for completeness.
3. Subject 6103 (Study 196, ropinirole CR) had an AE reported as "melanoma removal right ear," but actual pathology was "basal cell carcinoma" and this is not counted as a case of melanoma.
Note: This table summarizes events requiring narratives. Not all events requiring narratives comprise a "case" of an AE topic of special interest. Cases of AE topics of special interest were determined by another procedure that followed generation of this narrative list. Subjects could report more than one AESI.
Note: Differences between the Modified AESI Set and the All AESI Set are noted in bold font.

Sponsor's Summary About TEAEs of Special Interest

Using a well-defined screening process, databases were searched for AEs of special interest including the following topics: sudden onset of sleep; syncope; hypotension; fall/injury; hallucinations; withdrawal-emergent confusion and hyperpyrexia, NMS; compulsive behaviors consisting of pathological gambling and hypersexuality; QTc prolongation and arrhythmia; fibrosis; melanoma; and retinal pathology. The potential events were filtered to determine if the event was a "case" of special interest, that is, whether it satisfied the pre-specified criteria for the special interest topic and were judged likely or possibly an event of special interest following GSK medical review of the event narrative, including consideration of appropriate medical history and clinical and laboratory data.

In all of the controlled Phase 3 studies and the All PD Studies Pool, the most common AEs requiring a narrative for special interest topics among subjects who received ropinirole CR were fall (5% to 13%), hypotension (2% to 8%), and hallucinations (4% to 8%). The incidence of AEs requiring a narrative for these 3 AESI topics was generally similar between treatment groups within each study and across studies. All other AESI topics had low incidences of AEs (≤2%) that were generally similar across treatment groups. The profile for AESIs was similar across treatment groups for AEs requiring a narrative and those judged to be likely or possible cases. The AESI profile for ropinirole CR is generally comparable to that for ropinirole IR. No AESI resulted in withdrawal of more than 2% of subjects from the ropinirole CR treatment group and <1% of subjects in that group had SAEs reported for any of the 11 AESI topics. The AESIs were mild or moderate in almost all subjects (>99%) and occurred over a wide range of doses of ropinirole CR.

Data from healthy volunteers, subjects with fibromyalgia, and the OCEANS database (for SAEs from 248 and 196 not yet entered into the clinical trial database) supported these observations.

No new patterns were observed from these other data sources. In this comprehensive review of AEs of special interest, there were no new safety findings. The AESI profile for ropinirole CR is similar to, and no worse than, that for ropinirole IR.

Reviewer Comment

- These analyses did not suggest unique findings for ER ropinirole nor a serious suggestion that the risk of any of these TEAEs of special interest appears to be substantially greater than the risk for IR ropinirole. Many of the AESI are class dopaminergic adverse reactions.

- The increased frequency of possibly hypotensive events can be noted in the label.

- There did not appear to be any good cases of QTc prolongation nor cases of retinal pathology that appeared similar to the findings observed in preclinical studies.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Collection and Recording of Treatment-Emergent Adverse Events (TEAEs)

According to the sponsor, TEAEs were consistently solicited using a nonleading question at each study visit for each clinical study included in this ISS. AEs were also collected via spontaneous reports and subject diary reports in Studies 166, 167, 168, and 196. AEs collected from subject diaries were recorded into the CRF using the verbatim terms provided by the subjects. AEs were reported on the AE CRF for each study.

For all these studies, all AEs were recorded regardless of potential relationship to study drug; a change in intensity or frequency was recorded as a separate event; and AEs could include pre- or
post-treatment events resulting from protocol-mandated procedures (e.g., invasive procedures, modification of a previous therapeutic regimen).

For all PD studies, except for Study 168, any pre-existing conditions or signs and/or symptoms present prior to the start of the study (i.e., before informed consent) were recorded on the Medical/Surgical History section of the CRF, and any medical occurrences which occurred after informed consent was obtained but prior to administration of the first study drug dose were documented on the Baseline Signs and Symptoms section of the CRF. For Study 168, AEs that occurred prior to starting placebo run-in treatment were documented on the past and current medical conditions pages, as appropriate.

In some studies, AEs were recorded that had been present at baseline. However, the sponsor noted that for the NDA it re-analyzed data and utilized the standard definition for treatment-emergent adverse events (TEAEs) as those that were new during treatment or that had been present at baseline but became worse (increased severity or frequency) during treatment.

Coding

The individual clinical studies included in the CR development program had been coded using several dictionaries. **For the purposes of integrating TEAE data for the study groupings, TEAE data were recoded for all studies using MedDRA (version 9.0).** This recoding was done using an autoencoding process which enabled verbatim terms provided by the investigator to be coded by a computer against medical dictionaries for safety analysis and reporting processes. As a result all integrated AE data presentations provided in this section are based on this MedDRA coding (version 9.0).

TEAE data for the individual, controlled, Phase 3 studies (Studies 169, 228 and 168) were also recoded for consistency to MedDRA, version 9.0. Thus, new displays were

generated for this ISS for these studies. In contrast, when AE data are discussed for the individual dosing regimen studies (Studies 166 and 167) or the individual clinical pharmacology studies (Studies 161, 162, 163, 219, 164 and 165), they are the original data provided in the CSRs which was coded with the dictionary listed above.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Listing 5.7 showed the coding/mapping of verbatim terms (VTs) to preferred terms (PTs) for TEAEs in the ISS. Overall, the coding/mapping of VTs to PTs seemed reasonable.

7.1.5.3 Incidence of common adverse events

The incidence ($\geq$ 2 %) of more common TEAEs in the various individual studies and in pools of these studies was assembled.

Table 93 shows the incidence of TEAEs with ER ropinirole or placebo in the pivotal, randomized, double-blind, placebo-controlled Study 169. The most common TEAEs (based upon an absolute incidence of $\geq$ 5 % for ER ropinirole and shown in descending order) was dyskinesia, nausea, dizziness, somnolence, hallucination, and orthostatic hypotension. Pooled analyses of all controlled Parkinson's Disease studies (Table 94) and a pool of studies 169, and 228 (Table 95) in advanced Parkinson's Disease showed a generally similar profile in terms of the relatively most common TEAEs during ER ropinirole treatment as was shown in study 169. In addition, the profile of TEAEs occurring in study 228 for ER ropinirole was also generally similar to results in study 169 with respect to the relatively most common TEAEs.