Parameter unit	Reference	Tablet A	Tablet B	Tablet C
$AUC_{(0-t)}$ ng.h/mL				
N	14	15	13	14
Geometric Mean	6.58	6.17	6.47	5.67
CV_b (%)	49.9	52.4	52.5	47.8
k_{el} h^{-1}				
N	14	15	13	14
Geometric Mean	0.167	0.127	0.142	0.136
CV_b (%)	18.3	20.1	22.8	18.3
$t_{1/2el}$ h				
N	14	15	13	14
Geometric Mean	4.15	5.44	4.88	5.09
CV_b (%)	18.3	20.1	22.8	18.3
t_{max} h				
N	14	15	13	14
Geometric Mean	7.61	10.0	9.45	10.5
CV_b (%)	109.0	35.9	48.1	52.0
$AUC_{(0-t)}$ Ratio[1]				
N	14	15	13	14
Geometric Mean	1.77	1.81	1.66	1.76
CV_b (%)	53.3	47.8	53.6	51.5

1. Metabolite SKF104557 / Ropinirole AUC(0-t) ratio

Table 6. Summary of ropinirole primary and secondary PK parameters (Part II)

Parameter unit	Tablet C alone (Part I)	Tablet C with Domperidone	Tablet C with food
$AUC_{(0-\infty)}$ ng^1h/mL			
N	14	13	13
Geometric	5.95	5.92	7.86
Mean	46.7	58.9	47.0
CV_b (%)			
Comparison:		Tablet C with Domperidone / Tablet C from Part I	Tablet C with food / Tablet C from Part I
Point Estimate		0.977	1.30
95% C.I.		(0.79, 1.20)	(1.06, 1.60)
C_{max} ng/mL			
N	14	13	13
Geometric	0.280	0.316	0.414
Mean	50.7	48.7	49.8
CV_b (%)			
Comparison:		Tablet C with Domperidone / Tablet C from Part I	Tablet C with food / Tablet C from Part I
Point Estimate		1.10	1.44
95% C.I.		(0.95, 1.28)	(1.24, 1.68)

Table 7. Summary of ropinirole tertiary PK parameters (Part II)

Parameter unit	Tablet C alone (Part I)	Tablet C with Domperidone	Tablet C with Food
DF			
N	14	13	13
Geometric Mean	0.516	0.710	0.765
CV_b (%)	62.0	50.4	28.1
C_{min} ng/mL			
N	14	13	13
Geometric Mean	0.130	0.127	0.156
CV_b (%)	60.3	67.0	51.6
k_{el} h^{-1}			
N	14	13	13
Geometric Mean	0.136	0.158	0.141
CV_b (%)	18.3	22.2	27.2
$t_{½el}$ h			
N	14	13	13
Geometric Mean	5.09	4.38	4.93
CV_b (%)	18.3	22.2	27.2
t_{max}			
N	14	13	13
Geometric Mean	10.5	11.7	7.94
CV_b (%)	52.0	43.5	38.8
$AUC_{(0-t)}$ Ratio[1]			
N	14	13	13
Geometric Mean	1.76	1.62	1.57
CV_b (%)	51.5	53.8	48.7

Reviewer's note:

- Administration of ropinirole CR after a high-fat breakfast resulted in higher Cmax (44%) and AUC(0-∞) (30%) compared with the fasted condition.

Safety Summary:

There were no deaths, severe AEs, or AEs leading to withdrawal, and there was no change in AE profile for tablet C with or without high-fat food. Eleven of 16 subjects experienced a total of 30 adverse events (AEs). The most frequent AEs were headache (11 AEs), flatulence (10 AEs) and diarrhea (7 AEs), while asthenia and dizziness were single occurrences. All AEs were of mild (headache, asthenia and dizziness) to moderate (diarrhea and flatulence) intensity. There was no report of nausea and vomiting. Although low in overall incidence, there appeared to be a trend between the onset of diarrhea (8.5-15 hours) and the tmax (9.5-14 hours) for ropinirole. Ropinirole IR (0.25 mg Tiltab tablet, tid) and Ropinirole Geomatrix 0.75 mg CR formulations (tablets A, B and C) were generally well tolerated.

CONCLUSION:

- All CR formulations tested showed a PK profile preferable over the reference IR formulation of ropinirole, as defined by a lower degree of fluctuation in the presence of a >80% relative bioavailability.

- Tablet C showed higher Cmin values and lower Cmax values compared with tablets A and B. Tablet C was chosen as the most appropriate CR formulation for further

investigation, because adequate systemic exposure was combined with the lowest degree of fluctuation.

- Co-administration of domperidone at 2x10mg doses, tid did not significantly alter the PK and tolerability profiles of ropinirole from tablet C under fasted state.

- High-fat food increased the bioavailability of ropinirole from 0.75 mg tablet C, as indicated by a 44% increase in Cmax and a 30% increase in AUC. No occurrence of dose dumping or change in the tolerability profile of ropinirole was reported.

- There was no clinically relevant change in the metabolite/parent AUC(0-t) ratio between the IR and CR formulations of ropinirole. Also co-administration of either domperidone or a high fat breakfast with CR formulation did not markedly alter the extent of metabolism of ropinirole.

Study SK&F-101468/162

A four-way cross-over, placebo- and IR-controlled study to compare the single-dose pharmacokinetics of ropinirole from CR-formulations (doses of 0.75 mg and 3 mg) and from the IR-formulation in healthy male and female volunteers

Principal Investigator: [redacted] b(4)
Study Center:

Study Period: May 12, 2000 - July 19, 2000

Objectives:

Primary:

- To assess dose proportionality of the controlled-release formulation of ropinirole (0.75 mg vs. 3 mg)

Secondary:

- To assess the reproducibility of the PK of ropinirole CR 0.75 mg tablets vs. ropinirole IR 0.25 mg tablets (x 3)
- To assess the safety and tolerability of ropinirole from the CR formulations used in this study

Drug Products:

CR formulations: Ropinirole CR (Geomatrix) was supplied as three-layer (light yellow, white, light yellow), round, 9 mm diameter, uncoated tablets containing either 0.75 mg (batch no: B572) or 3 mg (batch no: B581)
IR formulation: Film-coated pentagonal 0.25 mg Tiltab tablets (batch no: N98217).
Matching Placebo tablets (batch no: B492)
Domperidone: 10 mg tablets (Motilium; batch no: 199281) (Byk Gulden Lomberg Chem. Fabrik GmbH, Konstanz, Germany)

Study Design:

This was a four-way, cross-over study, in which subjects were randomized to receive either single doses of double-blind ropinirole CR 0.75 mg, ropinirole CR 3 mg or placebo, or three, 8-hourly doses of open-label ropinirole IR 0.25 mg, in each of four study periods. The treatment periods were separated by a washout period of 7 days. The subjects crossed over to a different treatment regimen in each period of the study and received concomitant domperidone (20 mg tid) with each regimen. A total of 34 healthy, non-smoking, non-vegetarian subjects (15 males and 19 females), aged 30-50 years, inclusive, weighing >50 kg, were planned for the study.

Subjects were required to abstain from taking any prescribed medication or OTC medicine for periods starting 14 and 7 days, respectively, before the first dose of study medication and ending at completion of the study. The non-high fat meals did not contain possible CYP1A2-inducing constituents (broccoli, Brussels sprouts, cabbage etc.). Each morning dose of study medication, including the 2nd and 3rd doses of IR

formulation, was given 30 min after the start of a standard breakfast (non-high fat) which was provided after fasting for at least 9.5 hours. The first domperidone dose preceded ropinirole or placebo administration by one hour. Blood samples were taken for PK determinations up to 36 hours postdose and safety was assessed throughout the study.

Safety Assessments:
Safety assessments included adverse events (AEs), vital signs, ECG data (pre-dose, 1, 2, 4, 8, 12, 16, 24 and 36 h after each morning dosing), clinical laboratory parameters, and changes in erectile function.

Pharmacokinetics Assessments:
PK blood samples were collected for the analysis of plasma concentrations of ropinirole and its metabolites (SKF 104557 and SKF 89124) at following time points:
For IR: pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 8.25, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 16.25, 16.5, 17, 17.5, 18, 19, 20, 22, 24, 28, 32 and 36 h post morning dose.
For CR: pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 32 and 36 h after dosing.

Plasma samples were stored at approximately -20°C until assayed at [redacted] using a validated LC-MS/MS method for the plasma concentrations of ropinirole and its metabolites (SK&F-104557 and SK&F-89124). [redacted] was used as internal standard. The calibration standards for ropinirole and SKF-89124 were 20-5000 pg/mL and for SKF-104557 were 50-5000 pg/mL. HPLC-MS/MS data were acquired, processed (integrated) and a weighted $1/x^2$ linear regression calibration plot of peak area ratio vs. plasma Ropinirole, SKF-89124, SKF-104557 was constructed and applied to the data using computer software. Concentrations of Ropinirole, SKF-89124 and SKF-104557 in study samples were determined from the calibration plot. Quality control (QC) samples were realized by spiking blank plasma samples with known amounts of SKF 101468, SKF 89124 and SKF 104557 (50, 1000 and 4000 pg/mL for SKF 101468 and SKF 89124, and 100, 1000 and 4000 pg/mL for SKF 104557). The lower limit of quantification (LLQ) for ropinirole (SK&F-101468) and SK&F-89124 assay was 20 pg/mL and for SK&F-104557 was 50 pg/mL, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification of 5 ng/mL. Inter-day and intra-day accuracy and precision were <15% (mostly <10%).

b(4)

Table 1. Assay validation for Study SK&F-101468/162

			Ropinirole	SK&F-89124	SK&F-104557
Method:			LC/MS/MS	LC/MS/MS	LC/MS/MS
Standard curve	Range:		20~5000 pg/mL	20~5000 pg/mL	50~5000 pg/mL
		Precision:	1.77~3.93 %	2.25~5.38 %	2.00~4.46 %
		Accuracy:	-2.00~1.50 %	-4.86~2.83 %	-2.10~0.93 %
	Linearity:		$r^2 = 0.9989$	$r^2 = 0.9968$	$r^2 = 0.9977$
LOQ	LLOQ:		20 pg/mL	20 pg/mL	50 pg/mL
QC	Low:		50 pg/mL	50 pg/mL	100 pg/mL
		Precision:	5.00 %	11.06 %	5.70 %
		Accuracy:	-0.80 %	0.20 %	-1.10 %

Med:		1000 pg/mL	1000 pg/mL	1000 pg/mL
	Precision:	2.84 %	6.60 %	5.82 %
	Accuracy:	1.60 %	0.10 %	2.00 %
High:		4000 pg/mL	4000 pg/mL	4000 pg/mL
	Precision:	3.12 %	4.67 %	4.52 %
	Accuracy:	1.13 %	2.28 %	1.88 %

Pharmacokinetic Analysis:
The following pharmacokinetic parameters for ropinirole were estimated by standard non-compartmental methods: AUC(0-∞), AUC(0-t), Cmax, Cmin, Cavg, C24, DF (degree of fluctuation of plasma concentrations), tmax, t½ and the relative bioavailability of the CR formulation compared to the IR formulation, and the ratio of AUC(0-t) metabolite : parent for both metabolites.

Statistical Analysis:
Dose proportionality of the CR formulation was assessed using ANOVA for dose-normalized (to a 0.75 mg dose) AUC(0-∞) and Cmax from CR 0.75 and CR 3 mg. Point estimates and 90% confidence intervals (CIs) for the mean ratios (CR 3.0 mg vs. CR 0.75 mg reference dose) for ln-transformed AUC(0-∞) and Cmax were constructed. Dose proportionality was concluded if the 90% CIs for dose-normalized AUC(0-∞) and Cmax were wholly contained within the interval 0.80 to 1.25.

To assess the relative bioavailability of the CR formulation relative to the IR, the geometric mean ratios (0.75 mg CR : 0.75 mg IR) for Cmax and AUC(0-∞) values were calculated using the same methods, however, 95% CIs were calculated.

Reviewer's note:
No rationale was provided by the sponsor for using 95% CIs, instead of the 90% CIs, for assessing the relative bioavailability.

RESULTS

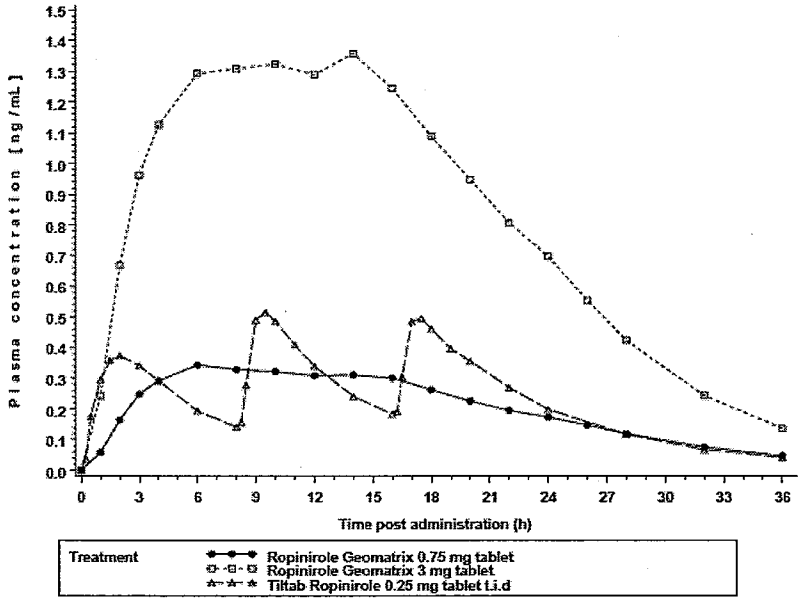
Demographics of Subjects:
A total of 34 subjects (15 males and 19 females) were enrolled (as shown in the Table 2 below) and 30 subjects (15 males and 15 females) completed the study as scheduled. Female Subjects # 07, 23 and 24 withdrew informed consent for personal reasons and Subject 107 withdrew due to unintended pregnancy during study.

Mean (Range)		Age [years]	Weight [kg]	Height [cm]	Body Mass [kg/m^2]
Male	(n=15)	37.3 (30-49)	68.8 (60.0-76.2)	177 (166-185)	22.0 (19.3-26.3)
Female	(n=19)	39.6 (31-50)	60.6 (50.4-73.8)	164 (155- 174)	22.5 (19.9-28.0)
Overall	(n=34)	38.6 (30-50)	64.2 (50.4-76.2)	170 (155-185)	22.2 (19.3-28.0)

Pharmacokinetic Summary:

The mean plasma concentrations of ropinirole for the IR formulation (0.25 mg at 8-hour intervals) and the CR formulation (0.75 mg and 3 mg) are shown in Figure 1. The summary of PK parameters and statistics are shown in Tables 3. PK parameters were obtained for 33 of 34 subjects from the IR doses and for 30 and 31 subjects from the ropinirole 0.75 mg and 3 mg CR doses, respectively.

Figure 1. Mean ropinirole plasma concentration-time profiles following oral administration of the IR (3 x 0.25 mg tid) and CR (0.75 mg and 3 mg) formulations



Following oral administration of the CR formulation, plasma ropinirole concentrations increased up until about 6 h post-dose and then plateaued until approximately 16 h post-dose.

Table 3. Summary of ropinirole dose-normalized PK results (geometric mean (CV%))

Parameter (unit)	IR 3 x 0.25 mg (n = 33)	CR 0.75 mg (n = 30)	CR 3 mg (n = 31)
AUC(0-∞) (ng·h/mL)	7.59 (68.1)	6.87 (61.3)	6.92 (51.7)
Cmax (ng/mL)	0.51 (55.3)	0.34 (50.4)	0.36 (45.0)
Cmin (ng/mL)	0.15 (89.1)	0.14 (78.8)	0.14 (80.7)
DF	1.16 (38.3)	0.61 (66.0)	0.59 (106)
tmax[a]	1.50 (0.5 – 4.0)[b]	8.00 (3.0 – 16.0)	10.0 (3.0 – 18.0)
t½	4.23 (20.9)	4.92 (25.0)	4.53 (19.4)

a. median (range)

b. based on time after final IR dose (16 h after 1st dose)

Reviewer's note:

- Dose-normalized AUC(0-∞) and Cmin values were similar for the IR and CR formulations. Dose-normalized Cmax values were generally lower for the CR formulation compared to the IR formulation.
- The degree of fluctuation in plasma concentrations for the CR formulation was approximately half that of the IR formulation.
- Tmax for the IR formulation was generally attained prior to 4 h post dose, whereas for the CR formulation, Tmax was generally achieved between 8 and 10 h post-dose.
- For AUC(0-∞), Cmax and Cmin, the between-subject variability was generally lower for the CR formulation compared with the IR formulation.

Dose-normalized AUC(0-∞) and Cmax, as well as point estimates and the 90% CIs, are presented in the following Figure 2 and Table 4 following single-doses of ropinirole CR 0.75 mg or ropinirole CR 3 mg. Results of relative bioavailability of CR formulation compared to the IR formulation is presented in Table 5.

Table 4. Statistical analysis for assessing the dose proportionality between 3 mg and 0.75 mg of CR formulation

Parameter	Comparison	Point Estimate	90% CI
AUC(0-∞)[a]	CR 3mg : CR 0.75mg	1.01	(0.94, 1.09)
Cmax[a]	CR 3mg : CR 0.75mg	1.05	(0.97, 1.14)

a. dose-normalized

Reviewer's note:

- The point estimates and 90% CI of the geometric mean ratios (CR 3 mg: CR 0.75 mg) for dose-normalized AUC(0-∞) and Cmax were within the predefined range (0.80, 1.25) for concluding dose-proportionality.
- Tmax and t½ were similar for both CR doses.

Figure 2. Dose normalized AUC and Cmax values vs. dose of ropinirole from CR formulations

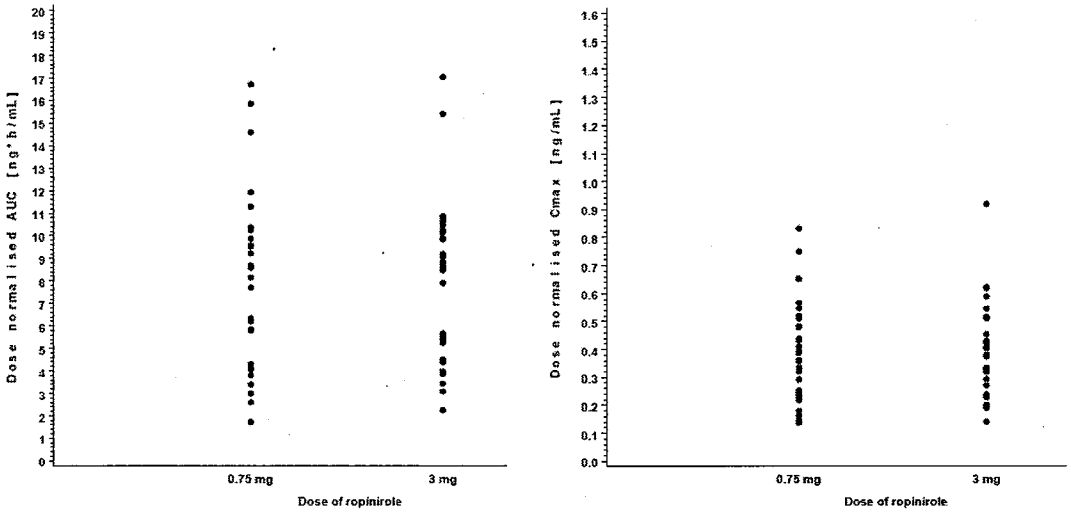


Table 5. Summary of the statistical analysis for the relative bioavailability of CR vs. IR formulations of same 0.75 mg dose

Parameter	Comparison	Point Estimate	95% CI
AUC(0-∞)	CR 0.75 mg : IR	0.958	(0.84, 1.10)
Cmax	CR 0.75 mg : IR	0.693	(0.60, 0.80)
Cmin (ng/mL)	CR 0.75 mg : IR	0.9777	(0.77, 1.25)
DF (Degree of Fluctuation)	CR 0.75 mg : IR	0.5011	(0.40, 0.63)

Reviewer's note:

- The bioavailability of the CR formulation was, on average, 96% of the IR formulation. Cmax was, on average, ~31% lower for ropinirole CR, compared with ropinirole IR.

Table 6. Ratios of metabolite-to-parent drug for AUC(0-∞) following oral administration of IR and CR doses

	IR	**CR 0.75 mg**	**CR 3 mg**
SKF-104557 : ropinirole	1.51 (1.23, 1.85) (n = 33)	1.64 (1.38, 1.95) (n = 30)	1.60 (1.38, 1.85) (n = 31)
SKF-89124 : ropinirole	0.017 (0.0131, 0.0217) (n = 25)	0.014 (0.0029, 0.0686) (n = 5)	0.042 (0.0361, 0.0481) (n = 30)

Sponsor's Safety Summary:

During the study, 63 treatment-emergent AEs were reported in 40/95 treatment periods (42.1%) on ropinirole and 21 AEs were reported in 16/32 treatment periods (50.0%) on

placebo. Treatment-emergent AEs and Most common AEs are summarized in the Table 7 below:

Adverse Events	Treatment[a], No.(%) of subjects experiencing an AE			
(preferred term)	Placebo	IR 0.25 mg tid	CR 0.75 mg	CR 3 mg
Number (No.) of Subjects Exposed	32	34	30	31
No. (%) of subjects with an AE	16 (50.0)	16 (47.1)	12 (40.0)	12 (38.7)
No. (%) of subjects with a moderate intensity AE	5 (15.6)	5 (14.7)	3 (10.0)	1 (3.2)
Total Number AEs	21	22	22	19
Headache	7 (21.9)	5 (14.7)	6 (20.0)	4 (12.9)
Weariness	5 (15.6)	4 (11.8)	4 (13.3)	5 (16.1)
Flatulence	4 (12.5)	1 (2.9)	3 (10.0)	2 (6.5)
Dizziness	1 (3.1)	1 (2.9)	1 (3.3)	3 (9.7)
Nausea	--	1 (2.9)	2 (6.7)	2 (6.5)

Of the 84 AEs reported in this study, 65 (77.4%) were of mild intensity, 17 (20.2%) were moderate and none were severe. No clinically meaningful abnormal laboratory safety measurements, vital signs, physical examination findings, or ECG findings were reported.

CONCLUSION:

- AUC(0-∞) and Cmax values for ropinirole were approximately dose proportional over the CR dose range of 0.75~3 mg.

- Lower bioavailability (96%) and Cmax (30% lower) values, as well as between-subject variabilities for all exposure measures, were observed for ropinirole CR formulations relative to the IR formulation.

- The systemic exposure to the inactive metabolite, SKF-104557, was approximately 50% higher than parent for the IR formulation, and approximately 60 to 65% higher than parent for the CR formulation.

- The systemic exposure to the active metabolite, SKF-89124, was approximately 2% of that seen for the parent drug for 0.75 mg doses of CR and IR (0.25 mg tid) and approximately 4% of the parent drug for the higher dose of 3 mg CR.

Study SK&F-101468/163

Title: A double-blind, two-way cross-over, placebo-controlled single dose and repeat dose study to investigate the pharmacokinetics of ropinirole after single and multiple doses of a CR-formulation in healthy male and female subjects b(4)

Principal Investigator:
Study Center:

Study Period: 06 Jun 2000- 25 Aug 2000

Objectives:
Primary:

- To investigate the pharmacokinetic profile of ropinirole CR after single and multiple doses
- To examine the accumulation ratios resulting from repeat dosing of this formulation (1.0 mg od ropinirole CR - Geomatrix) for seven days

Secondary:

- To compare the safety and tolerability of ropinirole CR, after single and multiple dosing, with placebo

Drug Products:
Ropinirole CR-RLS tablets: 1 mg uncoated tablet (batch no. B5774).
Matching placebo tablets (batch no. B492)
Domperidone: 10 mg tablets (Motilium; batch no. 199281 and 199291) (Byk Gulden Lomberg Chem. Fabrik GmbH, Konstanz, Germany)

Study Design:
This was a double-blind, two-way crossover, placebo-controlled, randomized single and repeat dose study in 28 healthy subjects (14 males and 14 females planned) aged 30 to 50 years, inclusive. Eligible subjects were randomized to receive 1 mg ropinirole CR (Geomatrix) tablets or placebo, once per day in the morning, over 9 days, without dosing on Day 2, i.e., between the single dose (SD) and the multiple dose (MD) treatment periods.

The single dose and multiple dose phases of a treatment period were therefore separated by a wash-out period of 1 day, and the two treatment periods were separated by a wash-out period of 7 days. In each treatment period, on each dosing day, subjects were co-administered three consecutive doses of two 10 mg tablets of domperidone at 8-hourly intervals, starting one hour before administration of ropinirole CR or placebo. Subjects were fasted for at least 9 h prior to morning domperidone doses. Thirty minutes after domperidone dosing, subjects were given a standardized breakfast and they received blinded study treatment 30 min after the start of breakfast. Lunch, snack and dinner on Days 1, and 3 to 9 were provided 4 h 15 min, 9 h 15 min and 12 h 15 min, respectively, after dosing of the blinded study treatment. Subjects remained in-house from the evening

before the first dose until 24 h after the dose on Day 9. None of the subjects had received prescribed medication within 14 days, or OTC medicine within seven days, before the first dosing day.

Safety Assessments:
Safety assessments throughout the study included physical examination, vital signs measurements (supine and standing blood pressure and heart rate), 12-lead ECGs, clinical chemistry, haematology, urinalysis, and adverse event (AE) monitoring. Vital signs and 12-lead ECGs were recorded pre-dose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 22 and 24 h after morning dosing of ropinirole CR or placebo on Days 1, 2 and 9 of each study period. On Days 3 to 8, vital signs were measured and an ECG was recorded pre-dose and at 12 h post-dose.

Pharmacokinetics Assessments:
Blood samples were collected for determination of plasma concentrations of ropinirole and its two metabolites (SKF-104557 and SKF-89124) at the following time points:

- Day 1: pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 32 and 48 h post-dose
- Days 4, 5, 6, 7 and 8: pre-dose
- Day 9: pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 h post-dose

Plasma samples were stored at approximately -20°C until assayed at [redacted], using a validated LC-MS/MS method for the plasma concentrations of ropinirole and its metabolites (SK&F-104557 and SK&F-89124). [redacted] was used as internal standard. The calibration standards for ropinirole and SKF-89124 were 20-5000 pg/mL and for SKF-104557 were 50-5000 pg/mL. HPLC-MS/MS data were acquired, processed (integrated) and a weighted $1/x^2$ linear regression calibration plot of peak area ratio vs. plasma Ropinirole, SKF-89124, SKF-104557 was constructed and applied to the data using computer software. Concentrations of Ropinirole, SKF-89124 and SKF-104557 in study samples were determined from the calibration plot. Quality control (QC) samples were realized by spiking blank plasma samples with known amounts of SKF 101468, SKF 89124 and SKF 104557 (50, 1000 and 4000 pg/mL for SKF 101468 and SKF 89124, and 100, 1000 and 4000 pg/mL for SKF 104557). The lower limit of quantification (LLQ) for ropinirole (SK&F-101468) and SK&F-89124 assay was 20 pg/mL and for SK&F-104557 was 50 pg/mL, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification of 5 ng/mL. Inter-day and intra-day accuracy and precision were <15% (mostly <10%).

b(4)

Table 1. Assay validation for Study SK&F-101468/163

			Ropinirole	SK&F-89124	SK&F-104557
Method:			LC/MS/MS	LC/MS/MS	LC/MS/MS
Standard curve	Range:		20~5000 pg/mL	20~5000 pg/mL	20~5000 pg/mL
		Precision:	1.51~3.82 %	1.74~6.06 %	2.36~4.75 %
		Accuracy:	-3.12~2.70 %	-4.53~3.60 %	-3.43~2.40 %
	Linearity:		$r^2 = 0.9987$	$r^2 = 0.9960$	$r^2 = 0.9972$

LOQ	LLOQ:		20 pg/mL	20 pg/mL L	50 pg/mL
QC	Low:		50 pg/mL	50 pg/mL	100 pg/mL
		Precision:	3.46 %	6.82 %	6.53 %
		Accuracy:	-3.10 %	-1.48 %	-0.33 %
	Med:		1000 pg/mL	1000 pg/mL	1000 pg/mL
		Precision:	8.8 %	8.66 %	11.14 %
		Accuracy:	2.7 %	4.10 %	3.30 %
	High:		4000 pg/mL	4000 pg/mL	4000 pg/mL
		Precision:	4.8 %	6.69 %	8.59 %
		Accuracy:	5.9 %	3.53 %	0.30 %

Pharmacokinetic Analyses:

The following pharmacokinetic parameters for ropinirole were estimated by non-compartmental methods:

Primary endpoints:

- Single dose (Day 1) and steady-state (Day 9) AUC, Cmax, Cmin, and degree of fluctuation DF [(Cmax-Cmin)/Cavg] for ropinirole CR
- Attainment of steady-state for ropinirole CR based on pre-dose concentrations on Days 4, 5, 6, 7, 8, and 9, together with 24 h concentration on Day 9

Secondary endpoints:

- Observed and steady-state accumulation ratios (Ro and Rs) for ropinirole CR
- Single-dose tmax and t½, and steady-state tmax
- Single-dose (Day 1) and steady-state (Day 9) AUC(0-24) ratios
- Metabolite / parent AUC(0-24) ratios for both metabolites
- Metabolite/parent ratios at trough levels on Days 4, 5, 6, 7, 8 and 9 and at 24 h post-dose on Day 9 for both metabolites

RESULTS

Demographics of subjects:

Twenty-eight Caucasian subjects (16 males and 12 females) received at least one dose of study drug and were evaluable for safety. 24 subjects (13 males and 11 females) completed the study. Data from 27 subjects were evaluable for PK of ropinirole CR. Four subjects withdrew from the study: 3 subjects (#13, 22, 26) withdrew their informed consent for personal reasons and the fourth subject (#19) was withdrawn by the Investigator for experiencing first degree AV block from pre-dose on Day 3 in Period 1 (placebo) which was not recorded at screening. The disposition of the subjects enrolled is shown in the Table 2 below:

		Mean (Range)			
		Age [years]	**Weight [kg]**	**Height [cm]**	**Body Mass [kg/m^2]**
Male	(n = 16)	39.1 (30-50)	71.16 (54.8-84.5)	172.2 (154-180)	23.96 (18.5-28.4)
Female	(n = 12)	38.2 (30-49)	63.96 (53.7-73.7)	167.8 (158-180)	22.81 (18.5-27.3)

Overall	(n = 28)	38.7 (30-50)	68.07 (53.7-84.5)	170.3 (154-180)	23.47 (18.5-28.4)

Plasma concentration-time profiles:
Overall higher mean ropinirole and SKF-104557 levels and earlier mean maximum concentrations after repeated doses compared with a single dose are presented in Figure 1 and Figure 2.

Figure 1. Mean ropinirole plasma concentration-time curves after single and repeated oral administration of 1.0 mg od ropinirole CR

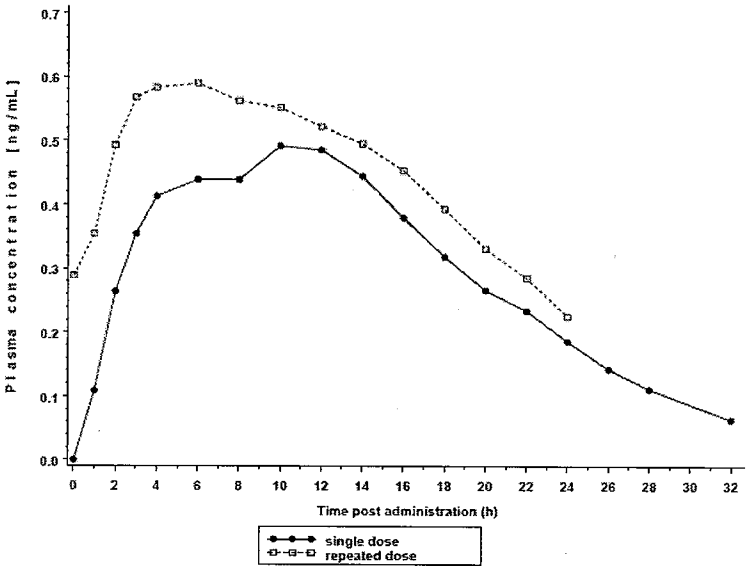
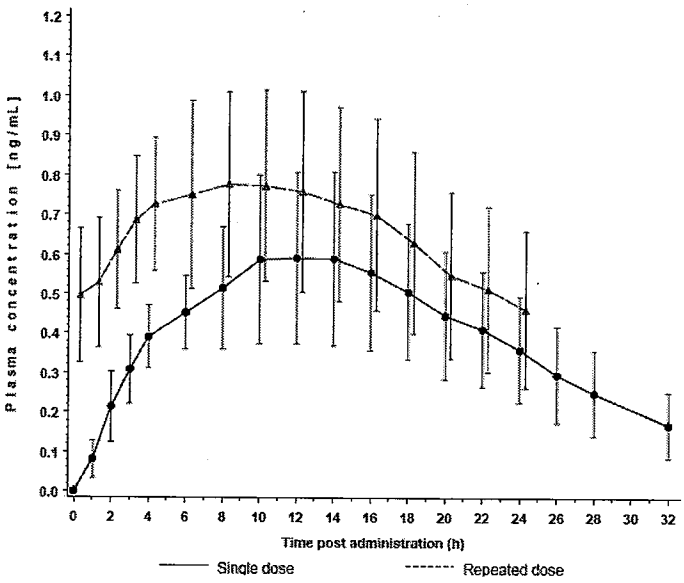


Figure 2. Mean SKF-104557 plasma concentration-time curves (+/- SD) after single and repeated oral administration of 1.0 mg od ropinirole CR



Attainment of steady-state:
Summary statistics for trough levels of ropinirole and SKF-104557 are shown in Table 3 below.

Table 3. Summary statistics for trough levels of ropinirole and SKF-104557

Day (n)	Day 4 (28)	Day 5 (28)	Day 6 (27)	Day 7 (27)	Day 8 (27)	Day 9 (26)	Day 9 (27)
Ropinirole							
Geometric mean	0.148	0.178	0.138	0.155	0.228	0.230	0.170
CVb (%)	135.2	115.2	157.2	146.1	75.7	91.2	98.6
SKF 104557							
Geometric mean	0.339	0.382	0.355	0.357	0.469	0.457	0.402
CVb (%)	83.8	82.5	83.8	84.4	34.1	48.3	66.7

Reviewer's note:

- Mean trough concentrations of SKF-104557 were ~2-fold higher than those of ropinirole. Mean trough concentrations of ropinirole and SKF-104557 were similar from Days 4 to 9, indicating the attainment of steady-state by Day 4 of dosing.

Single vs. repeat dose pharmacokinetics:
The PK parameters and the summary statistics for ropinirole following single and multiple doses of ropinirole CR are shown in the Tables 4-5.

Table 4. Summary of Single and Repeat Dose Ropinirole PK Parameters (geometric mean (CVb%)

Parameter	Single Dose (n=28)	Repeat Dose (n=27)

Cmax (ng/mL)	0.512 (48.3%)	0.633 (44.4%)
Tmax (h)[a]	10.0 (2.00 - 22.0)	6.00 (2.00 – 18.0)
AUC(0-24) (ng.h/mL)	7.64 (51.2%)	9.82 (51.7%)
AUC(0-∞) (ng.h/mL)	8.80 (56.1%)	Not Determined
t½ (h)	4.73 (22.6%)	Not Determined
Cmin (ng/mL)	0.138 (110%)	0.170 (98.6%)
DF	0.865 (75.0%)	1.02 (44.4%)

a. median (range)

Table 5. Summary of the statistical analysis for ropinirole (Day 9 : Day 1)

Parameter	Point Estimate	95% CI
Cmax (Repeat:Single)	1.24	[1.09 , 1.40]
Repeat AUC(0–24) : Single AUC(0-24) (Ro)	1.26	[1.05,1.50]
Repeat AUC(0–24) : Single AUC(0–∞) (Rs)	1.13	[0.96,1.33]
Cmin (Repeat:Single)	1.27	[0.90, 1.79]
DF	1.16	[0.88, 1.51]

Reviewer's note:

- The wide range of Tmax values (2~22 h) after single and repeat doses of ropinirole CR is likely a result of the generally flat concentration-time profiles at plateau.
- Results of point estimates indicate that systemic exposure to ropinirole (AUC(0-24) and Cmax) following repeat dosing was generally similar, though slightly higher (~25%) than after a single dose.
- The steady-state accumulation ratio (Rs) of 1.13 was close to unity.

Ratios of metabolite-parent drug:

Table 6. Ratios of AUC metabolite : AUC ropinirole following single and repeat administration of ropinirole CR

Parameter	Dosing	n	Geometric mean	CVb (%)	Minimum	Maximum
SKF-104557 AUC(0-24)	Single	28	10.5	27.9	5.50	16.4
	Multiple	27	15.2	34.5	6.53	24.3
SKF-104557/ropinirole	Single	28	1.37	40.3	0.746	2.77
	Multiple	27	1.55	33.2	0.980	3.08
SKF-89124 AUC(0-24)	Single	28	0.0957	134	0.0	0.355
	Multiple	27	0.329	120	0.0	0.915
SKF-89124/ropinirole	Single	11	0.0102	139	0.00195	0.0406
	Multiple	23	0.0309	100	0.00398	0.117

Reviewer's note:

- Overall exposure to SKF-104557, based on AUC(0-24), was approximately 1.5-fold higher than for ropinirole, whereas overall exposure to SKF-89124 was approximately 1.0 to 3% of that seen for ropinirole.

- AUC(0-24) of SKF-104557 increased by approximately 50% from the single dose geometric mean (CVb) of 10.5 (27.9%) ng·h/mL to 15.2 (34.5%) ng·h/mL at steady state. Mean trough concentrations of SKF-104557 were approximately 2-fold those of the parent compound without a major change during multiple dosing.

- SKF-89124 concentrations were very low overall and trough concentrations of this active metabolite could only be assessed for a minority of subjects. The SKF-104557 and SKF-89124 / parent AUC(0-24) ratios did not change remarkably over the course of multiple dosing.

Sponsor's Safety Summary:

- The proportion of subjects reporting AEs on SD and MD ropinirole CR was the same (9/28: 32.1%), and was similar to that for SD placebo (9/27: 33.3%), whereas the proportion of subjects reporting AEs on MD placebo was twice that on ropinirole CR.

- The most frequently reported AEs were headache (24 events) and asthenia (12 events), then diarrhea (5 events). The incidence of headache on ropinirole CR was similar to that seen in subjects on placebo, whereas the incidence of asthenia was higher on placebo (particularly during the MD phase). Diarrhea was only seen in the multiple dose phases of the study and was seen in more subjects on placebo than on ropinirole CR. There were no severe or serious (fatal or non-fatal) AEs reported in this study.

- With concomitant domperidone, characteristic peripheral dopaminergic AEs such as nausea and vomiting occurred at an extremely low incidence (< 3.7% in all treatment groups).

- The 1.0 mg od ropinirole CR plus domperidone and placebo plus domperidone were both well tolerated. There was no increase in frequency or intensity of AEs on ropinirole CR from SD to MD, whereas the frequency of AEs approximately doubled from SD to MD on placebo.

CONCLUSION:

- AUC(0-24) and Cmax values for ropinirole when administered as a CR formulation were approximately 25% higher at steady-state, compared with single dose values.

- The steady-state accumulation ratio was close to unity, suggesting a lack of significant accumulation and a time-invariance in PK properties after multiple doses.

- Steady-state concentrations of ropinirole and the inactive metabolite, SKF-104557, appeared to have been attained by Day 4, following once-daily dosing of 1.0 mg ropinirole CR tablet.

Study SK&F-101468/164

An open-label, randomised, two part study to investigate the relative bioavailability of Ropinirole CR and IR formulations and the effect of food on the pharmacokinetics of Ropinirole CR formulation in early stage Parkinson's disease patients

Principal Investigators and Study Centers:

- [redacted]
- [redacted]
- [redacted]

b(4)

Study Period: 17 July 2002 – 24 Sep. 2003

Objectives:

Primary:

- To determine the relative bioavailability at steady state of an 8 mg od dose of ropinirole controlled-release (CR), compared to 2.5 mg tid of ropinirole immediate release (IR)
- To determine the effect of food on steady-state bioavailability of an 8 mg od dose of ropinirole CR given to patients with early stage Parkinson's disease

Secondary:

- To confirm the safety and tolerability of 8 mg od ropinirole CR in early stage Parkinson's disease patients

Drug Products:

CR formulations: 0.5mg (batch number: 041017245) or 2mg (batch no. 041021146) of active drug substance, with matching placebo tablets (batch no. 041021074)

IR formulations: (TILTAB™) 0.5mg (batch no. NO1114), 2.0mg (batch no.: NO1116) of active drug substance, with matching placebo tablets (batch no. N01150)

Study Medication	Batch Number	Expiry Date
0.5 mg IR	NO1114	30 Jun 2004
2 mg IR	NO1116	30 Jun 2004
2 mg CR	NO2031-S2	31 Jul 2004
3 mg CR	NO2037-S2	30 Jun 2004
4 mg CR	NO2038-S2	31 Jul 2004
8 mg CR	NO2045-S2	31 Jul 2004

Dose Rationale:

Part A: Relative BA of CR vs. IR; dosed to a clinically-relevant steady state in Parkinson's disease patients using highest 8-mg CR and the available IR formulations

Part B: Food effect; 8 mg dose of ropinirole CR is in the middle of the anticipated efficacious dose range (6-12 mg)

Study Design:

Twenty-six male and female patients, aged 30 to 85 years inclusive, with a diagnosis of idiopathic Parkinson's disease according to modified Hoehn & Yahr Stage I-III criteria were enrolled. This was an open-label, randomized study conducted in two parts. In Part A, the relative bioavailability of the CR formulation was compared to that of the IR formulation. In Part B, a definitive evaluation of the effect of food on the pharmacokinetics (PK) of ropinirole CR was performed. Prior to participation in either Part A or Part B, all patients had to have received a dose of 8 mg od ropinirole CR for at least three days. The titration regimen used to achieve a dose of 8 mg ropinirole CR is shown the following table:

Week	Dose of ropinirole (mg)
1	2
2	3
3	4
4	6
5	8

Part A: patients were randomized to one of two treatment sequences; each treatment sequence comprised two periods. Upon completion of treatment sequence 1 or 2, patients either entered Part B of the study, with a minimum period of 3 days in between, or left the study.

Treatment Sequence 1 (CR-IR):

In Period 1, patients received 8 mg od ropinirole CR for 4-7 days. PK blood samples were taken on the last treatment day (PK-sampling). In Period 2, patients received ropinirole 7.5 mg IR (2.5 mg tid) for 4-7 days. PK blood samples were taken on the last treatment day.

Treatment Sequence 2 (IR-CR):

In Period 1, patients received ropinirole 7.5 mg IR (2.5 mg tid) for 4-7 days. PK blood samples were taken on the last treatment day. In Period 2, patients received 8 mg od ropinirole CR for 4-7 days. PK blood samples were taken on the last treatment day.

Part B comprised two treatment periods, separated by a 3-day steady state period. In the first treatment period, patients received ropinirole CR in either the fed or fasted state. Fasted state patients received a single dose of 8 mg ropinirole CR after an overnight fast of at least 10 h. The fed patients received a single dose of 8 mg ropinirole CR immediately after a standard, FDA-type high-fat breakfast which the patients started to eat 30 minutes (min) prior to dosing time. There was a minimum of 3 days between treatment periods, during which patients continued to take 8 mg CR od. After this, the patients started the second period, in which they 'crossed-over' to the alternative food condition. PK samples were taken before and after the day of dosing in Periods 1 and 2.

Dietary components and potential comedications that will likely have impact on the results via CYP1A2 mechanism were noted for the study.

Safety Assessments:
The safety and tolerability endpoints were adverse events (AEs), clinical laboratory tests, vital signs and electrocardiogram (ECG) parameters.

Pharmacokinetics Assessments:
The PK blood samples were collected for analysis of ropinirole and metabolite (SKF-89124 and SKF-104557) concentrations at the following time points:

- IR regimen: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 (immediately prior to 2nd IR dose), 8.25, 8.5, 9, 9.5, 10, 11, 12, 14, 16 (immediately prior to 3rd IR dose), 16.25, 16.5, 17, 17.5, 18, 19, 20, 22 and 24 h post-dose.
- CR regimen: 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 h post-dose.

Plasma samples were stored at approximately -20°C until assayed at ——————————— using a validated LC-MS/MS method for the plasma concentrations of ropinirole and its metabolites (SK&F-104557 and SK&F-89124). ——————— was used as internal standard. The calibration standards for ropinirole and SKF-89124 were 20-5000 pg/mL and for SKF-104557 were 50-5000 pg/mL. HPLC-MS/MS data were acquired, processed (integrated) and a weighted $1/x^2$ linear regression calibration plot of peak area ratio vs. plasma Ropinirole, SKF-89124, SKF-104557 was constructed and applied to the data using computer software. Concentrations of Ropinirole, SKF-89124 and SKF-104557 in study samples were determined from the calibration plot. Quality control (QC) samples were realized by spiking blank plasma samples with known amounts of SKF 101468, SKF 89124 and SKF 104557 (50, 1000 and 4000 pg/mL for SKF 101468 and SKF 89124, and 100, 1000 and 4000 pg/mL for SKF 104557). The lower limit of quantification (LLQ) for ropinirole (SK&F-101468) and SK&F-89124 assay was 20 pg/mL and for SK&F-104557 was 50 pg/mL, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification of 5 ng/mL. Inter-day and intra-day accuracy and precision were <15% (mostly <10%).

b(4)

Table 1. Assay validation for Study SK&F-101468/164

			Ropinirole	SK&F-89124	SK&F-104557
Method:			LC/MS/MS	LC/MS/MS	LC/MS/MS
Standard curve	Range:		20~5000 pg/mL	20~5000 pg/mL	20~5000 pg/mL
		Precision:	2.6~6.5 %	5.7~10.3 %	4.1~6.8 %
		Accuracy:	-1.2~1.3 %	-7.7~3.3 %	-2.1~2.8 %
	Linearity:		$r^2 = 0.9986$	$r^2 = 0.9966$	$r^2 = 0.9978$
LOQ	LLOQ:		20 pg/mL	20 pg/mL L	50 pg/mL
QC	Low:		50 pg/mL	50 pg/mL	100 pg/mL
		Precision:	6.0 %	11.3 %	9.9 %
		Accuracy:	-0.4 %	2.8 %	-1.2 %
	Med:		1000 pg/mL	1000 pg/mL	1000 pg/mL
		Precision:	3.6 %	9.3 %	5.7 %

	Accuracy:	2.9 %	6.5 %	-0.8 %
High:		4000 pg/mL	4000 pg/mL	4000 pg/mL
	Precision:	6.0 %	5.9 %	7.0 %
	Accuracy:	-0.3 %	5.4 %	0.1 %

Pharmacokinetic Analyses:

The following pharmacokinetic parameters for ropinirole were estimated by non-compartmental methods:

- Primary PK endpoints: dose-normalized AUC(0-24), Cmax, Cmin
- Secondary PK endpoints: Tmax, Degree of fluctuation (DF)

In addition, trough concentrations of ropinirole obtained on the 2 days prior to the PK sampling day, and on the PK-sampling day, were used to assess the attainment of steady state using visual inspection of plots.

Relative bioavailability (Part A): Point estimates and corresponding 90% CIs were estimated for dose-normalized ropinirole AUC(0-24), Cmax, and Cmin to assess the relative bioavailability of 8 mg od CR vs. 2.5 mg tid IR. Tmax and t½ were listed and summarized using summary statistics without formal statistical analyses.

Effect of food (Part B): Point estimates and corresponding 90% CIs were estimated for dose-normalized ropinirole AUC(0-24), Cmax, and Cmin between fed and fasted state to assess the effect of food on the highest 8-mg CR strength. Tmax was analyzed using the Wilcoxon Matched Pairs method to calculate the median difference between the fed and fasted regimens and 90% CI.

RESULTS

Demographics of Subjects:

Twenty-six patients with a diagnosis of idiopathic Parkinson's disease were enrolled. Three of them withdrew during the up-titration phase prior to randomization, so only 23 patients were randomized, of which 20 patients completed Part A of the study and 21 completed Part B. Twenty one of them (91.3%) were Caucasian, one was Hispanic and one was black. The disposition of the subjects enrolled is shown in the Table 2 below:

	Age [years]	**Height [cm]**	**Weight [kg]**	**Body Mass Index [kg/m2]**
Mean	67	171.8	84.5	28.7
(range)	(34 - 80)	(147.3 – 188.0)	(57.0 – 103.1)	(20.3 – 33.2)

For Part A, 19 out of 20 patients had evaluable PK data for both treatment periods and were therefore included in analysis. Patient #114 had multiple PK samples missing for IR treatment and no PK parameters could be determined, therefore this patient was excluded from analyses.

For Part B, all 21 patients were included in the summary statistics and analyses. Patient #204 had an incomplete PK profile for 8 mg CR ropinirole in the fasted state and, as

such, only Cmax and tmax were derived. Patient #101 had an incomplete PK profile for 8 mg CR ropinirole in the fed state, therefore only Cmax, Cmin and tmax were derived. Twenty patients therefore had evaluable data for AUC(0-24) and DF in fed and fasted states in Part B.

Relative Bioavailability:
Plasma concentration-time profiles of ropinirole for dosing regimen used to assess the relative BA of 8-mg od CR vs. 7.5-mg IR (2.5 mg tid) formulations were shown in Figure 1. A summary of ropinirole PK parameters and the statistical summary for the assessment is shown in Tables 3-4.

Figure 1. Mean ropinirole plasma concentrations-time profiles (8-mg od CR vs. 7.5-mg IR (2.5 mg tid))

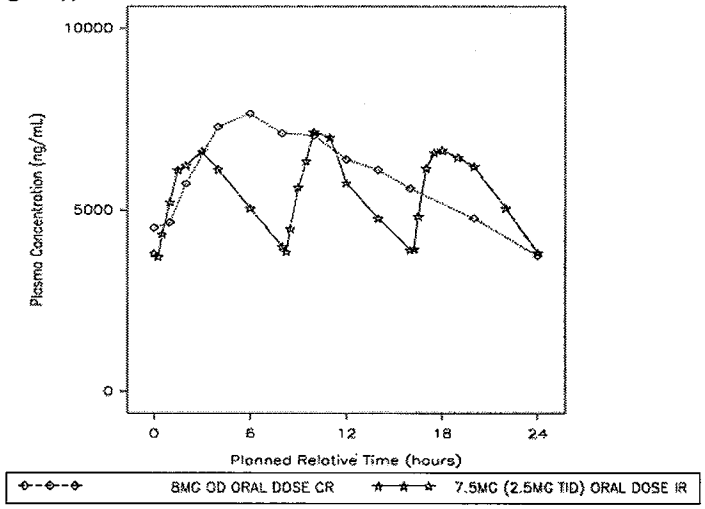


Table 3. Summary of ropinirole PK parameters

Parameter	8 mg ropinirole CR od (n = 19)	2.5 mg ropinirole IR tid (n = 19)
AUC(0-24) (ng.h/mL)	130 (103 -164)	120 (96.1 -150)
Cmax (ng/mL)	7.36 (5.85 -9.24)	7.87 (6.48 -9.57)
Cmin (ng/mL)	3.53 (2.55 -4.87)	3.40 (2.53 -4.57)
tmax (hours)[a]	6.05 (3.98 -20.0)	11.0 (0.55 -19.0)
DF[a]	0.70 (0.34 – 1.19)	0.79 (0.40 – 2.52)

Data: geometric mean (95% CI)
a. Median (range)

Table 4. Summary of the statistical analysis for ropinirole for the relative bioavailability of 8-mg od CR vs. 7.5-mg IR (2.5 mg tid)

Parameter (Dose-normalized)	Comparison	Ratio	90% CI	CVw(%)
AUC(0-24) (ng·h/mL)	CR:IR	1.02	(0.96, 1.09)	11.4
Cmax (ng/mL)	CR:IR	0.88	(0.78, 0.99)	21.5
Cmin (ng/mL)	CR:IR	0.98	(0.90, 1.06)	14.8

Reviewer's note:

- The ratios of dose-normalized AUC(0-24) and Cmin for 8 mg od ropinirole CR, relative to 2.5 mg tid ropinirole IR, were similar, being close to unity and with 90% CIs within the limits associated with bioequivalence (0.80 to 1.25).
- The dose-normalized Cmax for the CR formulation was, however, on average, 12% lower than for the IR formulation. The 90% CI for Cmax ratio fell slightly outside of the lower BE limit.

Effect of Food:

Plasma concentration-time profiles of ropinirole (including the fasted data from Part A) for dosing regimen used to assess the food effects, PK parameters, and the statistical summary are shown in Figure 2 and Tables 5-6.

Figure 2. Mean ropinirole plasma concentrations-time profiles following administration of 1 x 8 mg ropinirole CR with or without food

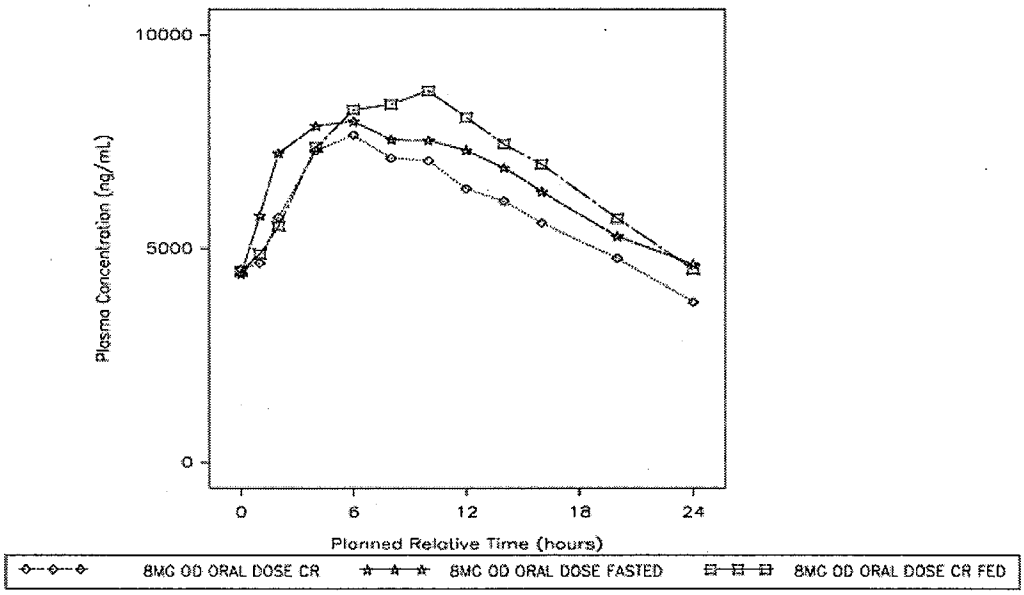


Table 5. Summary of ropinirole pharmacokinetic parameters

Parameter	Fed (n = 20)	Fasted (n = 20)
AUC(0-24) (ng·h/mL)	147 (115 - 189)	139 (107 - 115)
Cmax (ng/mL)	8.73 (7.08 - 10.8)[a]	7.59 (6.01 - 9.58)[a]

Cmin (ng/mL)	3.77 (2.72 - 5.24)[a]	3.94 (3.03 - 5.11)[a]
tmax (hours)[b]	10.00 (4.00 - 14.00)[a]	6.00 (2.00 - 14.00)[a]
DF[b]	0.74 (0.28 - 1.72)	0.58 (0.27 - 1.46)

Data: geometric mean (95% CI)
a. n = 21
b. Median(range)

Table 6. Summary of the statistical analysis for ropinirole for effect of food

Parameter (Dose-normalized)	Comparison	Ratio	90% CI	CVw(%)
AUC(0-24) (ng·h/mL)[a]	Fed : Fasted	1.06	(0.95, 1.19)	21.1
Cmax (ng/mL)[a]	Fed : Fasted	1.15	(1.01, 1.31)	25.3
Cmin (ng/mL)[a]	Fed : Fasted	1.96	(0.85, 1.08)	23.3
tmax (h)[b]	Fed - Fasted	2.00	(-0.02, 4.00)	

a. represents the ratio of geometric means between groups
b. represents the estimated median difference between groups

Reviewer's note:

- AUC(0-24) and Cmin were similar in the fed state and fasted states, based on the ratios being close to unity and the 90% CIs being within the BE limits (0.80 - 1.25).
- Cmax was, on average, 15% higher in the fed state than in the fasted state. The lower end of the 90% CI was greater than unity and higher end of 90% CI exceeded upper BE limit. The absorption of ropinirole CR at 1 x 8 mg appeared to be prolonged, as reflected by median prolonged Tmax by 2 hours (based on mean plasma concentration-time profiles shown in Figure 2), following a high fat breakfast compared to fasted state. This extent of changes in Cmax and Tmax are not considered to be clinically relevant in terms of safety or efficacy, in view of the relatively flat concentration-time profile of ropinirole.
- There was no evidence of dose dumping because of food.

Ratios of AUC(0-24) metabolite : AUC(0-24) ropinirole after dosing of ropinirole CR 8 mg in the fed and fasted state and ropinirole IR were estimated, as shown in the table below.

Table 7. Ratios of AUC(0-24) metabolite : AUC(0-24) ropinirole after dosing of ropinirole CR 8 mg in the fed and fasted state and ropinirole IR (2.5 mg tid)

Parameter	Part	Regimen	n	Geometric Mean (CVb%)
SKF-104557 : ropinirole	A	IR fed standard	20	1.19 (24.6%)
		CR fed standard	20	1.12 (22.9%)
	B	CR fasted	21	1.16 (26.8%)
		CR fed high fat	20	1.13 (25.1%)
SKF-89124 : ropinirole	A	IR fed standard	20	0.045 (24.2%)

		CR fed standard	20	0.043 (23.1%)
	B	CR fasted	21	0.043 (29.5%)
		CR fed high fat	20	0.042 (28.2%)

The ratio of metabolite : parent AUC(0-24) was similar for ropinirole CR and ropinirole IR. The systemic exposure (AUC(0-24)) to SKF-104557 was approximately 30% to 40% higher than the parent compound and systemic exposure to SKF-89124 was 5% that of the parent drug. Administration of ropinirole CR with food (non-high fat meal and high fat meal) did not affect the metabolite : parent ratio.

Sponsor's Safety Conclusion:

- The highest incidence of AEs occurred on the 2 mg dose of ropinirole in the up-titration phase. This was the first dose administered to patients entering the study who had not previously received ropinirole. The tolerability of ropinirole CR improved during the uptitration phase of the study.
- One patient experienced three SAEs during the study; confusion and hallucinations, which led to withdrawal from study medication, and a fatal myocardial infarction. None of these SAEs was considered by the investigator to be related to study medication, with the patient's history of coronary artery disease considered a contributing factor.
- The incidence of AEs was low on both the IR and CR formulations in the treatment phase of Part A of the study. This suggested that switching between the IR and CR formulations of ropinirole had no adverse effect on tolerability.
- There was a higher incidence of post-dose blood pressure decreases of potential clinical concern (PCC) and significant orthostatic BP decreases whilst patients were taking 2.5 mg tid IR, compared with 8 mg od CR ropinirole, but none was reported as an AE and no effect of switching between IR and CR was seen.
- There was no difference in the tolerability (AEs or vital signs changes) of 8 mg od CR ropinirole when it was administered to patients in either the fed or fasted state.
- There were no clinically significant post-dose effects on laboratory or ECG parameters.

CONCLUSION:

- Dose-normalized AUC(0-24) and Cmin were similar for the CR (8 mg od) and IR (2.5 mg tid) formulations of ropinirole. Dose-normalized Cmax was, on average, 12% lower for the CR formulation than for the IR formulation, but this was not considered to be of clinical relevance.

- There was no clinically relevant food effect on the pharmacokinetics of ropinirole following administration of the CR formulation. AUC(0-24), and Cmin were similar in both the fed and fasted state. Cmax was slightly higher (15%) and the median prolongation of Tmax was 2 hours in the fed state compared with the fasted state.

- The ratio of metabolite AUC(0-24) : parent AUC(0-24) was similar for ropinirole CR and ropinirole IR and food did not affect the metabolite : parent ratios.

Reviewer's comments:

- The study report is acceptable from a CPB perspective.
- The FDA's Guidance for Industry recommends that food effect bioavailability study be conducted in a single-dose study on the highest strength of a drug product intended to be marketed. The definitive food effect was studied at steady-state of the highest 8-mg/day dose level, instead of on a single 8-mg dose. The study design is considered acceptable in view of the tolerability reasons and the up-titration dosing regimen.
- Study 164 for food effect was not conducted using TBM formulation but is considered acceptable in view of same manufacturing site, identical core composition, size and shape, with the exception of coating color and debossings.

Study SK&F-101468/165

An open-label, up-titration study to assess the dose proportionality of Ropinirole CR and to demonstrate the bioequivalence of Ropinirole CR (1 x 8 mg) compared to Ropinirole CR (4 x 2 mg) in Parkinson's Disease patients not receiving other dopaminergic therapies

Principal Investigators: [redacted] b(4)

Study Centers: Five centers in the United States and one center in France.
Study Period: 18 Sep 2003 – 28 Jun 2004

Objectives:

Primary:

- To demonstrate the dose proportionality of ropinirole controlled-release (CR) over a dose range of 2 to 8 mg, in patients with idiopathic Parkinson's disease
- To demonstrate the bioequivalence of ropinirole CR (1 x 8 mg) compared to ropinirole CR (4 x 2 mg).

Secondary:

- To confirm the safety and tolerability of ropinirole CR over a dose range of 2-8 mg in patients with idiopathic Parkinson's disease

Drug Products:

CR formulations: colored, film-coated capsule shaped tablets; 2mg (batch no. N02032-S1 (US centers) and N02033-S1 (French center)), 4 mg (batch no. N02040-S1 (all centers)), and 8 mg (batch no. N02047-S1 (US centers) and N02046-S1 (French center)) of active drug substance; all had expiry date of 30 June 2004.

Study Design:

This was an open-label, multi-center study in patients who had a diagnosis of idiopathic Parkinson's disease according to modified Hoehn & Yahr Stage I-III criteria. Sufficient eligible male and female patients, aged 30 years or greater, were enrolled to ensure ≥22 evaluable subjects. Patients were randomized to one of two sequences (ABCDE or ABCED), and each patient received treatments ABC followed by either treatment DE or ED. The 5 treatments were as follows:

A : Ropinirole CR 2 mg od (1 x 2 mg)
B : Ropinirole CR 4 mg od (1 x 4 mg)
C : Ropinirole CR 6 mg od (3 x 2 mg)
D : Ropinirole CR 1 x 8 mg od (1 x 8 mg)
E : Ropinirole CR 4 x 2 mg od (4 x 2 mg)

Patients received starting doses of ropinirole CR od at 2 mg/day with a weekly dose escalation of 2 mg (2, 4, 6, 8 mg). Patients took the majority of their study medication at home and completed diary cards. For the 2 mg and 4 mg dose levels, patients attended

the clinic after they had received at least three sequential days of dosing, for 24 h of PK and safety evaluations. At these PK clinic visits, ropinirole CR was administered after breakfast, and food and drink consumption was standardized. For the 4 mg dose level, patients also attended the clinic for PK trough sampling. A pre-dose PK blood sample was taken on each of the two days preceding the PK clinic visit. For the 6 mg dose level, patients continued taking their medication at home and attended the clinic for safety evaluations, but PK assessments were not done.

At the 8 mg dose level, patients were randomized to one of two treatment sequences:

- Sequence 1: Patients received ropinirole CR 1 x 8 mg od for one week (Week 4) and ropinirole CR 4 x 2 mg od for the next week (Week 5). The number of days dosing at 8 mg could be adjusted to fit in with the PK clinic visit schedule.
- Sequence 2: Patients received ropinirole CR 4 x 2 mg od for one week (Week 4) and ropinirole CR 1 x 8 mg od for the next week (Week 5). The number of days dosing at 8 mg could be adjusted to fit in with the PK clinic visit schedule.

For each treatment sequence, patients took their medication at home. After at least 3 sequential days of dosing they attended the clinic for PK and safety evaluations. On this clinic day, ropinirole CR was administered after standardized food and drink. Dosing and PK visit schedule are shown in the table:

Week	Days[a]	Ropinirole CR Dose	PK Trough Samples	PK Clinic Visits
1	1 – 7	2 mg/day (1 x 2 mg)	---	Days 4, 5, 6 or 7
2	8 - 14	4 mg/day (1 x 4 mg)	Pre-dose PK sample for 2 days prior to PK visit [b]	Days 12, 13 or 14
3[c]	15 -21	6 mg/day (3 x 2 mg)	---	---
4	22 – 28[d]	8 mg/day (1 x 8 mg or 4 x 2 mg)	---	Days 25, 26, 27 or 28[d]
5	29 – 35[e]	8 mg/day (4 x 2 mg or 1 x 8 mg)	---	Days 32, 33, 34 or 35[e]
6		Down-titration	---	---

Upon completion of the last PK evaluation visit, patients could (1) return to long term safety study (196), in which some of the patients entered in this study had previously participated, or enter long term safety study 248, (2) Receive appropriate pharmacotherapy from the investigator or from the patient's primary physician, or (3) switch from ropinirole CR 8 mg od to ropinirole IR 7.5mg (2.5mg tid) or down-titrate. All patients were required to attend the clinic for a follow-up visit 7 (+2) days after discharge from the study center.

Restriction and documentation for prior and concomitant medications, OTC or herbal remedies, dietary components, hormone replacement therapy, and/or any drugs that will likely have impact on the results via CYP1A2 mechanism were noted for the study.

Safety Assessments:
Study assessments throughout the study included 12-lead ECGs, vital signs, safety laboratory evaluation, and assessments of AEs.

Pharmacokinetics Assessments:

The PK blood samples were collected for analysis of plasma ropinirole levels at the following time-points during each of the inpatient PK clinic visits: pre-dose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 h (i.e., before the next dose of study medication) post-dose. For the 4 mg dose level only, a pre-dose PK blood sample was taken on each of the two days preceding the PK clinic visit. Samples were stored frozen at approximately - 20°C until analyzed at [redacted]

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Plasma samples were stored at approximately -20°C until assayed at [redacted], using a validated LC-MS/MS method for the plasma concentrations of ropinirole and its metabolites (SK&F-104557 and SK&F-89124). [redacted] was used as internal standard. The calibration standards for ropinirole and SKF-89124 were 20-5000 pg/mL and for SKF-104557 were 50-5000 pg/mL. HPLC-MS/MS data were acquired, processed (integrated) and a weighted $1/x^2$ linear regression calibration plot of peak area ratio vs. plasma Ropinirole, SKF-89124, SKF-104557 was constructed and applied to the data using computer software. Concentrations of Ropinirole, SKF-89124 and SKF-104557 in study samples were determined from the calibration plot. Quality control (QC) samples were realized by spiking blank plasma samples with known amounts of SKF 101468, SKF 89124 and SKF 104557 (50, 1000 and 4000 pg/mL for SKF 101468 and SKF 89124, and 100, 1000 and 4000 pg/mL for SKF 104557). The lower limit of quantification (LLQ) for ropinirole (SK&F-101468) and SK&F-89124 assay was 20 pg/mL and for SK&F-104557 was 50 pg/mL, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification of 5 ng/mL. Inter-day and intra-day accuracy and precision were most <15%.

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Table 1. Assay validation for Study SK&F-101468/165

			Ropinirole	SK&F-89124	SK&F-104557
Method:			LC/MS/MS	LC/MS/MS	LC/MS/MS
Standard curve	Range:		20~5000 pg/mL	20~5000 pg/mL	20~5000 pg/mL
		Precision:	2.2~6.7 %	4.6~19.0 %	3.9~7.8 %
		Accuracy:	-3.5~4.0 %	-5.3~3.2 %	-2.3~2.9 %
	Linearity:		$r^2 = 0.9986$	$r^2 = 0.9966$	$r^2 = 0.9978$
LOQ	LLOQ:		20 pg/mL	20 pg/mL L	50 pg/mL
QC	Low:		50 pg/mL	50 pg/mL	100 pg/mL
		Precision:	4.8 %	9.6 %	6.7 %
		Accuracy:	-0.3 %	-3.5 %	0.4 %
	Med:		1000 pg/mL	1000 pg/mL	1000 pg/mL
		Precision:	4.0 %	10.0 %	4.6 %
		Accuracy:	-6.0 %	-6.6 %	-2.3 %
	High:		4000 pg/mL	4000 pg/mL	4000 pg/mL
		Precision:	4.4 %	10.3 %	12.5 %
		Accuracy:	-2.6 %	1.4 %	-4.2 %

Reviewer's note:

The precision for the highest 5000 pg/mL of calibration standard curve for SKF-89124 in human plasma exceeded 15% of CV.

Pharmacokinetic Analyses:
The following pharmacokinetic parameters for ropinirole were estimated by non-compartmental methods:

- Primary PK endpoints: AUC(0-24), Cmax, and Cmin
- Secondary PK endpoints: Tmax

Dose proportionality assessment: To assess dose proportionality of ropinirole CR over 2-8 mg dose range (i.e., CR 1 x 2 mg (treatment A), 1 x 4 mg (treatment B) and 1 x 8 mg (treatment D)), the estimated mean slope and 90% confidence interval (CI), based on the power model as described below, were constructed for exposure measures (AUC(0-24), Cmax, and Cmin) of each treatment. Dose proportionality would be demonstrated if the 90% CIs of the estimated mean slopes of the exposure measures were completely contained within the standard range of 0.80~1.25 and the revised range of 0.839~1.161 (when taking into account the dose range being studied).

$$\text{parameter} = e^{a} (\text{dose})^{b}$$

$$\text{i.e., } \log(\text{parameter}) = a + (b * \log(\text{dose}))$$

(where a is the intercept, depending on subjects, and b is the slope, measuring the extent of dose proportionality.)

Relative bioavailability assessment: Point estimates and corresponding 90% CIs were estimated for exposure measures (AUC(0-24), Cmax, and Cmin) to assess the relative bioavailability of ropinirole CR 1 x 8 mg vs. CR 4 x 2 mg (treatment D vs. treatment E). Equivalence would be demonstrated if the 90% CIs for the ratios of exposure measures were completely contained within the interval of 0.80~1.25.

RESULTS

Demographics of Subjects:
Of the 28 patients who were randomized, 23 (82.1%) were Caucasian, 3 (10.7%) were American Hispanic, 1 was black and one was Greek. Twenty-one of the 28 patients (75.0%) were male and 7 (25.0%) were female. The other demographic data are summarized in table below:

	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m^2]
Mean (SD)	67 (11.5)	170.0 (9.8)	84.6 (18.8)	29.2 (5.9)
range	47 - 87	152.0 – 196.0	49.1 – 128.1	21.2 – 50.0

Six patients (#30, 37, 49, 50, 63, and 64) were withdrawn from the study, of which 5 were withdrawn due to AEs and 1 withdrew consent. Twenty-two patients completed the study and were included in the PK analyses.

Pharmacokinetic Summary:
Plasma concentration-time profiles of ropinirole following administration of ropinirole CR 1 x 2 mg (Treatment A), 1 x 4 mg (Treatment B), 1 x 8 mg (Treatment D), and 4 x 2 mg (Treatment E) are shown in Figures 1-2.

Figure 1. Median steady state ropinirole plasma concentrations-time profiles by treatments (N=22)

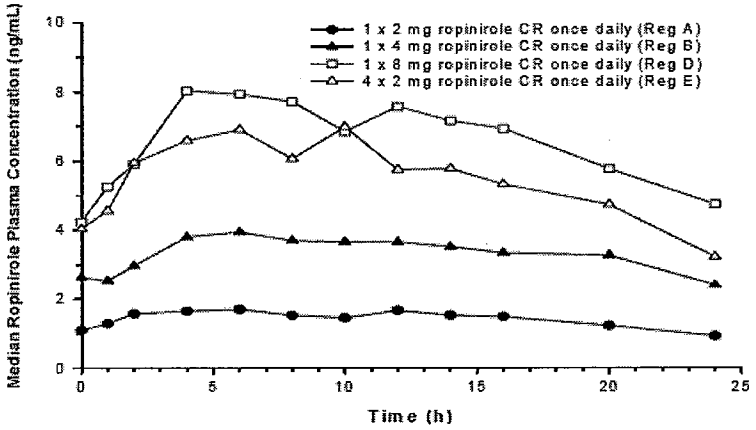
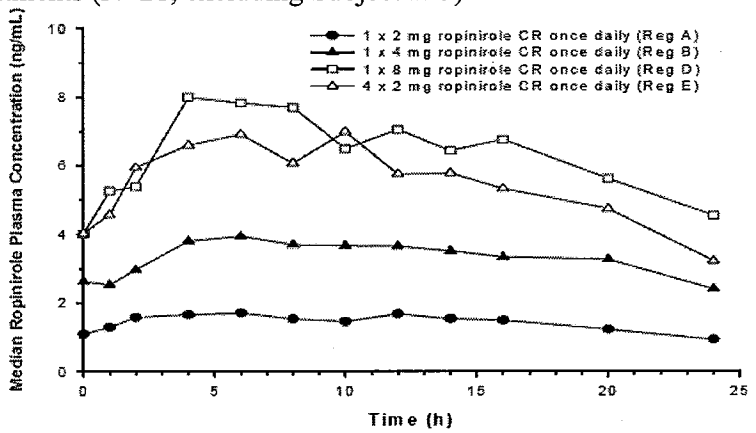


Figure 2. Median steady state ropinirole plasma concentrations-time profiles by treatments (N=21, excluding Subject #25)



Reviewer note:
One subject (#25) had approximately 4-fold higher ropinirole plasma level for CR 1 x 8 mg than that observed when the same dose was administered as CR 4 x 2 mg and was considered as an outlier.

The PK parameters and the summary statistics for ropinirole following administration of ropinirole obtained from various treatments are shown in Tables 2-3.

Table 2. Summary of the PK results (N=22)

Dose of ropinirole CR	AUC(0-24) (ng·h/mL)[a]	Cmax (ng/mL)[a]	Cmin (ng/mL)[a]	Tmax (h)[b]
1 x 2 mg	37.9 (56.7)	2.16 (50.6)	1.13 (76.5)	7.00 (1.00-20.00)

1 x 4 mg	76.3 (54.7)	4.19 (50.7)	2.36 (65.8)	6.00 (4.00-24.00)
1 x 8 mg	168 (69.1)	9.30 (67.2)	4.74 (88.0)	6.00 (2.00-20.00)
4 x 2 mg	152 (56.8)	8.50 (49.2)	4.49 (66.1)	10.00 (2.00-20.00)

a. geometric mean (CV%)
b. median (range)

Table 3. Summary of the PK results (N=21, excluding Subject #25)

Dose of ropinirole CR	AUC(0-24) (ng·h/mL)[a]	Cmax (ng/mL)[a]	Cmin (ng/mL)[a]	Tmax (h)[b]
1 x 2 mg	37.0 (56.6)	2.13 (51.3)	1.09 (76.8)	6.00 (1.00-20.00)
1 x 4 mg	74.2 (54.1)	4.08 (50.1)	2.28 (64.3)	6.00 (4.00-24.00)
1 x 8 mg	156 (56.1)	8.61 (53.7)	4.39 (77.1)	6.00 (2.00-16.00)
4 x 2 mg	148 (56.5)	8.32 (49.2)	4.35 (65.5)	10.00 (2.00-20.00)

a. geometric mean (CV%)
b. median (range)

Dose Proportionality:
Statistical summary for the dose proportionality assessment (power model) are shown in Table 4.

Table 4. Summary of the Slope and 90% Confidence Intervals for ropinirole exposure measures from the Power Model with and without the outlier

Parameter	Slope	90% CI	Slope	90% CI
	(N=22)		(N=21)	
AUC(0-24) (ng·h/mL)	1.073	(0.991, 1.156)	1.036	(0.978, 1.095)
Cmax (ng/mL)	1.053	(0.959, 1.147)	1.009	(0.950, 1.068)
Cmin (ng/mL)	1.036	(0.904, 1.168)	1.002	(0.878, 1.126)

Reviewer's note:

- The estimated slopes obtained from the power models for AUC(0-24), Cmax, and Cmin were close to unity, indicating that the PK parameters for ropinirole were approximately linear over the dose range 2 to 8 mg.
- When including all subjects, the 90% CIs of the mean slopes for AUC(0-24), Cmax, and Cmin were completely contained within the sponsor's predefined limits of (0.80, 1.25), with or without excluding an outlier. With the sponsor's revised limits of (0.839, 1.161), the 90% CIs for AUC(0-24) and Cmax were also contained within these limits, however, the upper end of the 90% CI for Cmin (i.e., 1.168) fell marginally outside the limits

- When excluding the outlier, the 90% CIs of the mean slopes were completely within the predefined or revised limits. Therefore, dose proportionality for ropinirole AUC(0-24), Cmax, and Cmin from CR formulations could be concluded.

Relative Bioavailability:
Statistical summaries for the assessment for the relative bioavailability of ropinirole CR 1 x 8 mg vs. 4 x 2 mg (treatment D vs. treatment E) are shown in Table 5.

Table 5. Summary of the statistical analysis for ropinirole for assessing ropinirole CR 1 x 8 mg vs. 4 x 2 mg (Treatment D vs. Treatment E)

Parameter	Comparison	Ratio	90% CI	CVw%
AUC(0-24) (ng·h/mL)	D:E	1.10 1.05[a]	(0.95, 1.26) (0.93, 1.18)[a]	27.5 22.2[a]
Cmax (ng/mL)	D:E	1.09 1.03[a]	(0.93, 1.27) (0.90, 1.18)[a]	31.1 25.4[a]
Cmin (ng/mL)	D:E	1.04 1.01[a]	(0.90, 1.21) (0.88, 1.15)[a]	29.3 26.2[a]

a. Results without data from the outlier (subject #25)

Reviewer's note:
- The 90% CI for Cmin was contained within the BE limits (0.80, 1.25). However, the 90% CI for AUC(0-24) and Cmax fell slightly outside the upper BE limit when include data of an outlier.
- Dosage strength equivalence of ropinirole 1 x 8 mg vs. 4 x 2 mg CR formulations was demonstrated after excluding the outlier, since the 90% CIs for AUC(0-24), Cmax, and Cmin were all completely contained within the range of 0.80-1.25.

Sponsor's Safety Summary:
- The highest incidence of AEs occurred on the lowest dose of ropinirole CR, 2 mg od. This was the first dose administered to patients entering the study, the majority of whom had not previously received ropinirole. The tolerability of ropinirole CR improved during up-titration of the ropinirole dose level.
- One patient experienced an SAE during the study; severe pain in the left thigh, which started prior to study medication and was considered unrelated to study medication. This SAE led to withdrawal from the study after the first dose of study medication. This was the only severe AE reported.
- Ropinirole CR (2 to 8 mg od) was generally well-tolerated in patients with Parkinson's disease and tolerability improved as the dose was up-titrated.
- The incidence of AEs was similar on the ropinirole CR 1 x 8 mg od (7/22 patients: 31.8%) and 4 x 2 mg od (8/23 patients: 34.8%) dosage regimens.
- There was a similar incidence of post-dose blood pressure decreases of potential clinical concern (PCC) and
- orthostatic BP decreases of PCC while patients were taking the ropinirole CR 1 x 8 mg od (3/22 patients: 13.6%) and 4 x 2 mg od (4/23 patients: 17.4%) dosage regimens.

- There were no clinically significant post-dose effects on laboratory or ECG parameters.

CONCLUSION:

- Dose proportionality was demonstrated for AUC(0-24) and Cmax, based on the sponsor's predefined dose proportionality limits. Dose proportionality for Cmin was demonstrated when the PK outlier (Patient 25) was excluded from the analysis.

- Bioequivalence of ropinirole CR 1 x 8 mg and ropinirole CR 4 x 2 mg was demonstrated for Cmin, but for AUC(0-24) and Cmax the upper end of the 90% CIs fell slightly outside the upper limit of 1.25. However, BE was demonstrated for all exposure measures when the PK outlier (Patient 25) was excluded from the analysis.

Study SK&F-101468/219

An open label, randomized, five-way crossover single-dose pharmacokinetic study to assess dosage strength equivalence of ropinirole CR in healthy male and female volunteers

- Principal Investigators: [redacted] b(4)
- Study Centers: James Lance GlaxoSmithKline Medicines Research Unit, Australia
- Study Period: 22 Apr 2002 – 27 Jun 2002

Objectives:

- To assess the dosage strength equivalence of ropinirole CR tablets
- To assess the dose proportionality of ropinirole CR tablets

Drug Products:

Study Drug	Batch number	Storage conditions	Expiry Date
Ropinirole CR tablets, 1mg	N01265	20 to 25°C	31 May 03
Ropinirole CR tablets, 2mg	N01266		31 May 03
Ropinirole CR tablets, 3mg	N01271		31 May 03
Domperidone tablets, 10mg	01KV853	Below 30°C	31 Oct 05
Domperidone tablets, 10mg	01KV831		31 Oct 05

Ropinirole CR tablets were manufactured by GlaxoSmithKline and domperidone tablets were manufactured by [redacted] b(4)

Study Design:

This was a single-centre, open label, randomized, five-way cross-over, single-dose pharmacokinetic study in 35 healthy, non-smoking subjects (27 males and 8 females), aged 18-50 years, inclusive, to assess dosage strength equivalence of ropinirole CR 1+1mg, 2mg, 1+1+1mg and 3 mg. During each of the five treatment periods (each with a two-night stay in the center), eligible subjects were randomized to receive one of the following five treatment periods of ropinirole CR:

- Regimen A ropinirole CR 1mg (1 tablet)
- Regimen B ropinirole CR 1+1mg (2 tablets)
- Regimen C ropinirole CR 2mg (1 tablet)
- Regimen D ropinirole CR 1+1+1mg (3 tablets)
- Regimen E ropinirole CR 3mg (1 tablet)

Subjects received their tablets in the morning 30min after the start of the standard breakfast. Subjects also received 3 doses of 2x10mg tablets of domperidone at 8h intervals on each dosing day to diminish peripheral dopaminergic side effects. The first dose of domperidone was given 1 h before the ropinirole doses, with subsequent doses

been given at 7h and 15h after dosing with ropinirole. At each study session, blood samples were collected from each subject for the analysis of ropinirole and its metabolites (SKF-89124 and SKF-104557). There was a follow-up visit 7~14 days after the last dosing. Dietary components and potential comedications that will likely have impact on the results via CYP1A2 mechanism were noted for the study.

Safety Assessments:
Safety parameters comprised adverse events (AEs and SAEs), clinical laboratory evaluations, vital signs, alcohol breath test, tests for HIV, hepatitis B and C, urine drug screen, urine pregnancy test for females, and 12-lead ECG.

Pharmacokinetics Assessments:
The PK blood samples were collected for analysis of ropinirole and its metabolites (SKF-89124 and SKF-104557) plasma levels at the following time-points during each of the inpatient PK clinic visits: pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 32 and 36 hours post-dose.

Plasma samples were stored at approximately -20°C until assayed at [redacted] using a validated LC-MS/MS method for the plasma concentrations of ropinirole and its metabolites (SK&F-104557 and SK&F-89124). [redacted] was used as internal standard. The calibration standards for ropinirole and SKF-89124 were 20-5000 pg/mL and for SKF-104557 were 50-5000 pg/mL. HPLC-MS/MS data were acquired, processed (integrated) and a weighted $1/x^2$ linear regression calibration plot of peak area ratio vs. plasma Ropinirole, SKF-89124, SKF-104557 was constructed and applied to the data using computer software. Concentrations of Ropinirole, SKF-89124 and SKF-104557 in study samples were determined from the calibration plot. Quality control (QC) samples were realized by spiking blank plasma samples with known amounts of SKF 101468, SKF 89124 and SKF 104557 (50, 1000 and 4000 pg/mL for SKF 101468 and SKF 89124, and 100, 1000 and 4000 pg/mL for SKF 104557). The lower limit of quantification (LLQ) for ropinirole (SK&F-101468) and SK&F-89124 assay was 20 pg/mL and for SK&F-104557 was 50 pg/mL, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification of 5 ng/mL. Inter-day and intra-day accuracy and precision were <10%.

b(4)

Table 1. Assay validation for Study SK&F-101468/219

			Ropinirole	SK&F-89124	SK&F-104557
Method:			LC/MS/MS	LC/MS/MS	LC/MS/MS
Standard curve	Range:		20~5000 pg/mL	20~5000 pg/mL	20~5000 pg/mL
		Precision:	1.58~4.73 %	2.41~5.78 %	2.30~4.88 %
		Accuracy:	-2.51~2.75 %	-7.88~5.92 %	-4.18~3.67 %
	Linearity:		$r^2 = 0.9993$	$r^2 = 0.9977$	$r^2 = 0.9983$
LOQ	LLOQ:		20 pg/mL	20 pg/mL L	50 pg/mL
QC	Low:		50 pg/mL	50 pg/mL	100 pg/mL
		Precision:	5.37 %	9.23 %	7.27 %
		Accuracy:	-1.75 %	-6.98 %	-5.14 %
	Med:		1000 pg/mL	1000 pg/mL	1000 pg/mL

	Precision:	2.95 %	6.52 %	5.56 %
	Accuracy:	-2.50 %	-1.31 %	0.92 %
High:		4000 pg/mL	4000 pg/mL	4000 pg/mL
	Precision:	2.82 %	5.50 %	4.60 %
	Accuracy:	0.82 %	4.66 %	5.01 %

Pharmacokinetic Analysis:

The following pharmacokinetic parameters for ropinirole were estimated using non-compartmental methods: Cmax, AUC(0-t), AUC(0-∞), AUC(0-24), Tmax, and t½. All PK parameters were listed and summarized using descriptive statistics (sample size, mean, geometric means, standard deviation, median, minimum and maximum) by dose level.

Dosage strength equivalence: The primary comparisons were to assess dosage strength equivalence of ropinirole CR 1+1mg vs. CR 2mg (Regimen B vs. C) and ropinirole CR 1+1+1mg vs. CR 3mg (Regimen D vs. E). The point estimates and the corresponding 90% CIs for the ratios of ln-transformed Cmax, AUC(0-t), and AUC(0-∞) between two treatments will be obtained using ANOVA. Equivalence would be demonstrated if the 90% confidence interval for the ratios of AUC(0-∞), AUC(0-t) and Cmax were completely contained within the BE limits (0.80, 1.25) for each dose strength comparison.

Dose proportionality assessment: Dose proportionality across 3 dose levels using 1 x 1mg, 1 x 2mg and 1 x 3mg tablets was assessed by fitting the estimates of $\log_e$-transformed parameter AUC(0-∞), AUC(0-t) and Cmax for the various dose levels to the power model as shown below. Individual slopes were derived for each subject. The power model was fitted with $\log_e$(dose) as fixed effect and subject as random. The estimated mean slope (b) and 90% confidence intervals were constructed for each parameter.

RESULTS

Demographics of Subjects:

Thirty-five subjects (27 males and 8 females) were initially recruited, as shown in the summary of demographic characteristics in Table 2 below:

Characteristic		Ropinirole (N=35)
Age (years)	Mean±SD Range	27±6.3 (18-44)
Height (cm)	Mean±SD Range	176±10.0 (160-196)
Weight (kg)	Mean±SD Range	73.3±9.86 (55.2-100.0)
BMI (kg/m^2)	Mean±SD Range	23.5±2.18 (19.9-28.9)
Sex (n%)	Male Female	27 (77%) 8 (23%)
Race (n%)	Caucasian Oriental	33 (94%) 2 (6%)

Two subjects (#19 and 34) were withdrawn from the study due to AEs of furunculosis of the back with associated cellulitis, and periodontitis, considered as unrelated to the study medication. Two subjects (#17 and 21) were withdrawn due to protocol deviations. A total of 31 subjects (25 males and 6 females) completed the study (88.6%) and received all 5 treatments.

Pharmacokinetic Summary:

Plasma concentration-time profiles and PK results of ropinirole following administration of ropinirole CR 1mg (Treatment A), 1+1mg (Treatment B), 2mg (Treatment C), 1+1+1mg (Treatment D), and 3mg (Treatment E) are shown in Figure 1 and Table 3.

Figure 1. Mean plasma ropinirole concentration-time profiles by treatment

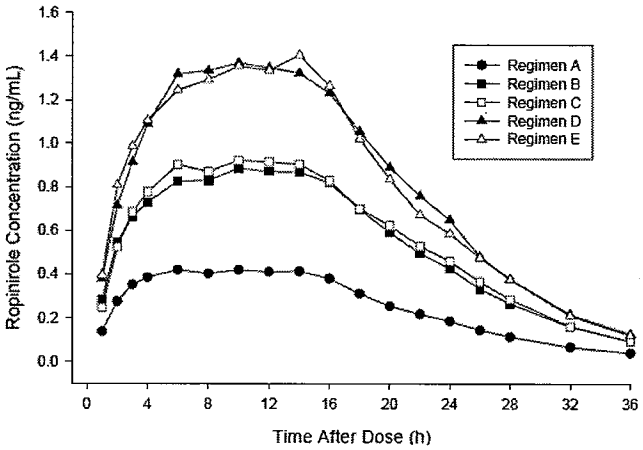


Table 3. Summary of ropinirole pharmacokinetic parameters [geometric mean (range)]

Regimen	1mg (A)	1+1mg (B)	2mg (C)	1+1+1mg (D)	3mg (E)
N	32	33	33	33	31
AUC(0-∞)[1] (ng.hr/mL)	8.50 (3.45-16.4)	18.4 (8.43-38.1)	20.0 (6.86-34.9)	28.1 (8.85-51.1)	27.5 (7.42-49.1)
AUC(0-t) (ng.hr/mL)	8.34 (3.32-15.8)	18.3 (8.23-36.4)	19.3 (6.72-33.5)	27.2 (8.74-49.7)	26.9 (7.28-47.3)
AUC(0-24) (ng.hr/mL)	7.45 (3.32-13.1)	15.9 (6.87-31.6)	16.6 (6.72-26.8)	23.9 (8.69-45.6)	23.7 (7.28-40.3)
Cmax (ng/mL)	0.493 (0.274-0.861)	0.996 (0.477-2.17)	1.07 (0.562-2.03)	1.49 (0.760-3.04)	1.58 (0.691-2.83)
Tmax[2] (h)	10.0 (3.00-16.0)	10.0 (3.00-18.0)	10.0 (3.00-24.0)	10.0 (4.00-18.0)	12.0 (3.00-26.0)
$t_{1/2}$[1] (h)	4.93 (3.46-9.67)	4.74 (3.35-7.26)	4.69 (2.79-8.32),	4.67 (3.01-7.89)	4.71 (3.42-6.76)

1. N for 1mg = 31, 1+1mg = 27, 2mg = 30, 1+1+1mg = 31, 3mg = 29

2. Tmax data presented as median (range)

Relative Bioavailability:
Statistical summaries for the assessment for the relative bioavailability of 5 dosing regimens of ropinirole CR are shown in Table 4.

Table 4. Summary of the statistical analysis for ropinirole for assessing ropinirole CR Regimen B vs. C and Regimen D vs. E

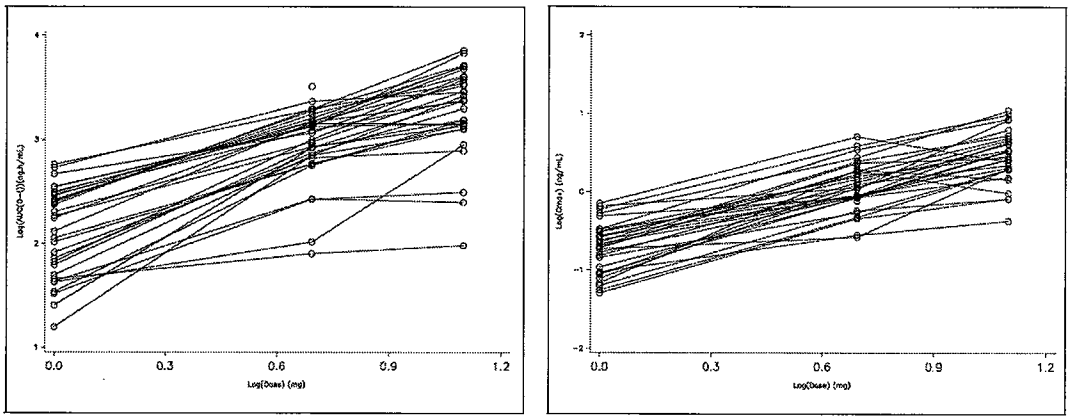
Parameter	Comparison	Point Estimate	90% CI
AUC(0-∞) (ng·hr/mL)	B:C	1.01	(0.92, 1.11)
	D:E	0.99	(0.90, 1.08)
AUC(0-t) (ng·hr/mL)	B:C	0.97	(0.89, 1.06)
	D:E	1.01	(0.92, 1.10)
Cmax (ng/mL)	B:C	0.94	(0.87, 1.03)
	D:E	0.94	(0.86, 1.02)

Reviewer's note:

- The 90% CIs for AUC(0-∞), AUC(0-t) and Cmax for the comparisons B:C and D:E were within the BE acceptance range of 0.80-1.25. Therefore, dosage strength equivalence was demonstrated between ropinirole CR 1+1mg and CR 2mg and between ropinirole CR 1+1+1mg and CR 3mg.
- The CVb% ~40%, similar across dose strengths for exposure measures. The CVw% for AUC(0-∞), AUC(0-t), and Cmax were 20.6%, 20.7% and 20.2%, respectively.

Dose Proportionality:
Representative plots of ropinirole log-transformed AUC(0-t) and Cmax vs. loge-transformed ropinirole CR dose for visual assessment of dose proportionality are shown in Figure 2 below.

Figure 2. Individual ropinirole AUC(0-t) and Cmax values vs. ropinirole CR dose



Statistical summary for the dose proportionality assessment (power model) are shown in Table 5.

Table 5. Summary of the Slope and 90% Confidence Intervals for ropinirole exposure measures from the Power Model

Parameter	Slope	90% CI
AUC(0-∞) (ng·hr/mL)	1.11	(1.00, 1.21)
AUC(0-t) (ng·hr/mL)	1.08	(0.98, 1.19)
Cmax (ng/mL)	1.07	(0.99, 1.15)

Reviewer's note:

- The sponsor did not pre-define the limits for 90% CI using Power Model for this study. However, based on visual assessments and the point estimate of the slope (i.e., close to unity) for each parameter, the dose proportionality for ropinirole AUC and Cmax from CR formulations across the dose range of 1-3 mg could be concluded.

CONCLUSION:

- Dosage strength equivalence of ropinirole CR tablets up to 3 mg was demonstrated.
- Dose proportional increases in AUC and Cmax were observed over the dose range 1 to 3 mg.
- Ropinirole CR single doses of up to 3 mg were generally well tolerated by healthy volunteers when administered concurrently with domperidone

Study SK&F-101468/166

A Phase II, randomized, double-blind, active-controlled , dose-escalation study to determine the maximum well-tolerated starting dose of ropinirole controlled-release (CR) in Parkinson's Disease patients not receiving other dopaminergic therapies

Principal Investigator and Study Center:
19 centers in 4 countries: US (13), France (4), Belgium (2), The Netherlands (1)
Study Period: 01 November 2000-03 October 2001

Objectives:
Primary:

- To identify the maximum well-tolerated starting dose of ropinirole controlled-release (CR) tablets given once daily (od) in patients with Parkinson's disease

Secondary:

- To compare the tolerability of once daily doses (1 to 5mg) of ropinirole CR with three times daily doses (tid) of 0.25mg ropinirole immediate release (IR) when each was administered for 7 days
- To assess the pharmacokinetic (PK) profile of the ropinirole CR formulation in patients with Parkinson's disease.

Drug Products:

Study medication	Batch number
Ropinirole IR 0.25mg tablets	N99219
IR placebo	M96380
Ropinirole CR 1mg tablet	B574
Ropinirole CR 3mg tablet	B581
CR placebo	B492

Study Design:
This was a multi-center, randomized, double-blind, double-dummy, active-controlled, 2-arm, parallel-group, dose-escalation study of ropinirole CR 1mg, 2mg, 3mg, 4mg and 5mg, using ropinirole IR 0.75mg/day as comparator. The study duration included a screening within 14 days prior to enrolment, a seven-day treatment period, and a follow-up examination on Day 14. Each subsequent cohort was to be initiated only if safety and tolerability in the preceding cohort was confirmed by TAP (Tolerance Assessment Panel) as satisfactory. Efficacy was not assessed.

Eligible subjects must be males and females aged ≥30 years with Parkinson's disease (Hoehn & Yahr Stage I~III) with no more than 6 weeks of previous treatment with L-dopa were enrolled. A total of 80 patients were planned, and 64 patients were randomized in a ratio of 3:1 to receive CR or IR. Patients took one IR tablet (active or matching placebo) plus two CR tablets (active or matching placebo) in the morning and one IR tablet (active or matching placebo) at noon and in the evening. Five dose cohorts (1mg, 2mg, 3mg, 4mg, or 5mg) for ropinirole CR were originally planned (Cohorts A-E). TAP concluded after the 3mg dose evaluation that it was safe to proceed but the sponsor

decided to stop after Cohort C (see table below). Protocol was amended to include extension phase to obtain blood pressure data for 2-mg doses prior to the initiation of Cohort C.

Cohort	Treatment assignment	N	Ropinirole IR administered	Ropinirole CR administered
A	IR	4	0.25 mg tid	None (matching placebo)
A	CR	12	None (matching placebo)	1 mg od
B	IR	4	0.25 mg tid	None (matching placebo)
B	CR	12	None (matching placebo)	2 mg od
B-extension	IR	4	0.25 mg tid	None (matching placebo)
B-extension	CR	12	None (matching placebo)	2 mg od
C	IR	4	0.25 mg tid	None (matching placebo)
C	CR	12	None (matching placebo)	3 mg od

Study medication was taken with or immediately after meals

Treatment with selegiline was permitted providing the current stable dose was maintained during study participation. Treatment with hormone replacement therapy, and/or other drugs known to substantially induce or inhibit CYP1A2 was allowed, but the dose of these agents was to remain stable from 7 days prior to enrolment through Day 14. Domperidone could be taken, but Treatment with other dopaminergic therapy within 2 weeks before enrolment and during the study was not allowed.

Safety Assessments:
The safety variables were adverse events (AEs), physical examination, vital signs including assessment of orthostatic changes in BP and pulse rate, Nausea Visual Analog Scale (NVAS), Epworth Sleepiness Scale, clinical chemistry, haematology, and urinalysis, and 12-lead ECG (one at screening, one at baseline (pre-dose on Day 1) and three at 4, 12 and 24 hours after the first dose on Day 1).

Pharmacokinetics Assessments:
The PK blood samples were collected for the analysis of plasma ropinirole concentrations at predose and at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours following the first dose on Day 1. At predose on Day 4 and on Day 8, blood samples for measurement of the trough (predose) plasma concentrations of ropinirole, SK&F 104557, and SK&F 89124 were also collected.

Plasma samples were stored at approximately -20°C until assayed at _____ _____ using a validated LC-MS/MS method for the plasma concentrations of ropinirole and its metabolites (SK&F-104557 and SK&F-89124). _____ was used as internal standard. The calibration standards for ropinirole and SKF-89124 were 20-5000 pg/mL and for SKF-104557 were 50-5000 pg/mL. HPLC-MS/MS data were acquired, processed (integrated) and a weighted $1/x^2$ linear regression calibration plot of peak area ratio vs. plasma Ropinirole, SKF-89124, SKF-104557 was constructed and applied to the data using computer software. Concentrations of Ropinirole, SKF-89124 and SKF-104557 in study samples were determined from the calibration plot. Quality control (QC) samples were realized by spiking blank plasma samples with known amounts of SKF 101468, SKF 89124 and SKF 104557 (50, 1000 and 4000 pg/mL for SKF 101468 and SKF 89124, and 100, 1000 and 4000 pg/mL for SKF 104557). The lower limit of quantification (LLQ) for ropinirole

b(4)

(SK&F-101468) and SK&F-89124 assay was 20 pg/mL and for SK&F-104557 was 50 pg/mL, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification of 5 ng/mL. Inter-day and intra-day accuracy and precision were <10%.

Table 1. Assay validation for Study SK&F-101468/219

			Ropinirole	SK&F-89124	SK&F-104557
Method:			LC/MS/MS	LC/MS/MS	LC/MS/MS
Standard curve	Range:		20~5000 pg/mL	20~5000 pg/mL	20~5000 pg/mL
		Precision:	1.19~5.13 %	1.92~5.11 %	1.76~4.68 %
		Accuracy:	-6.40~5.02 %	-8.00~6.76 %	-4.40~2.60 %
	Linearity:		$r^2 = 0.9974$	$r^2 = 0.9946$	$r^2 = 0.9975$
LOQ	LLOQ:		20 pg/mL	20 pg/mL L	50 pg/mL
QC	Low:		50 pg/mL	50 pg/mL	100 pg/mL
		Precision:	5.33 %	6.51 %	6.77 %
		Accuracy:	1.40 %	1.40 %	-1.10 %
	Med:		1000 pg/mL	1000 pg/mL	1000 pg/mL
		Precision:	4.62 %	5.61 %	4.47 %
		Accuracy:	-0.50 %	1.80 %	-1.60 %
	High:		4000 pg/mL	4000 pg/mL	4000 pg/mL
		Precision:	4.17 %	5.11 %	4.79 %
		Accuracy:	4.20 %	7.08 %	2.78 %

Pharmacokinetics Analysis:

Day 1 Cmax, Tmax, AUC(0-24) (or AUC0-t), and Cmin were determined using non-compartmental analysis. On Days 4 and 8, predose trough concentrations (i.e., Cmin) and metabolite/parent Cmin ratio were assessed. Data were summarized for all patients with pharmacokinetic data and for those patients who did not receive CYP1A2 inducers or inhibitors. Descriptive statistics (arithmetic mean, SD, median, minimum, maximum, geometric mean, and between-patient coefficient of variation) were calculated for each treatment group.

PK analyses were performed on all patients and on the subgroup who did not use CYP1A2 inducers or inhibitors. However, this preliminary assessment of dose-linearity was based on those patients who did not receive these medications.

RESULTS

Demographics of Subjects:

Demographic and baseline characteristics are summarized in Table 2 below:

	IR tid	CR od				
	0.25mg N=16	1mg N=12	2mg N=12	2mg-ext N=12	2mg-pooled N=24	3mg N=12
Age (yrs)						
Mean (SD)	60.9 (9.2)	62.2 (6.4)	68.3 (8.6)	58.5 (11.3)	63.4 (11.0)	62.8 (12.5)
Range	45-76	52-73	52-80	41-78	41-80	37-78
<65, n (%)	11 (68.8)	8 (66.7)	3 (25.0)	8 (66.7)	11 (45.8)	8 (66.7)
65-75, n (%)	4 (25.0)	4 (33.3)	6 (50.0)	3 (25.0)	9 (37.5)	1 (8.3)
>75, n (%)	1 (6.3)	0	3 (25.0)	1 (8.3)	4 (16.7)	3 (25.0)
Sex n (%)						
Male	10 (62.5)	8 (66.7)	7 (58.3)	5 (41.7)	12 (50.0)	8 (66.7)
Female	6 (37.5)	4 (33.3)	5 (41.7)	7 (58.3)	12 (50.0)	4 (33.3)
Race n (%)						
Caucasian	15 (93.8)	12 (100.0)	12 (100.0)	12 (100.0)	24 (100.0)	11 (91.7)
Black	1 (6.3)	0	0	0	0	0
Hispanic	0	0	0	0	0	1 (8.3)
Height, (cm)						
Mean (SD)	171.8 (9.5)	174.4 (13.2)	171.2 (8.9)	166.5 (9.0)	168.9 (9.0)	173.4 (11.7)
Weight, (kg)						
Mean±SD	78.8 (14.0)	85.1 (18.9)	75.1 (21.0)	82.0 (19.8)	78.6 (20.3)	83.8 (14.3)
BMI, kg/cm^2						
Mean±SD	26.5 (2.7)	27.8 (4.5)	25.3 (5.3)	29.6 (6.8)	27.4 (6.4)	27.8 (3.4)
Disease Duration (yrs)						
Mean (SD)	2.5 (2.3)	2.1 (1.7)	1.6 (1.0)	3.0 (2.3)	2.3 (1.8)	3.7 (1.8)
Range	0.3-7.6	0.3-5.6	0.4-3.1	0.2-6.4	0.2-6.4	0.1-5.7
Hoehn & Yahr n (%)						
Stage 1 to 1.5	9 (56.3)	6 (50.0)	7 (58.3)	4 (33.3)	11 (45.8)	5 (41.7)
Stage 2 to 2.5	6 (37.5)	6 (50.0)	5 (41.7)	8 (66.7)	13 (54.2)	7 (58.3)
Stage 3	1 (6.3)	0	0	0	0	0
Randomised	16 (100)	12 (100)	12 (100)	12 (100)	24 (100)	12 (100)
Completed	16 (100)	12 (100)	12 (100)	12 (100)	24 (100)	11 (91.7)
Withdrawn	0	0	0	0	0	1 (8.3)
AE	0	0	0	0	0	1 (8.3)

Pharmacokinetic Summary:

Only ropinirole PK properties are presented in this section. Mean ropinirole plasma concentration-time profiles by cohort with or without patients on CYP1A2 inhibitors/inducers are presented in Figures 1-2. Pharmacokinetic results and summary of the statistical analysis for dose proportionality based on parent drug levels from patients without using concomitant CYP1A2 inhibitors/inducers is shown in Table 2.

Figure 1. Mean ropinirole plasma concentration-time profiles by cohort

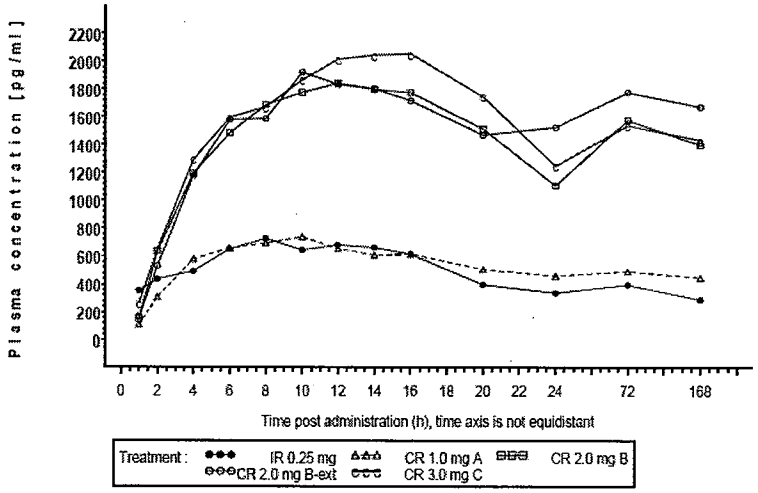


Figure 2. Mean ropinirole plasma concentration-time profiles by cohort without patients on CYP1A2 inhibitors/inducers

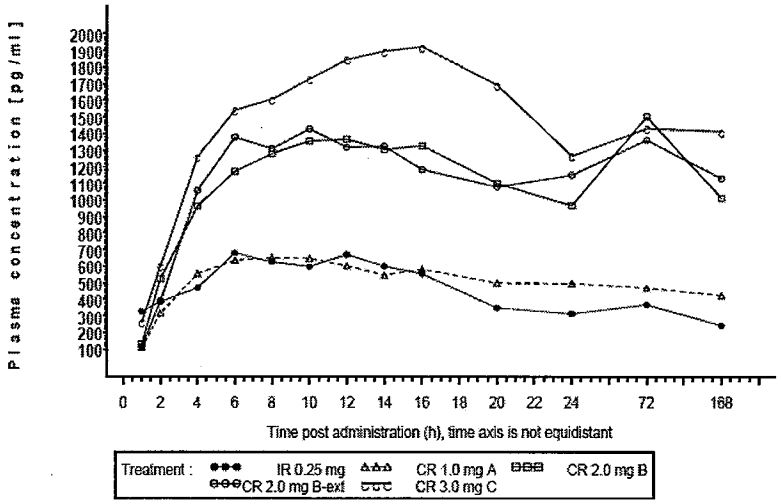


Table 3. Pharmacokinetic results excluding patients who took CYP1A2 inducers or inhibitors as concomitant medications

PK Parameter	IR	CR 1mg	CR 2mg	CR 2mg-extension	CR 2mg-combined	CR 3mg
	N=13	N=9	N=8	N=9	N=17	N=11
Day 1						
C_{max} (ng/mL)	0.746	0.709	1.49	1.39	1.44	1.97
t_{max}, median, hours	10.0	10.0	13.1	6.1	9.7	12.2
$AUC_{0\text{-}24}$ ng*hr/mL	10.2	10.5	23.3	19.9	21.4	31.5
C_{min} (C24) (ng/mL)	0.179	--	0.918	0.792	0.852	0.987
Day 4						
Cmin (ng/mL)	0.276	0.401	1.44	0.897	1.08	1.18
Day 8						
Cmin (ng/mL)	0.167	0.338	0.644	0.794	0.720	1.025

Data are presented as geometric mean values.

Reviewer's note:

- Plasma concentrations of ropinirole rose slowly after oral administration of CR tablets and reached peak levels at approximately 10-12 hours post-dose.
- After approximately 16 hours post-dose, there was an apparent monoexponential decline in ropinirole plasma concentrations.
- Predose Cmin data from Days 2, 4, and 8 suggested rapid attainment of steady state.
- Systemic exposure to ropinirole increased approximately proportionately with increased CR dose over the dose range 1 to 3mg.

- The sponsor reported approximately 2-fold higher SK&F-104557 level than ropinirole level for IR and CR formulations at all dose levels, based on Cmin on Days 4 and 8. For CR formulation, of those patients with quantifiable concentrations of SK&F-89124, the SK&F-89124 level (based on quantifiable levels) was approximately 5-6% of ropinirole level.

Sponsor's Safety Summary:

System Organ Class	IR tid	CR od				
	0.25mg n (%)	1mg n (%)	2mg n (%)	2mg-ext n (%)	2mg-pooled n (%)	3mg n (%)
All Patients	**N=16**	**N=12**	**N=12**	**N=12**	**N=24**	**N=12**
Any AE	14 (87.5)	9 (75.0)	11 (91.7)	8 (66.7)	19 (79.2)	9 (75.0)
Central & peripheral NS	7 (43.8)	2 (16.7)	6 (50.0)	3 (25.0)	9 (37.5)	7 (58.3)
Gastrointestinal System	4 (25.0)	2 (16.7)	4 (33.3)	3 (25.0)	7 (29.2)	5 (41.7)
Cardiovascular General	6 (37.5)	6 (50.0)	7 (58.3)	4 (33.3)	11 (45.8)	3 (25.0)
Body as a whole -general	5 (31.3)	1 (8.3)	2 (16.7)	2 (16.7)	4 (16.7)	2 (16.7)
Psychiatric	1 (6.3)	1 (8.3)	3 (25.0)	0	3 (12.5)	1 (8.3)
Autonomic Nervous System	1 (6.3)	1 (8.3)	2 (16.7)	1 (8.3)	3 (12.5)	1 (8.3)
Dopaminergic use	**N=6**	**N=8**	**N=4**	**N=7**	**N=11**	**N=9**
Any AE	4 (66.7)	7 (87.5)	4 (100)	4 (57.1)	8 (72.7)	6 (66.7)
Central & peripheral NS	2 (33.3)	2 (25.0)	2 (50.0)	2 (28.6)	4 (36.4)	5 (55.6)
Gastrointestinal System	2 (33.3)	2 (25.0)	0	1 (14.3)	1 (9.1)	3 (33.3)
Cardiovascular General	2 (33.3)	4 (50.0)	3 (75.0)	2 (28.6)	5 (45.5)	3 (33.3)
Body as a whole -general	1 (16.7)	1 (12.5)	0	2 (28.6)	2 (18.2)	1 (11.1)
Psychiatric	0	1 (12.5)	1 (25.0)	0	1 (9.1)	0
Autonomic Nervous System	0	1 (12.5)	1 (25.0)	0	1 (9.1)	1 (11.1)
Dopaminergic non-use	**N=10**	**N=4**	**N=8**	**N=5**	**N=13**	**N=3**
Any AE	10 (100)	2 (50.0)	7 (87.5)	4 (80.0)	11 (84.6)	3 (100)
Central & peripheral NS	5 (50.0)	0	4 (50.0)	1 (20.0)	5 (38.5)	2 (66.7)
Gastrointestinal System	2 (20.0)	0	4 (50.0)	2 (40.0)	6 (46.2)	2 (66.7)
Cardiovascular General	4 (40.0)	2 (50.0)	4 (50.0)	2 (40.0)	6 (46.2)	0
Body as a whole -general	4 (40.0)	0	2 (25.0)	0	2 (15.4)	1 (33.3)
Psychiatric	1 (10.0)	0	2(25.0)	0	2 (15.4)	1 (33.3)
Autonomic Nervous System	1 (10.0)	0	1 (12.5)	1 (20.0)	2 (15.4)	0

- Overall, ropinirole CR at the 1 mg, 2 mg and 3 mg doses evaluated and ropinirole IR had a favorable tolerability profile in patients with early-stage Parkinson's disease after 7 days of treatment.

- This study supports the use of starting doses of ropinirole CR of up to 3 mg od

CONCLUSIONS

- The 2 mg dose was chosen as the starting dose for up-titration for future clinical studies, since this dose had a favorable tolerability profile and yielded a simple titration regimen.

- The pharmacokinetics were approximately dose-proportional over the ropinirole CR dose range of 1~3mg.

13 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 3

4.3. Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-008	Brand Name	REQUIP® XL 24 HOURS™
OCP Division (I, II, III)	DCP-1	Generic Name	Ropinirole hydrochloride
Medical Division	HFD-120	Drug Class	Nonergoline dopamine agonist
OCP Reviewer	Ta-Chen Wu, PhD	Indication(s)	Treatment of signs and symptoms of idiopathic Parkinson's Disease (PD)
OCP Team Leader	Ramana Uppoor, PhD	Dosage Form	Extended-Release (CR) Tablets 2mg, 3mg, 4mg, and 8 mg
		Dosing Regimen	• Recommended starting dose is 2 mg QD for 1 [redacted] followed by increments of 2 mg/day [redacted] [redacted] a maximum of 24 mg/day
Date of Submission	02/09/07	Route of Administration	Oral
Estimated Due Date of OCP Review	10/21/07	Sponsor	GlaxoSmithKline
PDUFA Due Date	12/09/07	Priority Classification	S
Division Due Date	11/07/07		

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Clin. Pharm. and Biopharm. Information

Summary: The sponsor is seeking approval of a new extended-release formulation of REQUIP® (ropinirole hydrochloride) XL 24 HOURS™ for the treatment of signs and symptoms of idiopathic Parkinson's Disease (PD) at both early and advanced stages. The reference product, REQUIP™ (IR) Tablets, was originally approved in 1996, under NDA 20-658, as monotherapy in early state PD and as adjunctive therapy to L-dopa in advanced state PD. According to the Sponsor, the simplified titration regimen with once daily dosing is expected to improve compliance, whereas patients already on IR tablets can switch overnight to the nearest equivalent dose of CR tablets taken with or without food (Appendix 1). Ropinirole CR tablets consist of 3-layer core in which the central, active-containing, slow-release layer is sandwiched between two [redacted] inactive barrier layers. The TBM formulations of different strengths are compositionally proportional (Appendix 2). b(4)

The clinical development program was designed to assess the efficacy and safety of ropinirole CR in PD patients. Ropinirole CR has been evaluated in 6 clinical pharmacology studies and 8 clinical trials (including four Phase 1, five Phase 2, and four Phase 3 studies, and an additional Phase 2 study in Fibromyalgia patients) (Appendix 3). Biopharmaceutics program focused on relative bioavailability, food effects, dose-proportionality and dosage strength equivalence. Clinical pharmacology program focused on single- and multiple-dose PK and sources of inter-subject variability based on population PK analysis on data from Phase 3 efficacy studies (168 and 169).

Phase 1 studies:

- Study 161: optimal CR formulation selection (A, B, and C; prototype 0.75 mg) for further development, effect of high-fat food, and drug interaction potential with domperidone, in healthy subjects
- Study 162: compared single dose PK of CR tablets (0.75mg and 3 mg) vs. IR 0.25mg tid, dose proportionality, in healthy subjects
- Study 163: compared single vs. multiple dose PK (1 mg ropinirole CR; 1 day vs. 7 days) in healthy subjects
- Study 219: dose strength equivalence and dose proportionality (CR 1x1mg, 2x1mg, 1x2mg, 3x1mg, 1x3mg) in healthy subjects

Phase 2 studies:

- Study 164: compared relative bioavailability of CR tablet (highest 8 mg strength) vs. IR tablet at steady-state in PD patients, food effect
- Study 165: investigated dose-proportionality (2-8 mg CR tablets) and dosage strength equivalence (2 x 4 mg CR tablet vs. 1 x 8 mg CR tablet TBM formulations at steady-state) in PD patients
- Study 166: to determine the maximum well-tolerated starting dose in PD patients, IR 0.25 mg tid vs. CR 1, 2, 3, mg/day
- Study 167: to determine the optimum initial dose titration regimen in PD patients, IR 0.25, 0.5, 0.75, 1 mg tid vs. CR 2, 3, 4, 6, mg/day and CR 2, 4, 6, 8 mg/day
- Study 196: long-term continuation study from Studies 167 and 164 for long-term safety in PD patients (ongoing)

Phase 3 studies:

- Study 169: pivotal placebo-controlled study (adjunctive therapy with L-dopa), CR 2-24 mg/day
  Primary efficacy endpoint: mean change from baseline in awake time "off" at Week 24 LOCF
- Study 168: controlled active-comparator study (monotherapy), CR 2-24 mg/day vs. IR 0.25-8 mg tid
- Study 228: controlled active-comparator study (adjunctive therapy with L-dopa 50-1000mg/day), CR 2-24 mg/day
- Study 248: open-label extension study in subjects from Studies 165, 168, and 169 (ongoing)

Exposure-response relationship was also evaluated (Study 168). Clinical efficacy was primarily demonstrated in pivotal Phase 3 confirmatory efficacy Study 169 (superiority to placebo), supported by results from Phase 3 Study 168 (non-inferiority to IR). Switching from IR to CR tablets was primarily supported by results of Studies 164 and 168. Long-term safety data are provided by ongoing Studies 196 and 248. A combined PK/PD assessment of ropinirole concentrations vs. QT measurement from Studies 168 and 169 and Fibromyalgia study ROF102100 was also included.

In vitro dissolution testing was conducted in 3 media of different pH values (0.1M HCl, and pH 6.8, and 7.5 citrate buffers) on prototypes, early clinical formulation (round, uncoated), and late clinical formulation (TBM, capsule-shape, film-coated), across the range of tablet strengths. Additional testing was conducted with 2mg and 8mg strengths in Simulated Gastric Fluid or SGF containing 24% (v/v) ethanol for potential dose dumping effect. An in-vitro/in-vivo correlation (IVIVC) model was developed based on data from the proposed dissolution test in pH 4 citrate buffer (USP II paddles at 100 rpm; same medium for Requip IR) and single-dose PK studies (161, 162, and 164).

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	*X*			
Tabular Listing of All Human Studies	*X*			
HPK Summary	*X*			
Labeling	*X*			Non-annotated Word and annotated PDF files provided
Reference Bioanalytical and Analytical Methods	X			Validation report provided
I. Clinical Pharmacology	-	-	-	
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		Studies 161, 162, 163, 219: - up to 3 mg/day (due to dopaminergic side effect)
multiple dose:	X	1		Studies 163 - fed, CR 1.0 mg (7 days)
Patients-				
single dose:	X	1	-	Study 166 (determine maximum tolerated starting dose - CR 1, 2, 3 mg vs. IR 0.25 mg tid active control
multiple dose:	X	3	-	Study 164: - Part A: fed, relative BA of IR vs. CR (up-titrated to 8 mg) - Part B: food effect, 8 mg CR Study 165: - dose proportionality (2, 4, 6, 8 mg) - dose strength equivalence (CR 1 x 8 mg vs. 4 mg x 2) Study 167 (determine CR titration regimen) - Regimen A (2, 3, 4, 6 mg) - Regimen B (2, 4, 6, 8 mg) vs. reference IR (0.25, 0.5, 0.75, 1.0 mg tid)
Dose proportionality -				
fasting / non-fasting single dose:	X	2	-	Studies 162 (fed), 219 (fed)
fasting / non-fasting multiple dose:	X	1	-	Study 165 (fed)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	*X*	1	-	Study 161 (effect of domperidone on 0.75-mg CR tablet)
In-vivo effects of primary drug:				
In-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	-	-	-	Pop PK (Phase 3 efficacy trials)

gender:	-	-	-	Pop PK (Phase 3 efficacy trials)
pediatrics:	-	-	-	Request for waiver of pediatric studies
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	X	2	-	Study 167 (preliminary efficacy) Study 196 (uncontrolled, ongoing long-term extension to Studies 164 & 167, interim report)
Phase 3:	X	3 (controlled, safety, efficacy & PK data) + 1 (uncontrolled, safety data)		Controlled trials: 1. Study 168 - efficacy, safety & PK, 2-24 mg/day CR vs. IR, non-inferiority, monotherapty) - primary endpoint: mean absolute change from baseline in UPDRS 2. Study 169 - efficacy, safety & PK, 2-24 mg/day CR vs. placebo, adjunct therapy with L-Dopa) - Primary endpoint: mean absolute change from baseline in awake time "off" at week 24 3. Study 228 - efficacy, ongoing, 2-24 mg/day CR vs. Sinemet 50-1000 mg, onset of motor complications (no report) Uncontrolled trials: 1. Study 248 - safety, ongoing long-term extension to Studies 165, 168, 169 (no report)
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2	-	Studies 168 & 169
Population Analyses -				
Data rich:	-	-	-	(Studies 164 & 165 for model building)
Data sparse:	X			Study 168/169 (including exploratory QT assessment)
II. Biopharmaceutics			-	
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	X	-	-	Study 162: - dose proportionality (0.75, 3 mg) - CR 0.75mg, 3mg vs. IR 0.25 mg tid (IR as Reference)
Bioequivalence studies -				

traditional design; single / multi dose:	X	3	-	Study 165: - dose proportionality (2, 4, 6, 8 mg) - dose strength equivalence (CR 1 x 8 mg vs. 4 mg x 2) Study 219: - dose proportionality and dose strength equivalence (1mg, 2 x 1mg, 2mg, 3 x 1mg, 3mg)
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	X	2		Study 161: - on prototype Tablet C) Study 164: - Part B, on highest 8 mg strength)
Dissolution:	X			Only raw data provided for formulations used in Studies 161, 162 and 164 (8 mg strength) for IVIVC purpose
(IVIVC):	X	1	-	Study HM2005/00124/00: - using dissolution and PK data from Studies 161, 162 and 164 - Internal validation (Study 161); external validation (Studies 162 and 164)
Bio-waiver request based on BCS	-	-	-	
BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X	70		
Total Number of Studies	X	14	12	
Filability and QBR comments				

	"X" if yes	*Comments*
Application filable ?	*X*	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward the following comments to the Sponsor: 1. Please provide all the PK and in-vitro dissolution data used for establishing IVIVC in SAS .XPT files.
QBR questions (key issues to be considered)	• Proper selection of starting dose and titration regimen • Dose proportionality and relative BA between CR and IR to facilitate the switching • from IR to CR dosing, as well as concern for therapeutic equivalence • Any safety concern for the switching, as well as adequate PK/PD assessment for • effect on QT • Sources of inter-subject variability based on population PK analysis on Phase 3 data • Food effect on BA of CR formulations • Linkage of [redacted] CR-RLS formulations to the clinical formulations • BE of various strengths of the TBM formulations • Adequately and appropriately validated bioanalytical methods • IVIVC results substantiated by the data? • Adequate characterization of the in vitro dissolution • Adequate evaluation for potential dose-dumping for CR-RLS formulation as a result of interaction with alcohol	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

b(4)

CC: NDA 22-008, HFD-850(Electronic Entry or Lee), HFD-120(Daugherty), HFD-860 (R. Uppoor, M. Mehta

Appendix 1. Conversion from Ropinirole IR Tablets to CR Tablets

	Recommended switch (total daily dose,mg)							
Ropinirole IR	0.75-2.25	3-4.5	6	7.5-9	12	15-18	21	24
Ropinirole CR	2	4	6	8	12	16	20	24

Appendix 2. Quantitative Composition for Proposed Strengths

Component	Quantity (mg/tablet)						Function	Reference to Standard
	Upper Barrier Layer[1]	Active Layer 2 mg	Active Layer 3 mg	Active Layer 4 mg	Active Layer 8 mg	Lower Barrier Layer[1]		
Tablet Core								
Ropinirole HCl[2]	-	2.28	3.42	4.56	9.12	-	Active	GSK[3]
Hypromellose ;								USP
Lactose Monohydrate								USNF
Glyceryl Behenate								USNF
Mannitol								USP
Carboxymethylcellulose Sodium								USP
Hydrogenated Castor Oil								USNF
Povidone								USP
Maltodextrin								USNF
Magnesium Stearate								USNF
Colloidal Silicon Dioxide								USNF
Ferric Oxide (Yellow)								USNF
								USP
Total Layer weight								
Total Tablet Core Weight								

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Component	Quantity (mg/tablet)						Function	Reference to Standard
	Upper Barrier Layer	Active Layer 2 mg	Active Layer 3 mg	Active Layer 4 mg	Active Layer 8 mg	Lower Barrier Layer		
Film Coat								
								USP
Total Tablet Weight								

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Appendix 2. Tabular Listing of All Clinical Studies

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
SK&F-101468/168	Primary: demonstrate non-inferiority of ropinirole XL 24-hour to IR. Secondary: evaluate the safety profile, assess the PK of ropinirole XL 24-hour, support dose switching from ropinirole IR to XL 24-HOUR, investigate the superiority of ropinirole XL 24-hour	DB, AC, XO, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or ropinirole IR 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0mg three times daily; oral; 36 weeks.	161	Complete
SK&F-101468/169	Primary: evaluate the efficacy of ropinirole XL 24-hour as adjunctive therapy to L-Dopa Secondary: evaluate the safety profile of ropinirole XL 24-hour , assess the PK of ropinirole XL 24-hour	DB, PLC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or placebo; oral; 24 weeks.	393	Complete
SK&F-101468/165	Dose proportionality and dose strength equivalence	O, R, DR, XO	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0mg (both 1x 8mg and 2 x 4mg) once daily for one week; Oral; 5 weeks.	28	Complete
SK&F-101468/219	Dose strength equivalence and dose proportionality	O, R, XO	Healthy subjects	Ropinirole XL 24-hour 1.0mg, 2x 1.0mg, 2.0mg, 3 x 1.0mg and 3mg single dose; oral; 1 days treatment in each of the five treatment periods.	35	Complete
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
SK&F-101468/166	To identify the maximum well-tolerated starting dose of ropinirole XL 24-hour. To compare the tolerability of once daily doses of ropinirole XL 24-hour with three times daily doses of 0.25mg ropinirole IR. To assess the PK profile of ropinirole XL 24-hour.	DB, AC, R, DR	Parkinson's disease patients	Ropinirole IR 0.25mg three times daily compared with Ropinirole XL 24-hour 1.0, 2.0 or 3.0mg once daily in sequential cohorts; oral; 1 week.	64	Complete
SK&F-101468/167	Primary: To compare the safety and tolerability of two titration regimens of ropinirole XL 24-hour using the standard titration regimen of ropinirole IR as a reference. Secondary: Preliminary assessment of efficacy for the XL 24-HOUR arms.	DB, AC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 3.0, 4.0, 6.0mg once daily (Titration Regimen A) or ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0mg once daily (Titration regimen B) or ropinirole IR 0.25, 0.5, 0.75, 1.0mg three times daily (standard titration regimen of ropinirole IR) during the first four weeks of treatment; oral; 4 weeks.	75	Complete

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
SK&F-101468/168	Primary: demonstrate non-inferiority of ropinirole XL 24-hour to IR. Secondary: evaluate the safety profile, assess the PK of ropinirole XL 24-hour, support dose switching from ropinirole IR to XL 24-HOUR, investigate the superiority of ropinirole XL 24-hour	DB, AC, XO, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or ropinirole IR 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0mg three times daily; oral; 36 weeks.	161	Complete
SK&F-101468/169	Primary: evaluate the efficacy of ropinirole XL 24-hour as adjunctive therapy to L-Dopa Secondary: evaluate the safety profile of ropinirole XL 24-hour , assess the PK of ropinirole XL 24-hour	DB, PLC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or placebo; oral; 24 weeks.	393	Complete
SK&F-101468/228	Primary: To evaluate the time to onset of dyskinesia with ropinirole XL 24-hour compared with Sinemet in patients already being treated with levodopa. Secondary: To evaluate the efficacy of ropinirole XL 24-hour compared to Sinemet on (a) symptomatic control of PD and (b) non-motor symptoms of PD.	DB, AC,R	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or Sinemet total daily doses of 50, 100, 150, 200, 400, 600, 800, 1000mg; oral; 2 years.	208	Complete
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
SK&F-101468/196	To obtain long-term exposure information on subjects with Parkinson's disease receiving ropinirole XL 24-hour.	O	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily; oral; 5 years currently (flexible).	83	Interim
SK&F-101468/248	Primary: To evaluate the safety profile of ropinirole XL 24-hour during long term treatment in patients with early and advanced Parkinson's disease. Secondary: To collect patient preference data regarding od versus tid study medication.	O	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily; oral; 3 years currently (flexible).	412	None

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
Efficacy and Safety Studies: Other Study Reports						
ROF102100	Primary: To evaluate the analgesic efficacy of oral ropinirole XL 24-hour compared to placebo over a dose range in adult subjects with fibromyalgia. Secondary: Assessment of safety and tolerability. Additional evaluations of analgesic efficacy. PK of ropinirole and exploration of relationship between systemic exposure and clinical outcome.	DB. PLC, R	Patients with Fibromyalgia syndrome (FMS) as diagnosed by ACR (American College of Rheumatology) criteria.	Ropinirole XL 24-hour 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg or matching placebo once daily; oral;12 weeks.	181	Complete

OL = Open label
DB = Double-blind
DD = Double dummy
UC = Uncontrolled

XO = Crossover
PG = Parallel Group
PC = Placebo-controlled
AC = Active control
NR = Non-randomized
SB = Singl-blind

R = Randomized
RD = Rising Dose
IV = intravenous
CPSR = Clinical Pharmacology Study Report

PGx = pharmacogenetics

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

/s/

Ta-Chen Wu
11/14/2007 02:36:24 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
11/14/2007 02:46:39 PM
BIOPHARMACEUTICS
Dr.Mehul Mehta has verbally concurred with the phase 4 commitment in this review (note that this is the same request that was already included in the Requip CR (RLS) NDA review also). Since he is out of town for next 2 wks, I am signing off this review.

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-008**	**Brand Name**	**REQUIP® XL 24 HOURS™**
OCP Division (I, II, III)	**DCP-1**	**Generic Name**	**Ropinirole hydrochloride**
Medical Division	**HFD-120**	**Drug Class**	**Nonergoline dopamine agonist**
OCP Reviewer	**Ta-Chen Wu, PhD**	**Indication(s)**	**Treatment of signs and symptoms of idiopathic Parkinson's Disease (PD)**
OCP Team Leader	**Ramana Uppoor, PhD**	**Dosage Form**	**Extended-Release (CR) Tablets 2mg, 3mg, 4mg, and 8 mg**
		Dosing Regimen	**• Recommended starting dose is 2 mg QD for 1 [redacted] followed by increments of 2 mg/day [redacted] • [redacted] up to a maximum of 24 mg/day**
Date of Submission	**02/09/07**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**10/21/07**	**Sponsor**	**GlaxoSmithKline**
PDUFA Due Date	**12/09/07**	**Priority Classification**	**S**
Division Due Date	**11/07/07**		

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On Original

Clin. Pharm. and Biopharm. Information

Summary: The sponsor is seeking approval of a new extended-release formulation of REQUIP® (ropinirole hydrochloride) XL 24 HOURS™ for the treatment of signs and symptoms of idiopathic Parkinson's Disease (PD) at both early and advanced stages. The reference product, REQUIP™ (IR) Tablets, was originally approved in 1996, under NDA 20-658, as monotherapy in early state PD and as adjunctive therapy to L-dopa in advanced state PD. According to the Sponsor, the simplified titration regimen with once daily dosing is expected to improve compliance, whereas patients already on IR tablets can switch overnight to the nearest equivalent dose of CR tablets taken with or without food (Appendix 1). Ropinirole CR tablets consist of 3-layer core in which the central, active-containing, slow-release layer is sandwiched between two [redacted] inactive barrier layers. The TBM formulations of different strengths are compositionally proportional (Appendix 2).

The clinical development program was designed to assess the efficacy and safety of ropinirole CR in PD patients. Ropinirole CR has been evaluated in 6 clinical pharmacology studies and 8 clinical trials (including four Phase 1, five Phase 2, and four Phase 3 studies, and an additional Phase 2 study in Fibromyalgia patients) (Appendix 3). Biopharmaceutics program focused on relative bioavailability, food effects, dose-proportionality and dosage strength equivalence. Clinical pharmacology program focused on single- and multiple-dose PK and sources of inter-subject variability based on population PK analysis on data from Phase 3 efficacy studies (168 and 169).

Phase 1 studies:

Study 161: optimal CR formulation selection (A, B, and C; prototype 0.75 mg) for further development, effect of high-fat food, and drug interaction potential with domperidone, in healthy subjects

Study 162: compared single dose PK of CR tablets (0.75mg and 3 mg) vs. IR 0.25mg tid, dose proportionality, in healthy subjects

Study 163: compared single vs. multiple dose PK (1 mg ropinirole CR; 1 day vs. 7 days) in healthy subjects

Study 219: dose strength equivalence and dose proportionality (CR 1x1mg, 2x1mg, 1x2mg, 3x1mg, 1x3mg) in healthy subjects

Phase 2 studies:

Study 164: compared relative bioavailability of CR tablet (highest 8 mg strength) vs. IR tablet at steady-state in PD patients, food effect

Study 165: investigated dose-proportionality (2-8 mg CR tablets) and dosage strength equivalence (2 x 4 mg CR tablet vs. 1 x 8 mg CR tablet TBM formulations at steady-state) in PD patients

Study 166: to determine the maximum well-tolerated starting dose in PD patients, IR 0.25 mg tid vs. CR 1, 2, 3, mg/day

Study 167: to determine the optimum initial dose titration regimen in PD patients, IR 0.25, 0.5, 0.75, 1 mg tid vs. CR 2, 3, 4, 6, mg/day and CR 2, 4, 6, 8 mg/day

Study 196: long-term continuation study from Studies 167 and 164 for long-term safety in PD patients (ongoing)

Phase 3 studies:

Study 169: pivotal placebo-controlled study (adjunctive therapy with L-dopa), CR 2-24 mg/day

Primary efficacy endpoint: mean change from baseline in awake time "off" at Week 24 LOCF

Study 168: controlled active-comparator study (monotherapy), CR 2-24 mg/day vs. IR 0.25-8 mg tid

Study 228: controlled active-comparator study (adjunctive therapy with L-dopa 50-1000mg/day), CR 2-24 mg/day

Study 248: open-label extension study in subjects from Studies 165, 168, and 169 (ongoing)

Exposure-response relationship was also evaluated (Study 168). Clinical efficacy was primarily demonstrated in pivotal Phase 3 confirmatory efficacy Study 169 (superiority to placebo), supported by results from Phase 3 Study 168 (non-inferiority to IR). Switching from IR to CR tablets was primarily supported by results of Studies 164 and 168. Long-term safety data are provided by ongoing Studies 196 and 248. A combined PK/PD assessment of ropinirole concentrations vs. QT measurement from Studies 168 and 169 and Fibromyalgia study ROF102100 was also included.

In vitro dissolution testing was conducted in 3 media of different pH values (0.1M HCl, and pH 6.8, and 7.5 citrate buffers) on prototypes, early clinical formulation (round, uncoated), and late clinical formulation (TBM, capsule-shape, film-coated), across the range of tablet strengths. Additional testing was conducted with 2mg and 8mg strengths in Simulated Gastric Fluid or SGF containing 24% (v/v) ethanol for potential dose dumping effect. An in-vitro/in-vivo correlation (IVIVC) model was developed based on data from the proposed dissolution test in pH 4 citrate buffer (USP II paddles at 100 rpm; same medium for Requip IR) and single-dose PK studies (161, 162, and 164).

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Non-annotated Word and annotated PDF files provided
Reference Bioanalytical and Analytical Methods	X			Validation report provided
I. Clinical Pharmacology	-	-	-	
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		Studies 161, 162, 163, 219: - up to 3 mg/day (due to dopaminergic side effect)
multiple dose:	X	1		Studies 163 - fed, CR 1.0 mg (7 days)
Patients-				
single dose:	X	1	-	Study 166 (determine maximum tolerated starting dose - CR 1, 2, 3 mg vs. IR 0.25 mg tid active control
multiple dose:	X	3	-	Study 164: - Part A: fed, relative BA of IR vs. CR (up-titrated to 8 mg) - Part B: food effect, 8 mg CR Study 165: - dose proportionality (2, 4, 6, 8 mg) - dose strength equivalence (CR 1 x 8 mg vs. 4 mg x 2) Study 167 (determine CR titration regimen) - Regimen A (2, 3, 4, 6 mg) - Regimen B (2, 4, 6, 8 mg) vs. reference IR (0.25, 0.5, 0.75, 1.0 mg tid)
Dose proportionality -				
fasting / non-fasting single dose:	X	2	-	Studies 162 (fed), 219 (fed)
fasting / non-fasting multiple dose:	X	1	-	Study 165 (fed)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	-	Study 161 (effect of domperidone on 0.75-mg CR tablet)
In-vivo effects of primary drug:				
In-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	-	-	-	Pop PK (Phase 3 efficacy trials)
gender:	-	-	-	Pop PK (Phase 3 efficacy trials)

pediatrics:	-	-	-	Request for waiver of pediatric studies
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	X	2	-	Study 167 (preliminary efficacy) Study 196 (uncontrolled, ongoing long-term extension to Studies 164 & 167, interim report)
Phase 3:	X	3 (controlled, safety, efficacy & PK data) + 1 (uncontrolled, safety data)		Controlled trials: 1. Study 168 - efficacy, safety & PK, 2-24 mg/day CR vs. IR, non-inferiority, monotherapy) - primary endpoint: mean absolute change from baseline in UPDRS 2. Study 169 - efficacy, safety & PK, 2-24 mg/day CR vs. placebo, adjunct therapy with L-Dopa) - Primary endpoint: mean absolute change from baseline in awake time "off" at week 24 3. Study 228 - efficacy, ongoing, 2-24 mg/day CR vs. Sinemet 50-1000 mg, onset of motor complications (no report) Uncontrolled trials: 1. Study 248 - safety, ongoing long-term extension to Studies 165, 168, 169 (no report)
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2	-	Studies 168 & 169
Population Analyses -				
Data rich:	-	-	-	(Studies 164 & 165 for model building)
Data sparse:	X			Study 168/169 (including exploratory QT assessment)
II. Biopharmaceutics			-	
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	X	-	-	Study 162: - dose proportionality (0.75, 3 mg) - CR 0.75mg, 3mg vs. IR 0.25 mg tid (IR as Reference)
Bioequivalence studies -				

traditional design; single / multi dose:	X	3	-	Study 165: - dose proportionality (2, 4, 6, 8 mg) - dose strength equivalence (CR 1 x 8 mg vs. 4 mg x 2) Study 219: - dose proportionality and dose strength equivalence (1mg, 2 x 1mg, 2mg, 3 x 1mg, 3mg)
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	X	2		Study 161: - on prototype Tablet C) Study 164: - Part B, on highest 8 mg strength)
Dissolution:	X			Only raw data provided for formulations used in Studies 161, 162 and 164 (8 mg strength) for IVIVC purpose
(IVIVC):	X	1	-	Study HM2005/00124/00: - using dissolution and PK data from Studies 161, 162 and 164 - Internal validation (Study 161); external validation (Studies 162 and 164)
Bio-waiver request based on BCS	-	-	-	
BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X	70		
Total Number of Studies	X	14		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward the following comments to the Sponsor: 1. Please provide all the PK and in-vitro dissolution data used for establishing IVIVC in SAS .XPT files.		
QBR questions (key issues to be considered)	• Proper selection of starting dose and titration regimen • Dose proportionality and relative BA between CR and IR to facilitate the switching • from IR to CR dosing, as well as concern for therapeutic equivalence • Any safety concern for the switching, as well as adequate PK/PD assessment for • effect on QT • Sources of inter-subject variability based on population PK analysis on Phase 3 data • Food effect on BA of CR formulations • Linkage of TBM XL formulations to the clinical formulations • BE of various strengths of the TBM formulations • Adequately and appropriately validated bioanalytical methods • IVIVC results substantiated by the data? • Adequate characterization of the in vitro dissolution • Adequate evaluation for potential dose-dumping for XL formulation as a result of interaction with alcohol			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22-008, HFD-850(Electronic Entry or Lee), HFD-120(Daugherty), HFD-860 (R. Uppoor, M. Mehta)

Appendix 1. Conversion from Ropinirole IR Tablets to CR Tablets

	Recommended switch (total daily dose,mg)							
Ropinirole IR	0.75-2.25	3-4.5	6	7.5-9	12	15-18	21	24
Ropinirole CR	2	4	6	8	12	16	20	24

Appendix 2. Quantitative Composition for Proposed Strengths

Component	Quantity (mg/tablet)						Function	Reference to Standard
	Upper Barrier Layer[1]	Active Layer				Lower Barrier Layer[1]		
		2 mg	3 mg	4 mg	8 mg			
Tablet Core								
Ropinirole HCl[2]	-	2.28	3.42	4.56	9.12	-	Active	GSK[3]
Hypromellose								USP
Lactose Monohydrate								USNF
Glyceryl Behenate								USNF
Mannitol								USP
Carboxymethylcellulose Sodium								USP
Hydrogenated Castor Oil								USNF
Povidone								USP
Maltodextrin								USNF
Magnesium Stearate								USNF
Colloidal Silicon Dioxide								USNF
Ferric Oxide (Yellow)								USNF
								USP
Total Layer weight								
Total Tablet Core Weight								

b(4)

Component	Quantity (mg/tablet)						Function	Reference to Standard
	Upper Barrier Layer	Active Layer				Lower Barrier Layer		
		2 mg	3 mg	4 mg	8 mg			
Film Coat								
								USP

b(4)

Appendix 2. Tabular Listing of All Clinical Studies

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
SK&F-101468/168	Primary: demonstrate non-inferiority of ropinirole XL 24-hour to IR. Secondary: evaluate the safety profile, assess the PK of ropinirole XL 24-hour, support dose switching from ropinirole IR to XL 24-HOUR, investigate the superiority of ropinirole XL 24-hour	DB, AC, XO, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or ropinirole IR 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0mg three times daily; oral; 36 weeks.	161	Complete
SK&F-101468/169	Primary: evaluate the efficacy of ropinirole XL 24-hour as adjunctive therapy to L-Dopa Secondary: evaluate the safety profile of ropinirole XL 24-hour , assess the PK of ropinirole XL 24-hour	DB, PLC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or placebo; oral; 24 weeks.	393	Complete
SK&F-101468/165	Dose proportionality and dose strength equivalence	O, R, DR, XO	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0mg (both 1x 8mg and 2 x 4mg) once daily for one week; Oral; 5 weeks.	28	Complete
SK&F-101468/219	Dose strength equivalence and dose proportionality	O, R, XO	Healthy subjects	Ropinirole XL 24-hour 1.0mg, 2x 1.0mg, 2.0mg, 3 x 1.0mg and 3mg single dose; oral; 1 days treatment in each of the five treatment periods.	35	Complete
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
SK&F-101468/166	To identify the maximum well-tolerated starting dose of ropinirole XL 24-hour. To compare the tolerability of once daily doses of ropinirole XL 24-hour with three times daily doses of 0.25mg ropinirole IR. To assess the PK profile of ropinirole XL 24-hour.	DB, AC, R, DR	Parkinson's disease patients	Ropinirole IR 0.25mg three times daily compared with Ropinirole XL 24-hour 1.0, 2.0 or 3.0mg once daily in sequential cohorts; oral; 1 week.	64	Complete
SK&F-101468/167	Primary: To compare the safety and tolerability of two titration regimens of ropinirole XL 24-hour using the standard titration regimen of ropinirole IR as a reference. Secondary: Preliminary assessment of efficacy for the XL 24-HOUR arms.	DB, AC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 3.0, 4.0, 6.0mg once daily (Titration Regimen A) or ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0mg once daily (Titration regimen B) or ropinirole IR 0.25, 0.5, 0.75, 1.0mg three times daily (standard titration regimen of ropinirole IR) during the first four weeks of treatment; oral; 4 weeks.	75	Complete

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
SK&F-101468/168	Primary: demonstrate non-inferiority of ropinirole XL 24-hour to IR. Secondary: evaluate the safety profile, assess the PK of ropinirole XL 24-hour, support dose switching from ropinirole IR to XL 24-HOUR, investigate the superiority of ropinirole XL 24-hour	DB, AC, XO, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or ropinirole IR 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0mg three times daily; oral; 36 weeks.	161	Complete
SK&F-101468/169	Primary: evaluate the efficacy of ropinirole XL 24-hour as adjunctive therapy to L-Dopa Secondary: evaluate the safety profile of ropinirole XL 24-hour , assess the PK of ropinirole XL 24-hour	DB, PLC, R	Parkinson's disease patients	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or placebo; oral; 24 weeks.	393	Complete
SK&F-101468/228	Primary: To evaluate the time to onset of dyskinesia with ropinirole XL 24-hour compared with Sinemet in patients already being treated with levodopa. Secondary: To evaluate the efficacy of ropinirole XL 24-hour compared to Sinemet on (a) symptomatic control of PD and (b) non-motor symptoms of PD.	DB, AC,R	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily or Sinemet total daily doses of 50, 100, 150, 200, 400, 600, 800, 1000mg; oral; 2 years.	208	Complete
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
SK&F-101469/196	To obtain long-term exposure information on subjects with Parkinson's disease receiving ropinirole XL 24-hour.	O	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily; oral; 5 years currently (flexible).	83	Interim
SK&F-101469/248	Primary: To evaluate the safety profile of ropinirole XL 24-hour during long term treatment in patients with early and advanced Parkinson's disease. Secondary: To collect patient preference data regarding od versus tid study medication.	O	Parkinson's disease patients.	Ropinirole XL 24-hour 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg once daily; oral; 3 years currently (flexible).	412	None

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report
Efficacy and Safety Studies: Other Study Reports						
ROF102100	Primary: To evaluate the analgesic efficacy of oral ropinirole XL 24-hour compared to placebo over a dose range in adult subjects with fibromyalgia. Secondary: Assessment of safety and tolerability. Additional evaluations of analgesic efficacy. PK of ropinirole and exploration of relationship between systemic exposure and clinical outcome.	DB. PLC, R	Patients with Fibromyalgia syndrome (FMS) as diagnosed by ACR (American College of Rheumatology) criteria.	Ropinirole XL 24-hour 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0, 24.0mg or matching placebo once daily; oral;12 weeks.	181	Complete

OL = Open label
DB = Double-blind
DD = Double dummy
UC = Uncontrolled

XO = Crossover
PG = Parallel Group
PC = Placebo-controlled
AC = Active control
NR = Non-randomized
SB = Singl-blind

R = Randomized
RD = Rising Dose
IV = intravenous
CPSR = Clinical Pharmacology Study Report

PGx = pharmacogenetics

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/s/

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