CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

BLA:	22-008
Brand Name:	Requip XL
Generic Name:	Ropinirole
Sponsor:	GlaxoSmithKline
Type of Dosage Form:	Extended-Release Oral Tablets
Strengths:	2 mg, 3 mg, 4 mg, and 8 mg
Indications:	Treatment of Signs and Symptoms of Idiopathic Parkinson's Disease
OCP Reviewer:	Ta-Chen Wu, Ph.D.
OCP Team Leader:	Ramana S. Uppoor, Ph.D.
OCP Division:	DCP-1 HFD-860
OND Division:	Division of Neurology Drug Products HFD-120
Submission Date:	December 17, 2007, January 30, 2008, February 13, 2008, April 11, 2008 May 22, 2008 (E-Mail)
Type of Submission:	Complete Response to AE Letter

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1. EXECUTIVE SUMMARY

1.1. BACKGROUND

Requip® (Ropinirole hydrochloride) Tablets (immediate release or IR), were originally approved in 1997 in the U.S. ——— and NDA 20-658) in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg strengths for the treatment of idiopathic Parkinson's disease (PD) up to doses of 24 mg/day (8 mg tid). On 09 February 2007 the Sponsor submitted NDA 22-008 seeking approval for Requip (ropinirole hydrochloride) XL 24-Hour controlled-release formulations of 2 mg, 3 mg, 4 mg, and 8 mg strengths for the treatment of signs and symptoms of idiopathic Parkinson's disease (PD). The proposed extended release tablet formulations have an approximately 24 hours of release profile and are for allowing once-daily dosing. The new XL formulation is claimed to provide a better tolerability (due to slower absorption) and a longer duration of action compared to the approved IR formulation, and will allow the switching from IR Tablet to the XL formulation.

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In response to the Agency's AE Letter dated 7 December 2007, the Sponsor submitted series of responses to the Agency's comments and recommendations. As stated, the Sponsor has accepted the majority of the labeling recommendations. The Sponsor also provided an outline of the study proposals to address the Agency's request for a Phase 4 commitment to conduct a study to characterize the dose-response of ropinirole in patients with Parkinson's disease. The sponsor proposes to conduct the study in patients with advanced Parkinson's disease, with Requip XL as adjunctive treatment to L-dopa.

Comments with regard to clinical pharmacology deficiencies and recommendation for a Phase IV comment by the Office of Clinical Pharmacology were conveyed to the Sponsor via e-mail on 28 January 2008, as outlined below. The Sponsor has not provided responses to the OCP comments and recommendation in the current submissions for further review and comment.

Clinical Pharmacology Deficiency:

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

Phase IV Commitment:

The Sponsor should commit to the following recommendations and submit results to the Agency within 1 year from the date of approval:

- The Sponsor should evaluate whether ropinirole is a P-gp substrate and/or inducer for major CYP enzymes (e.g., CYP3A4) and, if so, any drug-drug interaction

potential through either mechanism. This can be accomplished through comprehensive literature or in vitro study as a Phase IV commitment.

In addition, the Sponsor submitted a new study report for a recently completed study (Study ROP109087) evaluating a 12-mg dosage strength of REQUIP XL. The Sponsor proposed to revise the labeling languages which describe an effect of food on the pharmacokinetics of ropinirole based on results of this study [redacted] b(4)

[redacted] Results of Study 164 indicated that food increased Cmax by an average 15% and prolonged time to Cmax by an average 2 hours, while having no impact on AUC of ropinirole. In the original NDA, results of another single-dose study of REQUIP XL 0.75mg in healthy volunteers (Study 161) showed a higher exposure of ropinirole (30% increase in AUC and 44% increase in Cmax) in the fed state, compared to fasted state.

To further support the revised labeling languages with regard to food effects on extent of absorption of ropinirole from REQUIP XL and unchanged Dosage and Administration information, the Sponsor re-examined the study (Study 164) [redacted] conducted additional analyses for individual plasma concentration-time profile of Study 164, Study 161, and Study ROP109087, as well as supporting formulation information and dissolution profiles for REQUIP XL 0.75, 8, and 12 mg. [redacted] b(4)

Study ROP109087 also evaluated the dose proportionality of the ropinirole XL tablet over the therapeutic dose range 4-12 mg and dosage strength equivalence between 3 x 4 mg and 1 x 12 mg.

1.2. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

1.2.1. Sponsor's Response to the Clinical Pharmacology Deficiency:

The Sponsor has not provided responses to the OCP comments on the clinical pharmacology deficiency and a Phase IV recommendation in the current submissions for further review and comment. The clinical pharmacology deficiency pertains to IVIVC. Since the Sponsor is not requesting a biowaiver based on the IVIVC at this time, this should not hold up the approval of Requip XL.

1.2.2. Results of Study ROP109087:

Study 109087:

This was an open, non-randomized sequential design, followed by a 3-period, randomized, crossover design and was conducted in 28 Parkinson's disease subjects. Objectives of the study was to demonstrate dose proportionality of ropinirole XL over the dose range 4-12 mg, to determine the food effect on the absorption of the highest 12-mg tablet strength, and to determine dosage strength equivalence for 1 x 12 mg tablet compared to 3 x 4 mg tablets at steady state. Subjects received study drug once daily starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8 and 12 mg dose levels administered). The 12 mg dose level included three dosing regimens: (1) 1 x 12 mg tablet for 3 days including steady state PK profile (fasted), (2) 1 x 12 mg tablet for 3 days including steady state PK profile (FDA "high fat" breakfast) and 3 x 4 mg for 3 days including steady state PK profile (fasted). Blood samples for PK evaluation of ropinirole, and its metabolites (SKF-104557 and SKF-89124) were collected at predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, an 24 hours postdose. Potential food effects and dosage strength equivalence were evaluated based on 90% confidence interval (CI) for the log-transformed exposure parameters. Dose proportionality was evaluated using Power Model.

Effects of food:

The food effect was evaluated at steady-state with the ——— 12-mg PR/CR ——— in Parkinson's disease patients. Results are shown in the Figure and Table below. High-fat food appears to have significant effects on AUC(0-24) and Cmax of ropinirole based on point estimates and the 90% CIs for both parameters. AUC(0-24) and Cmax were 20% and 44%, respectively, on average higher when 1 x 12 mg PR/CR formulation was administered under fed conditions, compared to fasted conditions. For AUC(0-24), the lower end of the 90% CI was greater than unity and higher end of 90% CI exceeded upper BE limit (0.80 - 1.25). For Cmax, both lower and upper ends of the 90% CI exceeded upper BE limit. Cmin or trough was similar under fasted or fed, as indicated by ratio and the 90% CI being within the BE limits. The absorption of ropinirole at 1 x 12 mg PR/CR appeared to be prolonged, as reflected by median prolonged Tmax by 3 hours (based on median of average differences).

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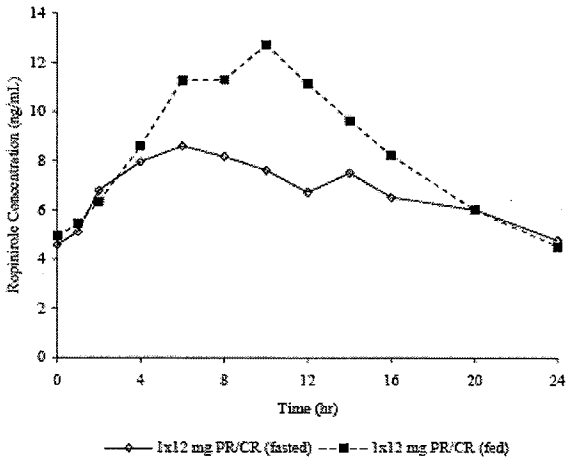


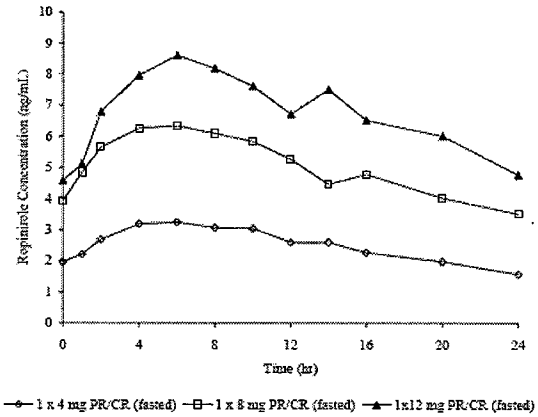
Parameter	Geometric LS Mean		Ratio	90% CI
	1 x 12 mg PR/CR (Fed)	1 x 12 mg PR/CR (Fasted)	Fed: Fasted	
AUC(0-24) (hr·ng/mL)	196.59	163.85	1.20	(1.12, 1.28)
Cmax (ng/mL)	13.03	9.02	1.44	(1.34, 1.56)
Cmin (ng/mL)	4.54	4.72	0.96	(0.86, 1.08)
Tmax[a] (hr)	10.00	4.02	3.01	(2.00, 4.01)

Comment:

- From a clinical pharmacology and biopharmaceutics perspective, there appears to be a more significant food effects with regard to AUC0-24 and Cmax on ropinirole absorption from 12-mg PR/CR formulation when compared to that observed for the lower strengths and as stated in the labeling in AE Letter.

Dose Proportionality:

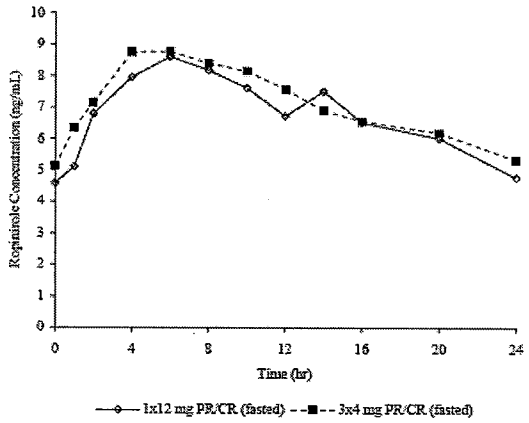
The dose proportionality over the dose range of 4-12 mg ropinirole PR/CR formulation at steady-state was demonstrated in patients with Parkinson's disease, The plasma ropinirole concentrations or exposure increased approximately dose-proportionately following administration of PR/CR 4 mg, 8 mg, and 1 x 12 mg in the fasted state, as shown in the Figure and Table below. The estimated slopes obtained from the power models for AUC(0-24), Cmax, and Cmin were close to unity, indicating the dose proportionality and linearity for ropinirole over the PR/CR dose range 4 to 12 mg at steady state. Results are consistent with the population PK analysis findings for Phase 3 clinical studies showing linear PK property without dose-dependent change in CL/F over the dose range of 2-24mg.



Parameter	Slope	Stand error	CVw%	90% CI
AUC(0-24) (ng·h/mL)	0.970	0.0455	18.06	(0.978, 1.095)
Cmax (ng/mL)	0.905	0.0415	16.45	(0.950, 1.068)
Cmin (ng/mL)	0.986	0.0639	25.61	(0.878, 1.126)

Dosage Strength Equivalence:

Dosage strength equivalence was demonstrated for 1 x 12 mg PR/CR ropinirole tablet and the 3 x 4 mg PR/CR ropinirole tablets at steady-state, under fasted conditions, in patients with Parkinson's disease, based on BE range of 80-125%, as shown in Figure and Table below.



Parameter	Geometric LS Mean		Ratio	90% CI
	1 x 12 m g PR/CR (Test)	3 x 4 m g PR/CR (Ref)	Test: Ref	
AUC(0-24) (hr·ng/mL)	163.85	173.18	0.95	(0.98, 1.01)
Cmax (ng/mL)	9.02	9.56	0.94	(0.88, 1.02)
Cmin (ng/mL)	4.72	5.07	0.93	(0.83, 1.04)
Tmax[a] (hr)	4.02	6.00		

1.2.3. Formulation and Dissolution Profiles:

Requip XL 0.75, 8 and 12mg tablets have been evaluated in Studies161, 164 and ROP109087, respectively, for food effects. The active layer for all tablet strengths is

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The composition of the upper and lower barrier layers of the tablets are identical and differ only in terms of weight. The composition of these strengths are shown in Table below.

Tablets Strength (mg)	0.75			8			12		
Component	Quantity (mg/ tablet)								
	Upper Barrier Layer	Active layer	Lower Barrier Layer	Upper Barrier Layer	Active layer	Lower Barrier Layer	Upper Barrier Layer	Active layer	Lower Barrier Layer
Tablet Core									
Ropinirole HCl	-	0.86[1]	-	-	9.12[1]	-	-	13.68[1]	-
Hypromellose									
Lactose Monohydrate									
Glyceryl behenate									
Mannitol									
Carboxymethylcellulose Sodium									
Hydrogenated Castor Oil									
Povidone									
Maltodextrin									
Magnesium Stearate									
Colloidal Silicon Dioxide									
Ferric Oxide (Yellow)									

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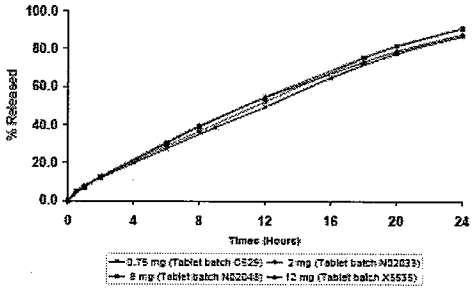
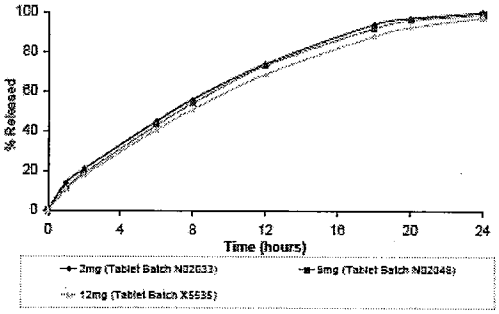
In-Vitro Dissolution Profiles:

The drug release profiles of various dosage strengths in different media are provided by the Sponsor to demonstrate the similar dissolution profile, independent of tablet strength.

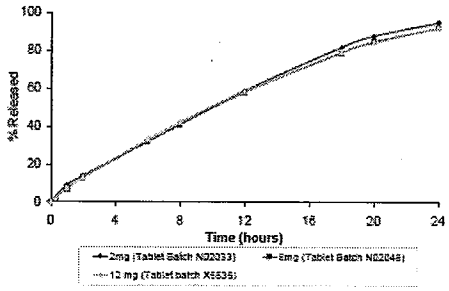
Dissolution of REQUIP XL Tablets 0.75, 2, 8 and 12mg in pH 4.0 Citrate Buffer



Dissolution of REQUIP XL Tablets 2, 8 and 12mg Simulated Gastric media



Dissolution of REQUIP XL Tablets 2, 8 and 12mg in pH 7.5 Citrate Buffer



1.2.4. Re-Analysis of Results of Food Effects:

Results of the Sponsor's re-examination for results of food effects and concentration-time profiles in Studies 164, 161, and ROP109087, to support the newly proposed labeling languages and an unchanged Dosage and Administration section are presented below.

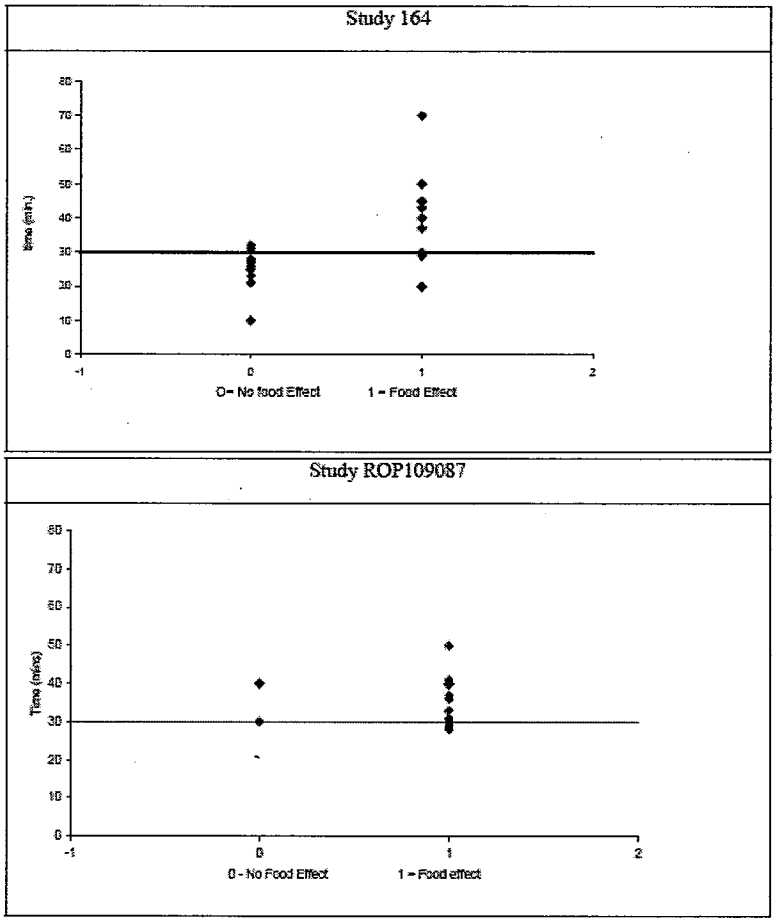
I. Comparison of the statistical results of food effects on absorption of ropinirole in Study 161, Study 164 and Study ROP109087:

	Study 161	Study 164	ROP 109087
Population	Volunteers	Patients	Patients
Dose	0.75 mg	8 mg	12 mg
Regimen	Single Dose	Steady-State	Steady State
Effect of Food on Cmax	1.44 (1.24, 1.68)	1.15 (1.01, 1.31),	1.44 (1.34, 1.56)
Effect of Food on AUC	1.30 (1.06, 1.60)	1.06 (0.95, 1.19)	1,20 (1.12, 1.28)
Effect of Food of Tmax	Not Analysed	2.00 (-0.02, 4.00)	3.01 (2.00, 4.01)

- Similar subject demographics between the studies and similar PK profiles between healthy subjects and patients are noted.

II. Dosing times and individual concentration-time profiles:

Dosing time of the study drug related to initiation of meal was reported as factor that had varied impact on ropinirole exposure observed in these studies. In fed state of Study 164, majority of patients who had an increase in ropinirole exposure took their dose greater than 30 minutes after initiating their meal whereas the majority of patients whose ropinirole exposure remained unchanged took their dose less than 30 minutes after initiating their meal. In fed state of study ROP109087, patients generally took their dose at around or greater than 30 minutes after initiation of their food. In fed state of Study 161, all subjects took their dose at 30 minutes after initiation of their food. The graphs below show the impact of dosing time relative to initiation of meal on ropinirole systemic exposure.



Results of statistical analysis for ropinirole PK parameters following 8 mg doses in Study 164, stratified by dosing time, are provided in the Tables below.

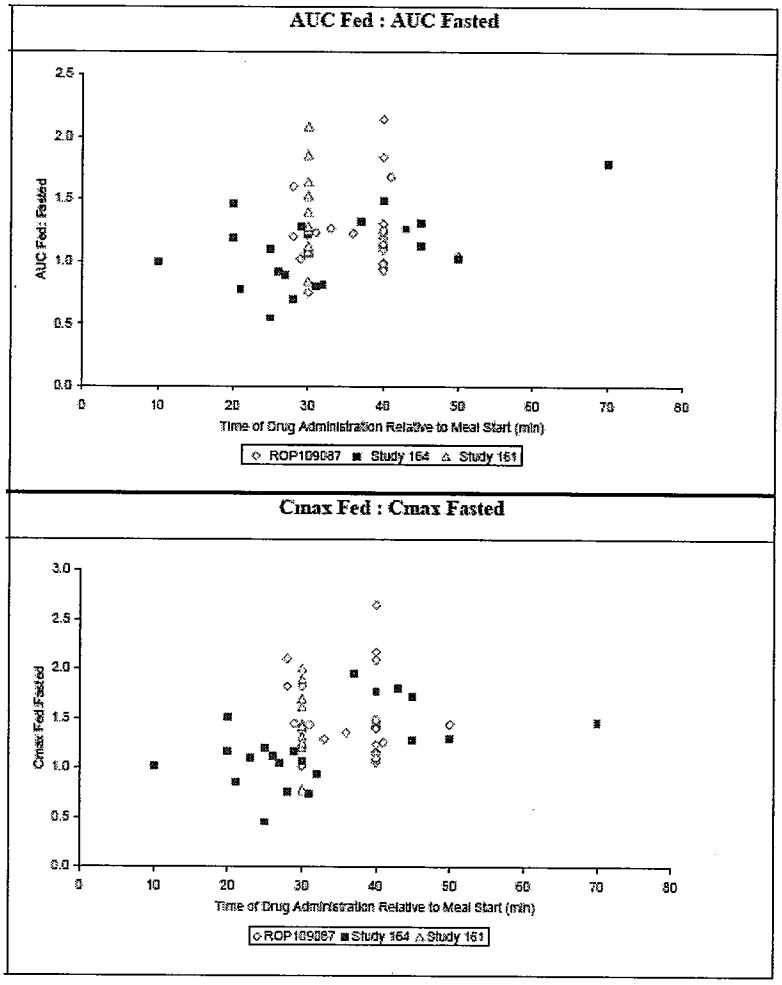
Original Analysis (Study 164)			
PK Parameter	n	Ratio	90% CI
AUC(0-24) (ng·h/mL)	20	1.06	(0.95, 1.19)
Cmax (ng/mL)	21	1.15	(1.01, 1.31)
Cmin (ng/mL)	21	0.96	(0.85, 1.08)

Analysis < 30 minutes of Initiation of Meal			
PK Parameter	n	Ratio	90% CI
AUC(0-24) (ng·h/mL)	10	0.95	(0.79, 1.14)
Cmax (ng/mL)	11	1.00	(0.83, 1.20)
Cmin (ng/mL)	11	0.99	(0.81, 1.22)

Analysis ≥ 30 minutes of Initiation of Meal			
PK Parameter	n	Ratio	90% CI
AUC(0-24) (ng·h/mL)	10	1.18	(1.03, 1.36)
Cmax (ng/mL)	10	1.35	(1.13, 1.61)
Cmin (ng/mL)	10	0.92	(0.77, 1.10)

- There was an approximately 35% increase in Cmax and18% increase in AUC after taking Requip XL ≥ 30 minutes (30~70 minutes) of initiation of meal vs. the fasted state, more in line with the results from Study 161 and Study ROP109087.
- There was an insignificant food effect after taking Requip XL within 30 minutes of initiation of meal vs. fasted state.
- These results indicate that an increase in systemic exposure is more likely with food when Requip XL is taken ≥ 30 minutes after initiation of the meal.

The Sponsor also reported higher fed-to-fasted ratios for Cmax and AUC for the majority of subjects who were dosed ≥ 30 minutes after initiation of their meal, as shown in graphs below.



The Sponsor reported no evidence for an increased incidence in adverse events (AEs) associated with the greater food effects on ropinirole exposure observed in Study 161 and Study ROP109087, compared with the fasted state. Summary of AEs by treatment in these studies, as provided by the Sponsor, is presented in the Table below.

Adverse Event (MedRA Preferred Term)	No (%) of Patient Sessions where AE was reported					
	Study 161		Study 164		ROP109087	
	REQUIP XL 0.75 mg fasted (n=14)	REQUIP XL 0.75 mg fed (n=13)	REQUIP XL 8 mg fasted (n = 21)	REQUIP XL 8 mg fed (n = 21)	REQUIP XL 12 mg fasted (n=25)	REQUIP XL 12 mg fed (n=25)
No of patients (%) with any AE	4 (28.6%)	2 (15.4%)	3 (14.3%)	4 (19.0%)	11 (44%)	4 (16%)
Dizziness	-	-	-	1 (4.8%)	3 (12%)	2 (8%)
Nausea	-	-	-	-	2 (8%)	-
Somnolence	-	-	-	-	1 (4%)	-
Headache	2 (14.3%)	1 (7.7%)	-	-	2 (8%)	1 (4%)
Insomnia	-	-	1 (4.8%)	-	-	-
Abdominal pain upper	-	-	-	-	1 (4%)	-
Abdominal pain	-	-	-	-	-	1 (4%)
Sinusitis	-	-	1 (4.8%)	1 (4.8%)	-	-
Constipation	-	-	-	-	1 (4%)	-
Dyspepsia	-	-	-	-	1 (4%)	-
Myocardial infarction	-	-	-	1 (4.8%)	-	-
Edema peripheral	-	-	-	1 (4.8%)	-	-
Throat irritation	-	-	-	1 (4.8%)	-	-
Skin neoplasm excision	-	-	1 (4.8%)	-	-	-
Diarrhea	2 (14.3%)	-	-	-	1 (4%)	-
Flatulance	2 (14.3%)	1 (7.7%)	-	-	-	-
Convulsion	-	-	-	-	1 (4%)	-
Tremor	-	-	-	-	1 (4%)	-
Influenza	-	-	-	-	1 (4%)	-
Nasal congestion	-	-	-	-	-	1 (4%)
Dermatitis contact	-	-	-	-	1 (4%)	1 (4%)

Reviewer comment:
While the analyses based on exact timing of food intake is suggestive, it is a post-hoc analysis and cannot be considered conclusive. The argument is quite weak. The more inconsistent dosing time related to initiation of meal in Study 164 may have attributed to greater variability in observed food effects. However, given the similarity in formulation and dissolution profiles of the 3 strengths, the BE established between 12 mg and lower strengths, and a small but consistent and significant food effect seen in all 3 studies, the food effect observed for 12 mg strength should be similar to that for lower strengths and results from these studies should be described in the PK section of label.

Sponsor's conclusion:

- The food effects observed in Study ROP109087 and Study 161 is more likely to be applicable to all tablet strengths.

- Results from Study ROP109087 and Study 161 describe the greatest magnitude of food effects observed with REQUIP XL and should be applicable to chronic dosing at steady-state. Therefore, the pertinent information should be included in the label.

- In view of no evidence for an increased incidence in AEs compared to the fasted state in these 3 studies and that the dosing in two Phase 3 studies was administered without regard to food, the labeling information in Dosage and Administration section should remain unchanged.

1.3. RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the sponsor's responses to the AE Letter dated 7 December 2007, as well as the study report for food effect. Since the Sponsor has not provided responses to the OCP comments on the clinical pharmacology deficiency and a Phase IV recommendation (as restated below) in the current submissions, no review is performed and no pertinent comment or recommendation is made at this point.

A clear food effect on systemic exposure of ropinirole from Requip XL was observed. The Sponsor's rationale for the revised labeling language pertaining to effect of food and an unchanged Dosage and Administration section, based on newly obtained results and re-examination of the PK data, appear reasonable and are acceptable from a clinical pharmacology and biopharmaceutics point of view, provided the Sponsor accepts our suggested label changes.

Phase IV Commitment:
The Sponsor should commit to the following recommendations and submit results to the Agency within 1 year from the date of approval:

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

Ta-Chen Wu, Ph.D.
Reviewer, Neurology Drug Products, DCP-1, OCP

Concurrence: Ramana S. Uppoor, Ph.D.
Deputy Director and Team Leader
Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 NDA 22-008
CSO/S.B. Daugherty
/TL Clin Pharm/R. Uppoor
HFD-860 /DD DCP-1/M. Mehta

2. LABELING RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the current proposed labeling and finds it generally acceptable from a clinical pharmacology and biopharmaceutics perspective. The Sponsor has accepted the changes recommended by the Office of Clinical Pharmacology for the proposed labeling for Requip® XL tablet for Parkinson's disease, as seen in the AE Letter. Information pertaining to food effect languages from Study 161 with 0.75 mg strength was added by the Sponsor in the revised labeling, as seen in Section 2.1., as provided to the Agency via E-mail on May 22, 2008. We recommend that the labeling languages which describe an effect of food based on results of Study ROP109087 be included in the label. The underlined text is the proposed change to the label language and the ~~strikethrough~~ is recommendation for deletion from the perspective of OCP.

2.1. Proposed Package Insert

24 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 7

2.2. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

Note: The "PR/CR" in individual study review section, as denoted in the current submission by the sponsor, is referred to the "XL" for the proposed indication.

Study ROP109087

An open label, repeat dose, dose escalation study conducted in Parkinson's disease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/CR) 12 mg tablets

Study Period: 16 April 2007 – 29 August 2007
Principal Investigators and Study Centers:

Investigator	Investigator/ Site/ Centre Number.	Hospital/ Institution and Address

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Objectives:
Primary:

- To demonstrate dose proportionality for ropinirole using an extended release (PR/CR) formulation of ropinirole over the dose range 4-12 mg
- To determine the effect of food administered as a high fat breakfast on the absorption of ropinirole PR/CR at 12 mg (highest tablet strength)
- To determine dosage strength equivalence for ropinirole PR/CR administered as 1 x 12 mg tablet compared with 3 x 4 mg tablets

Secondary:

- To further confirm the safety and tolerability of ropinirole PR/CR over a dose range of 2-12 mg

PR/CR formulations:
2mg (batch no. 051082675/X1550), 4mg (batch no. 051082675/X4159), 8mg (batch no. 051107497/X1793), 12mg (batch no. 061117912/X5535)

Study Design:
This study consisted of an open, non-randomized sequential design, followed by a 3-period, randomized, crossover design and was conducted in 36 male and female PD patients, 30-85 years of age, inclusive. Subjects (28 enrolled) received ropinirole PR/CR once daily (OD) starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8 and then 12 mg). The 12 mg/day dose level incorporated three dosing regimens; 1 x 12 mg tablet for three days including steady state PK profile (fasted), 1 x 12 mg tablet for three days including steady state PK profile (high fat fed) and 3 x 4 mg for three days including steady state PK profile (fasted). PK was also assessed for 4 mg and 8 mg dose level during dose escalation. Subjects were dosed once daily with ropinirole PR/CR in

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

Once subjects were titrated to 12 mg, they remained at this dose for the remainder of the study. At the 12 mg dose, subjects were randomized to one of 3 treatments with one of 6 sequences (EFG, EGF, FEG, FGE, GEF, GFE). Treatment assignment and sequence are shown in Tables below.

A:	2 mg PR/CR
B:	4 mg PR/CR
C:	6 mg PR/CR (1x4 mg PR/CR + 1x2 mg PR/CR)
D:	8 mg PR/CR
E:	1 x 12 mg PR/CR (fasted)
F:	1 x 12 mg PR/CR (high fat fed)
G:	3 x 4 mg PR/CR (fasted)

Dose Level	**Dosing Days**	**PR/CR Dose (mg)**	**PK Assessments**
1	1 - 7	2	-
2	8 - 14	4	Any day between Days 12-14, 4 mg steady state (fasted) (Treatment B)
3	15 - 21	6	-
4	22 - 28	8	Any day between Days 26-28, 8 mg steady state (fasted) (Treatment D)
5	29 - 37	12	Assessments on Days 31, 34 and 37. Randomized, 12 mg steady state: (i) Ropinirole PR/CR 1 x 12 mg tablet (fasted) (E) (ii) Ropinirole PR/CR 1 x 12 mg tablet (fed : standard high fat FDA breakfast) (F) (iii)Ropinirole PR/CR 3 x 4 mg tablets (fasted) (G)
	38-44	Down-titration	-

PR/CR Daily Dose (mg) at the end of the treatment phase	**Down Titration Schedule**	
	4 Days	3 Days
2	Not applicable	Not applicable
4	2	Not applicable
6	4	2
8	6	4
12	8	4

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

Pharmacokinetics Assessments:

Blood samples for PK evaluation of ropinirole, and its metabolites (SKF-104557 and SKF-89124) were collected at predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours postdose.

Plasma samples were stored at approximately -20°C until assayed at GlaxoSmithKline in Upper Merion, PA, US, using a validated HPLC-MS/MS method for the plasma concentrations of ropinirole and its metabolites (SK&F-104557 and SK&F-89124). The validated HPLC-MS/MS method was previous reviewed as part of ———— and found acceptable. The lower limit of quantification (LLQ) for SKF-101468 and SKF-89124 of 20 pg/mL and 50 pg/mL for SKF-104557, using a 500 µL aliquot of human plasma. Linearity was demonstrated up to the higher limit of quantification (HLQ) of 5000 pg/mL. Quality Control samples (QC), prepared at 4 to 5 different analyte concentrations. The Inter-day and intra-day accuracy and precision were <15%. b(4)

Pharmacokinetic Analyses:
The following pharmacokinetic parameters for ropinirole were estimated by non-compartmental methods: Steady-state dose-normalized AUC(0-24), Cmax, Tmax, Cmin (average of predose and 24-hour concentration)

Effect of food: 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 XL strength. Tmax was analyzed using the Wilcoxon Matched Pairs method to calculate the median difference between the fed and fasted regimens and 90% CI.

Dose proportionality: Dose proportionality of ropinirole was assessed by fitting the loge-transformed parameters AUC (0-24) and Cmax for ropinirole PR/CR 1 x 4 mg, 1 x 8 mg, and 1 x 12 mg under fasted conditions to the Power Model:

parameter = e^a $(dose)^b$

i.e., log(parameter) = a + (b * log(dose))

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

Dose proportionality was demonstrated if the 90% CI of the estimated mean slope of AUC (0-24) and Cmax were completely contained within the range 0.797~1.203. Cmin was analyzed using similar methods to the primary endpoints (AUC (0-24) and Cmax).

Dosage strength equivalence: Point estimates and corresponding 90% CIs were estimated for the ratio 1 x 12 mg fasted : 3 x 4 mg fasted for AUC(0-24) and Cmax. Cmin was analyzed using similar methods to the primary endpoints (AUC (0-24) and Cmax).

RESULTS

Demographics of Subjects: (Table 1)

Number of Subjects	Total
Number of subjects planned, N	36
Number of subjects randomised, N	28
Number of subjects included in the Safety population, n (%)	28 (100)
Number of subjects included in the PK population, n (%)	27 (96)
Number of subjects completed as planned, n (%)	25 (89)
Number of subjects withdrawn (any reason), n (%):	3 (11)
Reasons for subject withdrawal	
Adverse Event, n (%):	1 (4)
Other –n (%)	2 (7)
Demographics	
Age in years, Mean (SD; Range)	64.5 (8.56; 47-81)
Sex, n (%)	
Female:	14 (50)
Male:	14 (50)
BMI, Mean (SD; Range)	25.53 (3.326; 20 – 32)
Weight (kg), Mean (SD; Range)	73.4 (13.20; 54 – 96)
Height (cm), Mean (SD; Range)	169.3 (10.31; 145 – 186)
Race, n(%)	
White – White/Caucasian/European Heritage	27 (96)
White – Arabic/North Africa	1 (4)
Ethnicity, n(%)	0
Hispanic or Latino	0
Not Hispanic or Latino	28 (100)

Subjects #101, 104, and 106 withdrew from the study. PK samples of Subjects #101 and 104 were collected on Day 12-14 of 4 mg, so all subjects were included in PK analysis, except Subject #106 who had no PK data.

Pharmacokinetic Summary:

The representative mean plasma concentration-time profiles of ropinirole following Treatment B (4 mg), D (8 mg), and E (1 x 12 mg) of ropinirole PR/CP formulation under fasted conditions are shown in the Figure 1 below. PK profiles of both metabolites are not shown in this review, but they support the conclusions made in this review.

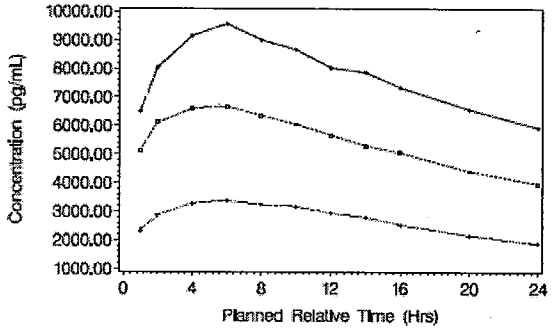


Table 2. Summary of ropinirole pharmacokinetic parameters by regimen

Regimen (Ropinirole PR/CR)	Ropinirole PK Parameter				
	N	AUC(0-24) (ng·hr/mL)	Cmax (ng/mL)	Tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg (fasted)	27	57.1 (59.3)	3.36 (48.9)	6.00 (2.03–14.00)	1.64 (71.5)
1 x 8mg (fasted)	25	118 (46.8)	6.63 (44.6)	4.03 (2.00–10.00)	3.58 (58.1)
1 x 12mg (fasted)	25	164 (52.3)	9.06 (48.5)	4.02 (2.00–16.00)	4.74 (64.5)
1 x 12mg (fed)	25	197 (51.6)	13.1 (49.7)	10.00 (4.00–12.00)	4.57 (81.2)
3 x 4mg (fasted)	25	173 (53.8)	9.57 (52.4)	6.00 (2.00–14.00)	5.07 (60.9)

a. Median(range)

Effect of Food:

Plasma concentration-time profiles of ropinirole for dosing regimen used to assess the food effects, PK parameters, and the statistical summary are shown in Figure 2 and Tables 3.

Figure 2. Median ropinirole plasma concentrations-time profiles following administration of 1 x 12 mg ropinirole PR/CR with (F) or without food (E)

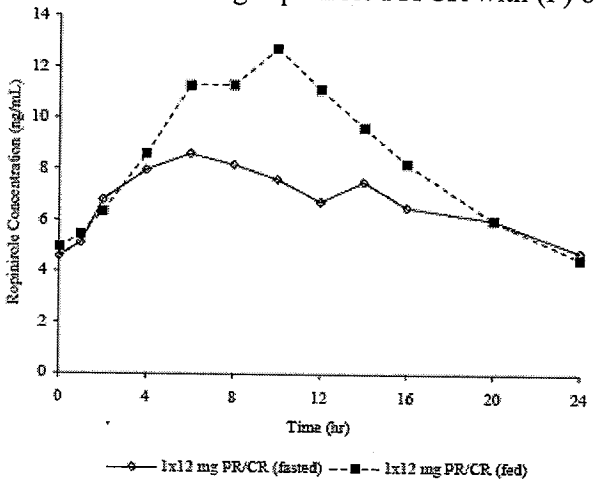


Table 3. Summary of ropinirole pharmacokinetic parameters and the statistical analysis for ropinirole for effect of food

Parameter	Geometric LS Mean		Ratio	90% CI	CVw%
	1 x 12 mg PR/CR (Fed)	1 x 12 mg PR/CR (Fasted)	Fed: Fasted		
AUC(0-24) (hr·ng/mL)	196.59	163.85	1.20	(1.12, 1.28)	14.08
Cmax (ng/mL)	13.03	9.02	1.44	(1.34, 1.56)	15.85
Cmin (ng/mL)	4.54	4.72	0.96	(0.86, 1.08)	24.51
Tmax[a] (hr)	10.00	4.02	3.01	(2.00, 4.01)	-

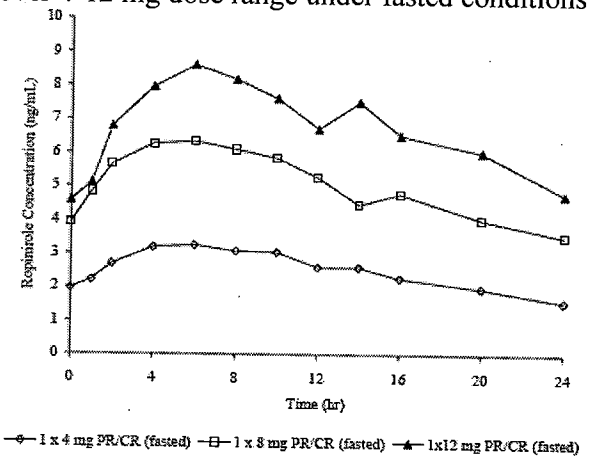
a. Median(range)

Reviewer's note:

- AUC(0-24) and Cmax were 20% and 44%, respectively, on average higher when 1 x 12 mg PR/CR formulation was administered under fed conditions.
- For AUC(0-24), the lower end of the 90% CI was greater than unity and higher end of 90% CI exceeded upper BE limit. For Cmax, both lower and upper ends of the 90% CI exceeded upper BE limit.
- Cmin was similar under fasted or fed, as indicated by ratio and the 90% CI being within the BE limits (0.80 - 1.25).
- The absorption of ropinirole PR/CR at 1 x 12 mg appeared to be prolonged, as reflected by median prolonged Tmax by approximately 3 hours as reported by the sponsor based on median of average differences. The sponsor attributed the delay in Tmax and the fast rate of rise in plasma concentration to the delay in gastric empting.

Dose Proportionality:

Figure 2. Median ropinirole plasma concentration-time profiles for Treatments B, D, E over 4-12 mg dose range under fasted conditions



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

Parameter	Slope	Stand error	CVw%	90% CI
AUC(0-24) (ng·h/mL)	0.970	0.0455	18.06	(0.978, 1.095)
Cmax (ng/mL)	0.905	0.0415	16.45	(0.950, 1.068)
Cmin (ng/mL)	0.986	0.0639	25.61	(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 of 4-12 mg.
- The 90% CIs of the mean slopes for AUC(0-24), Cmax, and Cmin were contained within the sponsor's predefined limits of (0.797, 1.203). Therefore, dose proportionality for ropinirole AUC(0-24), Cmax, and Cmin from PR/CR formulations could be concluded.

Dosage strength equivalence:

Plasma concentration-time profiles of ropinirole for dosing regimens used to assess the dosage strength equivalence of 1 x 12 mg and 3 x 4 mg, both under fasted conditions, are shown in Figure 3. A summary of the statistical summary for the assessment is shown in Tables 5.

Figure 3. Median ropinirole plasma concentrations-time profiles for Treatments E (1 x 12 mg, fasted) and G (3 x 4 mg, fasted)

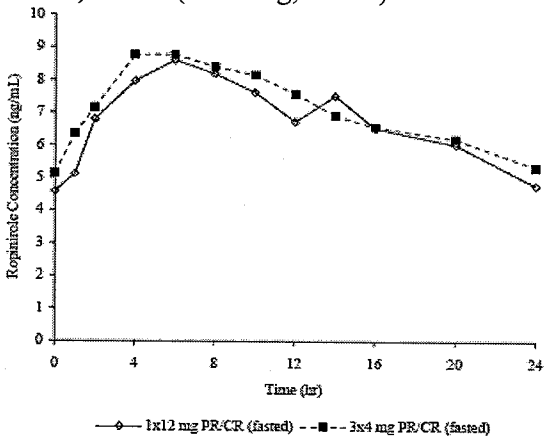


Table 5. Summary of the statistical summary

Parameter	Geometric LS Mean		Ratio	90% CI
	1 x 12 m g PR/CR (Test)	3 x 4 m g PR/CR (Ref)	Test: Ref	
AUC(0-24) (hr·ng/mL)	163.85	173.18	0.95	(0.98, 1.01)
Cmax (ng/mL)	9.02	9.56	0.94	(0.88, 1.02)
Cmin (ng/mL)	4.72	5.07	0.93	(0.83, 1.04)
Tmax[a] (hr)	4.02	6.00		

a. Median(range)

Reviewer's note:

- The ratios of exposure parameters, AUC(0-24), Cmax, and Cmin for 1 x 12 mg QD vs. 3 x 4 mg QD ropinirole PR/CR, were similar, being close to unity and with 90% CIs within the BE limits (0.80 - 1.25).

- The mean difference of Tmax is not statistically significant.

Sponsor's Safety Conclusion:

The sponsor reports that the 12 mg tablet fed was associated with higher plasma exposure but with a lower incidence of AEs (16% of subjects reporting an AE) compared to 12 mg fasted (44%) and 3 x 4 mg fasted (36%). The dosing regimen was reasonably well tolerated by PD subjects. The AEs were mostly mild to moderate in intensity. Three subjects experienced a total of 5 AEs which were of severe intensity (2x nausea, 1x abdominal pain upper; 1x syncope; 1x diarrhoea). The most frequently reported adverse events were headache, nausea and dizziness. No death and no unexpected or unknown AE occurred in this study.

CONCLUSION:

- There was a clear food effect from the OCP perspective. Under fed conditions ropinirole AUC(0-24) and Cmax were on average 20% and 44% higher, respectively and Tmax was delayed by approximately 3 hours compared to the fasted state.

- The pharmacokinetics of ropinirole were dose proportional over the dose range 4 to 12 mg PR/CR.

- Dosage strength equivalence was demonstrated for 1 x 12 mg PR/CR ropinirole tablet and the 3 x 4 mg PR/CR ropinirole tablets.

Reviewer's comments:

- As have commented previously for the food effect study in original NDA, 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 food effect was studied in this study at steady-state of the highest 12-mg/day dose level, instead of on a single 12-mg dose. The study design is considered acceptable in view of the tolerability reasons and the up-titration dosing regimen.

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/s/

Ta-Chen Wu
5/30/2008 03:04:24 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/30/2008 03:13:43 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY
REVIEW

NDA:	22-008
Brand Name:	Requip XL™ 24-Hour
Generic Name:	Ropinirole
Sponsor:	GlaxoSmithKline
Type of Dosage Form:	Extended-Release Oral Tablets
Strengths:	2 mg, 3 mg, 4 mg, and 8 mg
Indications:	Treatment of Signs and Symptoms of Idiopathic Parkinson's Disease
OCP Reviewer:	Ta-Chen Wu, Ph.D.
OCP Team Leader:	Ramana S. Uppoor, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
OCP Division:	DCP-1 HFD-860
OND Division:	Division of Neurology Drug Products HFD-120
Submission Date:	February 09, 2007 March 09, 2007 March 22, 2007 May 15, 2007 May 24, 2007 June 11, 2007 June 26, 2007 October 08, 2007
Type of Submission:	New, Standard NDA

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1. *EXECUTIVE SUMMARY*

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

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

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

1.1. Recommendations

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 22-008 acceptable from an OCP perspective provided that the Sponsor agrees with the Phase IV commitment. The recommended Phase IV commitment pertaining to investigation of whether ropinirole is a P-glycoprotein substrate and has CYP induction potential has been previously conveyed to the Sponsor for the ——— b(4)
——— application for Requip CR-RLS and should be applicable to the current submission. In addition, agreement on the labeling language should be reached between the Sponsor and the Agency.

Comments to be conveyed to the Sponsor:

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

acceptable. However, in future drug development programs, we recommend use of 50 rpm as paddle speed.

1.2. Phase IV Commitments

The Sponsor should commit to the following recommendations and submit results to the Agency within 1 year from the date of approval:

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

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Background:
Requip® Tablets (immediate release) contain ropinirole which is a non-ergoline dopamine agonist and is currently approved for the treatment of both idiopathic Parkinson's disease (up to doses of 24 mg/day or 8 mg tid) and Restless Leg Syndrome (up to doses of 4 mg once daily). With the current application, the Sponsor (GlaxoSmithKline) is seeking approval for Requip (ropinirole hydrochloride) XL 24-Hour controlled-release formulations of 2 mg, 3 mg, 4 mg, and 8 mg strengths for the treatment of signs and symptoms of idiopathic Parkinson's disease (PD). The proposed extended release tablet formulations have an approximately 24 hours of release profile and are expected to provide a longer duration of effect for allowing once-daily dosing for treating PD.

To support this New Drug Application, the Sponsor submitted a total of six clinical pharmacology studies and eight clinical trials (including four Phase 1, five Phase 2, and four Phase 3 studies, and an additional Phase 2 study in Fibromyalgia patients) for the evaluation of proposed ropinirole XL formulations.

Clinical pharmacology program focused on single- and multiple-dose pharmacokinetics in healthy subjects and in patients with Parkinson's disease, the selection for starting dose and titration regimen, exposure-response relationships based on Phase 3 study (Study 168), as well as generating individual estimates and sources of inter-subject variability based on population PK analysis on data from Phase 3 efficacy studies (168 and 169). Biopharmaceutics program focused on prototype formulation selection, relative bioavailability, food effects, dose-proportionality and dosage strength equivalence. The clinical development program was designed to assess the efficacy and safety of ropinirole XL in patients with Parkinson's disease. 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 performed (this study report has been previously reviewed as part of the [redacted] submission by the Agency's QT-IRT group). b(4)

Exposure-response relationships:

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

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

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

Exposure comparison (XL vs. IR) for dose conversion: The steady-state relative bioavailability of the ropinirole XL formulations (8.0 mg od) was compared with that of steady-state IR tablets (2.5 mg IR tid, or 7.5 mg/day) in patients with Parkinson's disease. Statistical analysis of PK data from this study showed that on a dose-for-dose basis the AUC(0-24) and Cmin of ropinirole XL were similar to that of ropinirole IR, whereas Cmax was ~12% lower compared with that of ropinirole IR. The 90% confidence intervals of exposure measures are contained within the BE range of 80-125%.

Proposed switching from IR to XL formulation: The conversion regimen from ropinirole IR to XL formulations was mainly based on achieving similar bioavailability or exposure measures as observed from Study 164 and the PK/PD analysis of Phase 3 efficacy results (Study 168). In Study 168, subjects were switched between ropinirole IR and XL based on the nearest available dose, whereas ropinirole exposure was maintained upon conversion. Results suggest that the dose of ropinirole XL tablets should be based on the closest total

daily dose of ropinirole IR that the patient was taking. The overall approach for conversion of patients currently on IR formulation to XL formulation is acceptable.

	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 XL	2	4	6	8	12	16	20	24

Selection for dose and dose regimen: The ropinirole XL starting dose (2 mg once daily) and up-titration scheme were mainly determined by safety and tolerability of the dose regimen conversion (Studies 166 and 167). The dose and dose regimen are appropriately selected from a clinical pharmacology and biopharmaceutics perspective.

Potential for QT or QTc prolongation: The exposure-response re-analysis was previously reviewed by Interdisciplinary Review Team for QT Studies (QT-IRT) ——————— for RLS. The overall review findings indicate that the effect of IR and CR-RLS on QT intervals at higher exposures achieved either due to drug interactions, hepatic failure, or at higher doses has not been systematically evaluated, and thus no change should be made to the current label. b(4)

General pharmacokinetic properties:
The general ADME characteristics of ropinirole were described in detail in the ropinirole NDA for the treatment of Parkinson's disease (NDA 20-658) and in label for approved Requip® Tablets.

Single dose vs. multiple dose PK parameters: The pharmacokinetic properties and systemic exposure to ropinirole were generally similar following single and multiple doses of XL tablet, as shown in following tables:

Parameter	Single Dose	Repeat Dose
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%)

Parameter	Point Estimate
Cmax (Repeat:Single)	1.24
Repeat AUC(0–24) : Single AUC(0-24) (Ro)	1.26
Repeat AUC(0–24) : Single AUC(0–∞) (Rs)	1.13
Cmin (Repeat:Single)	1.27

PK comparison between RLS patients and healthy volunteers: As described in (NDA 20-658) and as presented in Phase 1 and 2 studies in the current application for XL formulations,

the pharmacokinetics of ropinirole and major metabolites are similar in healthy subjects and patients with Parkinson's disease.

Intrinsic factors:
Based on the population PK analyses conducted for ropinirole IR and XL 24h for Parkinson's disease, CL/F for ropinirole was slightly lower (~13-15%) in patients who were ≥65 years of age compared to patients who were <65 years of age. This slightly lower clearance in patients ≥65 years of age would translate in to slightly higher exposure to ropinirole (~13-15%) in the elderly. Results for ropinirole XL are similar to that obtained with the previous analysis conducted for ropinirole IR. No dose adjustment is necessary. The current analysis also showed a trend for concomitant hormone replacement therapy (HRT) to decrease the clearance of ropinirole, as seen for IR. Inclusion of HRT as a covariate on the base model showed a 34% decrease in CL/F in patients taking HRT, similar to that observed in the IR analysis (33%).

Drug-drug interaction potential:
Information pertaining to drug-drug interaction potential for ropinirole primarily involving hepatic CYP1A2 is available in approved label for Requip IR Tablets. However, no pertinent information is available as to whether ropinirole is a P-gp substrate and/or inducer for major CYP enzymes, such as CYP3A4, in humans.

Dose proportionality:
Dose proportionality of ropinirole following administration of XL was investigated in patients with Parkinson's disease and in healthy subjects. The plasma ropinirole concentrations increased approximately dose-proportionately. The estimated slopes obtained from the power models for AUC(0-24), Cmax, and Cmin were close to unity, indicating the dose proportionality and linearity for ropinirole over the XL dose range 2 to 8 mg at steady state. The population pharmacokinetic analysis conducted in the Phase 3 clinical studies show linear Pharmacokinetic property without dose-dependent change in CL/F over the dose range of 2-24mg. In healthy subjects, dose proportionality was demonstrated between 0.75 mg and 3 mg ropinirole XL.

Relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation:
The relative bioavailability of the to-be-marketed formulations and those used in the clinical trials was not evaluated for the reasons of same manufacturing site, identical core composition, size and shape, with the exception of coating color and debossings.

Relative bioavailability of the proposed XL formulation to the Requip IR Tablets:
The relative bioavailability of ropinirole from equal dosage of these two formulations (XL 0.75 mg od vs. IR 0.25 mg tid) in healthy subjects was assessed. The AUC(0-∞) of the XL formulation was ~96% of the IR formulation, while Cmax was ~31% lower for ropinirole XL. On the other hand, as described above, the steady-state bioavailability of the ropinirole XL formulations (8.0 mg od) was comparable to that of steady-state IR tablets (2.5 mg IR tid, or 7.5 mg/day) in patients with Parkinson's disease, based on BE range of 80-125%.

Dosage strength equivalency:
The dosage strength equivalence of 1 x 8.0 mg vs. 4 x 2.0 mg ropinirole XL tablets at steady-state was demonstrated in patients with Parkinson's disease, based on BE range of 80-125%. In healthy subjects, the dosage strength equivalence following single doses of ropinirole XL tablets was demonstrated up to 3 mg strength (2 x 1.0 mg vs. 1 x 2.0 mg and 3 x 1.0 mg vs. 1 x 3.0 mg), based on BE range of 80-125%. No study was conducted to evaluate the dosage equivalence of the 4 mg strength. However, the linear pharmackinetic property, dose-proportionality in exposure parameters in Study 165 using 2 mg, 4 mg and 8 mg strengths, proportionally similar compositions, and similar dissolution profiles support the dosage equivalency for the lower 4 mg strength.

Effects of food:
The definitive food effect was evaluated at steady-state with the highest-strength 8-mg XL tablets in Parkinson's patients. High-fat food did not appear to have significant effects on AUC(0-24) and Cmin of ropinirole based on results of point estimates and the 90% CIs for both parameters. The Cmax was increased by 15%, with higher end of 90% CI slightly exceeding the upper BE limit. The absorption of ropinirole XL at 1 x 8 mg appeared to be prolonged, as reflected by median prolonged Tmax by 2 hours. However, the extent of change 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.

Potential dose-dumping in the presence of alcohol:
A slightly slower in vitro release profile was observed in the presence of 24% ethanol in simulated gastric fluid (SGF), indicating that the formulation is resistant to dose dumping under the test conditions.

In-vitro-in-vivo correlation (IVIVC) for ropinirole CR-RLS formulation:
The Sponsor developed a Level A IVIVC model based on the proposed dissolution test in pH 4 citrate buffer with three ropinirole controlled release formulations (XL) of fast, standard, and slow release characteristics. The predictability of the ropinirole XL IVIVC model was assessed by predicting in vivo concentration-time profiles via internal validation and external validation. The detailed review is available for [redacted] for CR-RLS formulation. For internal validation, all the prediction errors fell within the acceptance criteria (MAPPE <10%) for internal validation of an IVIVC according to the Agency's Guidance. However, results of the external validation was inconclusive for the highest 8 mg strength (i.e., absolute %PE values >10% for Cmax and AUC). Since external predictability is inconclusive for 8 mg, we recommend additional evaluation of predictability with other strengths and data sets and submitted prior to full application of this IVIVC for biowaiver.

b(4)

Dissolution specifications:
The proposed dissolution method is acceptable, however, a lower paddle speed of 50 rpm is preferred due to a lack of significant impact of paddle speed over the range tested. The proposed dissolution specifications are acceptable. The proposed dissolution method and specifications by the sponsor for ropinirole XL tablets are shown as follows:

Apparatus: USP Apparatus II (paddles)

Speed:	100 rpm
Medium:	pH 4.0 Citrate Buffer
Volume:	500 mL
Temperature:	37 ± 0.5 °C
Specifications:	

Time	% Dissolved
2 hour	
12 hours	
24 hours	

b(4)

Ta-Chen Wu, Ph.D.
Reviewer, Neurology Drug Products, DCP-1
Office of Clinical Pharmacology

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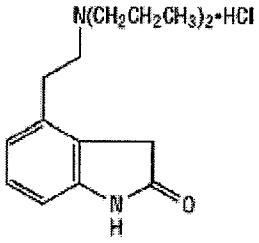
cc: HFD-120 NDA 22-008
CSO/SB Daugherty
/Biopharm/T.C. Wu
/TL Biopharm/R. Uppoor
HFD-860 /DD DCP-1/M. Mehta



Requip XL 24-Hour tablets are formulated as a three-layered tablet with a central, active-containing, slow-release layer, and 2 placebo outer layers acting as barrier layers which control the surface area available for drug release. All strengths are biconvex, capsule-shaped tablets (approximately 12.6 mm x 6.9 mm). Different debossings and film coat colors are used to aid identification. Each biconvex, —— film-coated tablet contains ropinirole hydrochloride equivalent to ropinirole 2, 3, 4, or 8 mg. Inactive ingredients consist of carboxymethycellulose sodium, colloidal silicon dioxide, glyceryl behenate, hydrogenated castor oil, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, mannitol, povidone, and one or more of the following: carmine, FD&C Yellow No. 6 aluminum lake, FD&C Blue No. 2 aluminum lake, ferric oxides (black, red, yellow), polyethylene glycol 400, titanium dioxide..

b(4)

Four dose strengths (2, 3, 4, and 8 mg) are proposed for the to-be-marketed Requip XL 24-Hour (ropinirole) film-coated tablets to cover the therapeutic dose range, with appearance and the composition described in Section 2.5.2.

2.1.3. What are the proposed mechanism of action and therapeutic indication?

Similar to Requip® IR Tablets, the proposed indication of Requip XL 24-Hour is for the treatment of signs and symptoms of idiopathic Parkinson's disease (PD).

According to the Requip® IR Tablet label, ropinirole hydrochloride is an orally administered non-ergoline dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 and D_3 dopamine receptor subtypes. Binding affinity to D_3 was higher than to D_2 or D_4 receptor subtypes. Ropinirole has moderate in vitro affinity for opioid receptors. Ropinirole and its metabolites have negligible in vitro affinity for dopamine D_1, 5-HT_1, 5-HT_2, benzodiazepine, GABA, muscarinic, α_1-, α_2-, and β-adrenoreceptors.

The precise mechanism of action of ropinirole as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of postsynaptic dopamine D2 type receptors within the caudate putamen in the brain. This conclusion is supported by studies that show that ropinirole improves motor function in various animal models of Parkinson's disease. In particular, ropinirole attenuates the motor deficits induced by lesioning the ascending nigrostriatal dopaminergic pathway with the neurotoxin 1 methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates. The relevance of D3 receptor binding in Parkinson's disease is unknown. Additional information is available in the approved Requip® IR label.

2.1.4. What are the proposed dosages and route of administration?

Ropinirole IR was approved for the treatment of Parkinson's disease up to doses of 8 mg tid (i.e., 24 mg/day). It is proposed that ropinirole XL be orally administered up to doses of 24 mg once daily (od) and that ropinirole XL can be taken with or without food.

Patients may be switched directly from Requip IR Tablets to XL 24-Hour formulation. The initial switching dose of Requip XL 24-Hour should most closely match the total daily dose of IR ropinirole. When ropinirole CR tablets are administered as adjunct therapy to L-dopa, it may be possible to reduce gradually the L-dopa dose, depending on the clinical response.

<u>Proposed up-titration regimen for ropinirole XL 24-Hour</u>:
The recommended starting dose is 2 mg taken once daily for 1 [redacted] followed by increases of 2 mg/day [redacted] b(4) a maximum of 24 mg once daily. In clinical trials, dosage was initiated at 2 mg and gradually titrated to therapeutic response. Doses greater than 24 mg/day have not been tested in clinical trials. The proposed up-titration scheme, compared to that of IR, is shown in Table 1:

[redacted]

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2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support this New Drug Application, the Sponsor submitted a total of six clinical pharmacology studies and eight clinical trials (including four Phase 1, five Phase 2, and four

Phase 3 studies, and an additional Phase 2 study in Fibromyalgia patients) for the evaluation of proposed ropiirole XL formulations.

Clinical pharmacology program focused on single- and multiple-dose pharmacokinetics in healthy subjects and in patients with Parkinson's disease, the selection for starting dose and titration regimen, exposure-response relationships based on Phase 3 study (Study 168), as well as generating individual estimates and sources of inter-subject variability based on population PK analysis on data from Phase 3 efficacy studies (168 and 169). Biopharmaceutics program focused on prototype formulation selection, relative bioavailability, food effects, dose-proportionality and dosage strength equivalence. The clinical development program was designed to assess the efficacy and safety of ropinirole XL in patients with Parkinson's disease. 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 performed (this study report has been previously reviewed as part of the ——————— submission by the Agency's QT-IRT group). The tabular listing of all clinical studies is presented in Table 2.

b(4)

Table 2. Clinical pharmacology programs and clinical trials for this NDA submission

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

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

In Phase 3 clinical trial (Study 168) for the early stage Parkinson's disease, the primary endpoint was the change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. In Phase 3 clinical trial (Study 169) for Patients with more advanced stage Parkinson's disease, the primary end point was the change from baseline in awake time "off", where awake time "off" relates to the number of awake hours per day that a patient suffers from symptoms of Parkinson's disease (bradykinesia). In both trials, the secondary endpoint was the Clinical Global Impression Global Improvement (CGI-I) scale, which evaluated the proportion of subjects with a score of much improved or very much improved.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes. The plasma levels of ropinirole (and primary active moiety) and its 2 major circulating metabolites, SKF-104557 and SKF-89124, were identified and measured using validated bioanalytical methods employing HPLC-MS/MS. The analytical methods for the reformulated ropinirole are consistent with that employed for the approval of the IR formulation and have also been reviewed for the proposed CR formulations for RLS. Detailed description of the analytical procedures is presented in the Analytical Section 2.6.

2.2.4. Exposure-response relationships

2.2.4.1. What are the characteristics of the exposure-response relationships for efficacy and safety, and are dose and dose regimen properly selected based on population PK and PK/PD analyses?

This OCP review of the Sponsor' population PK and PK/PD analyses are concurred by Dr. Yaning Wang of Pharmacometrics team.

(1) What are the characteristics of the population PK analysis?

The final model was a one compartment linear model with first order absorption and first order elimination. Input into the central compartment was modeled with two separate depot compartments for ropinirole IR and ropinirole XL, with a bolus into depot compartment 1 for ropinirole IR and a zero order input in to depot compartment 2 for ropinirole XL. The population PK parameters, inter-individual variability, random residual variability and the covariance estimates for the Final Model using data from Studies 169, 168 and 164 are presented in Table 3 below.

Table 3. Summary of population mean PK parameter estimates for Final Model

	CL/F (L/hr)[a]		V/F (L) (θ2)	Ka (h-1) (θ 3)	D2 (h) (θ 4)
	< 65 years	≥ 65 years			
Population Mean (95% CI) RSE	54.7 (50.4 – 59.0) 4.0%	47.7 (44.6 – 50.8) 3.3%	641 (560 – 722) 6.4%	2.35 (1.75 – 2.95) 13%	13.0 (11.8 – 14.2) 4.6%
IIV RSE	46.8% 10.8%		41% 15.3%		
IOV on CL/F RSE	30% (168), 15% (164), 23% (169) 15% (168), 50% (164), 17% (169)				
Correlation between CL and V = 0.827 Residual Error: Proportional CV=27.9% (RSE=6.4%), Additive SD= 0.34 ng/mL (RSE=31.5%)					
[a]CL/F = [CL/F= θ 1*AGE1 + θ 5*(1-AGE1)] where AGE1 = "0" for patients <65 years and AGE1="1" for patients ≥65 years F = Absolute Bioavailability, CI = confidence interval, CV%= coefficient of variation, RSE = relative standard error (SE/Parameter estimate*100, IIV = Inter-Individual Variability, IOV = Inter-Individual Variability, D2 = duration of zero order input for ropinirole CR into depot compartment 2.					

The population mean estimate of ropinirole oral clearance (CL/F) was 54.7 L/h in patients <65 years of age and 47.7 L/h in patients ≥65 years of age. The inter-individual variability for CL/F was ~47%. The population mean estimate of ropinirole oral volume of distribution (V/F) was 641 L, with an inter-individual variability of 41%. The results of the population pharmacokinetic analysis for ropinirole XL are similar to the results obtained with the previous analysis conducted for ropinirole IR.

The current analysis showed a trend for concomitant hormone replacement therapy (HRT) to decrease the clearance of ropinirole, but not statistically significant when tested as a covariate in addition to the age because of the small number of patients. Inclusion of HRT as a covariate on the base model showed a 34% decrease in CL/F in patients taking HRT, similar to that observed in the IR analysis (33%).

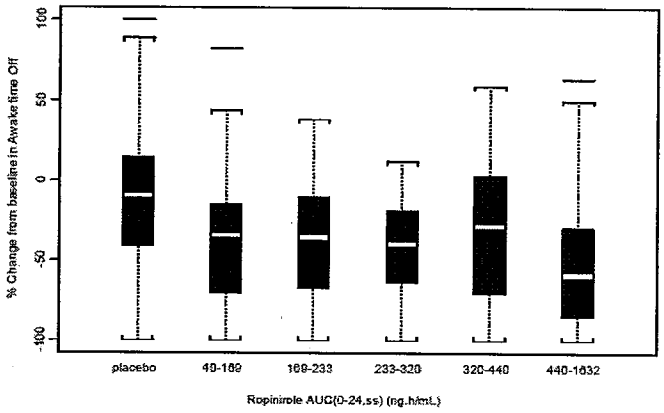
(2) What are the characteristics of the exposure-response relationships for efficacy?

Individual post-hoc estimates of CL/F were derived from the Final Model of population PK analysis for patients in Study 168 and Study 169, which were used to estimate the individual steady-state AUC(0-24,ss) values. The relationship between estimated ropinirole AUC(0-24,ss) and selected primary efficacy endpoints from Study 168 and Study 169 were constructed and analyzed by logistic regression.

Study 169:
The primary efficacy endpoint was awake time "off". A 20% decrease in awake time "off" from baseline was considered to be clinically relevant. Therefore, a patient with a ≥20% decrease in awake time "off" from baseline would be defined as a responder.

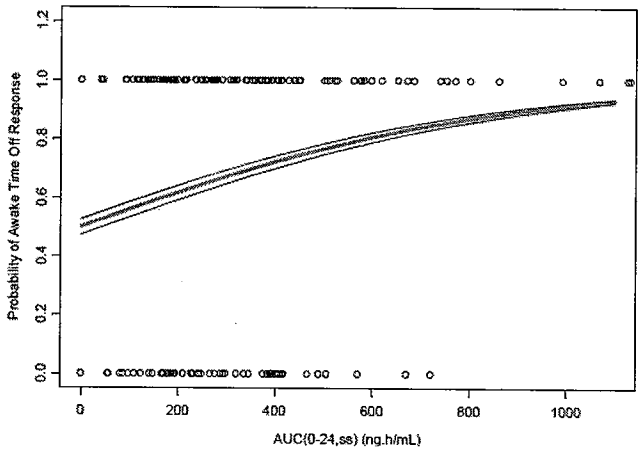
Graphical assessments of the exposure-response relationship, as shown in Figure 2, showed that there was small decrease in awake time "off" in patients receiving placebo (~10%). The median percent decrease in awake time "off" was between ~40 to 50% in the ropinirole treated patients. Higher systemic exposures of ropinirole appeared to be associated with a greater decrease in awake time "off".

Figure 2. Percent change from baseline in awake time off at week 24 by 5 percentile ranges of predicted AUC(0-24,ss) values in comparison with placebo(Study 169)



As shown in Figure 3 below, the logistic regression showed that the probability of a patient having a >20% decrease in awake time "Off" from baseline was approximately 0.4 for the placebo group and increased to a near total response rate at the higher systemic exposures to ropinirole. Results of PK/PD analysis in patients with advanced stage Parkinson's disease suggested that higher doses of ropinirole up to 24 mg may lead to improved probability of clinical response, in parallel with possible reduction in L-dopa dose.

Figure 3. Probability of patients having a >20% decrease from baseline in awake time "off" at week 24 (Study 169)

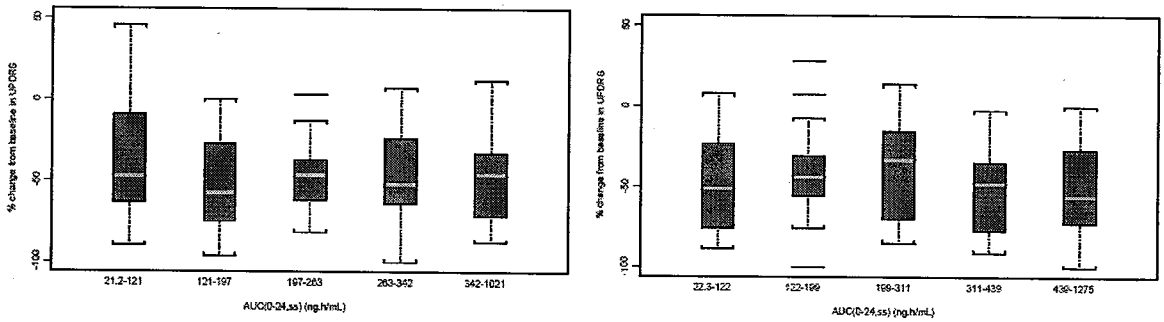


Study 168:

In Study 168, the primary endpoint was change from baseline in UPDRS motor-score. A 30% decrease in UPDRS motor score was considered to be indicative of clinical relevance. Therefore, a responder was defined as a patient with a ≥30% decrease in UPDRS motor score from baseline. Graphical assessments of the relationship between systemic exposure to ropinirole and percent change from baseline in UPDRS motor score showed that there was a

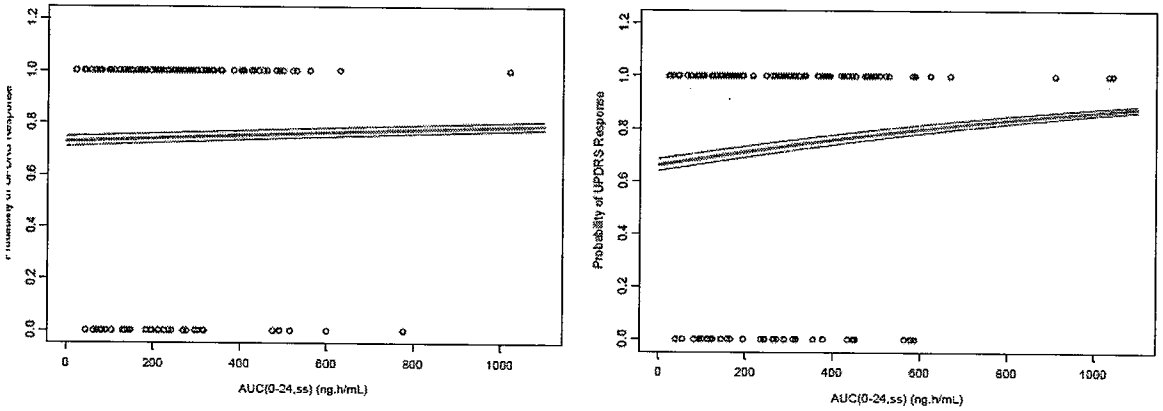
≥30% decrease from baseline. The median decrease was ~50% over the entire ropinirole systemic range for both ropinirole XL and ropinirole IR. Results are shown in Figure 4.

Figure 4. Percentage change from baseline in UPDRS by 5 percentile ranges of predicted AUC(0-24,ss) values following administration of ropinirole in Study 168 (Left: XL, Right: IR)



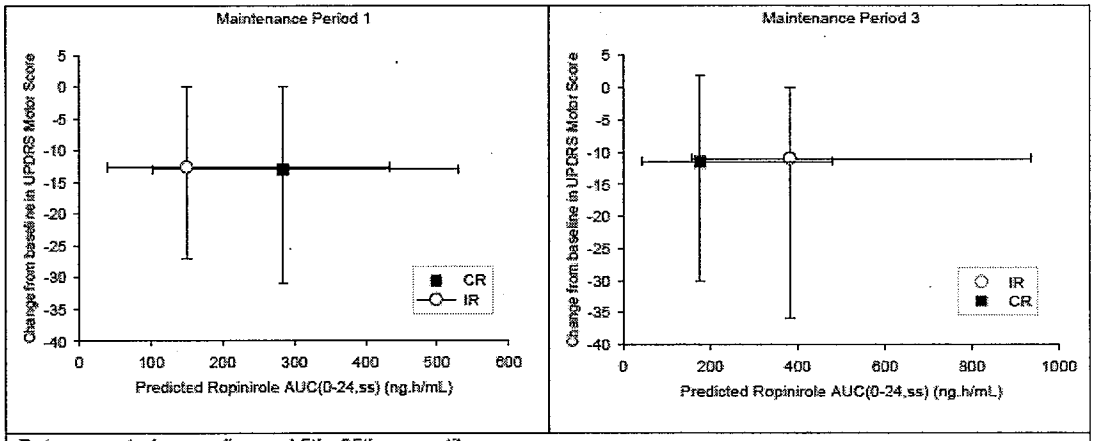
The logistic regression showed that the probability of a patient having a >30% decrease in UPDRS score was between 0.6 and 0.8 and the probability of response was similar for the ropinirole CR and IR. Results are shown in Figure 5.

Figure 5. Probability of UPDRS response for Ropinirole CR in Study 168 (Left: XL, Right: IR)



The analysis also demonstrated a flat exposure-response relationship for the UPDRS motor score over the entire ropinirole systemic exposure range that was included in the analysis, similar to that for IR. The probability of a patient being a responder to ropinirole was similar over the entire exposure range. The flat exposure-response relationship in Study 168 was further demonstrated by comparing the absolute change from baseline in UPDRS motor score and predicted AUC(0-24,ss) values for ropinirole CR and IR at the end of Maintenance Periods 1 or 3, as shown in Figure 6.

Figure 6. Absolute change from baseline in UPDRS vs. AUC(0-24,ss) for ropinirole XL and ropinirole IR in Maintenance Period 1 and Period 3 in study 168



Despite the almost 2-fold difference in AUC(0-24,ss) between the two formulations at the end of Maintenance Period 1 and Period 3, the mean change from baseline in UPDRS motor score were similar for the two regimens (XL and IR swtiching). Therefore, according to the Sponsor, maximal efficacy is likely to be associated with AUC(0-24,ss) values in the range ~150–200 ng·h/mL, corresponding to approximately 8–12 mg/day doses of ropinirole XL, in patients with this early stage of Parkinson's disease.

(3) Does the controlled-release formulation offer similar exposure to the approved immediate-release formulation when administered similar dose strengths?

Yes. The steady-state relative bioavailability of the ropinirole XL formulations (8.0 mg od) was compared with that of steady-state IR tablets (2.5 mg IR tid, or 7.5 mg/day) in patients with Parkinson's disease in Study 164. Statistical analysis of PK data from this study showed that on a dose-for-dose basis the AUC(0-24) and Cmin of ropinirole XL were similar to that of ropinirole IR, whereas Cmax was ~12% lower compared with that of ropinirole IR. The 90% confidence intervals of exposure measures are contained within the BE range of 80-125%. Details of the study results is available in Section 2.5.4.

(4) What is the proposed dose conversion scheme when patients are switched from IR to XL 24-Hour formulation?

The proposed dose conversion from ropinirole IR to XL is based on achieving similar bioavailability or exposure measures as observed from Study 164 and the PK/PD analysis of Phase 3 efficacy results (Study 168). In Study 168, subjects were switched between ropinirole IR and XL based on the nearest available dose. Pharmacokinetic data from this study showed that average systemic exposure to ropinirole was maintained upon conversion. Results suggest a possible formulation switching on a IR:XL of 1:1 ratio. Therefore, patients already receiving ropinirole IR tablets may be converted overnight to ropinirole XL tablets. The dose of ropinirole XL tablets should be based on the closest total daily dose of ropinirole

IR that the patient was taking. The overall approach for conversion of patients currently on IR formulation to XL formulation seems reasonable. The recommended dose conversion is shown in Table 4.

Table 4. Proposed conversion from Requip IR to ropinirole XL 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 XL	2	4	6	8	12	16	20	24

(5) Characteristics of the Exposure-Response Relationships for Safety (dose-response, concentration-response)

Dopaminergic side effects of ropinirole appear to be related to the rate of increase of systemic concentrations of ropinirole. The release rate for ropinirole XL ———— was designed to be slower than for the IR formulation ———— leading to a lower Cmax and a slower rate of rise to Cmax (median Tmax of approximately 6–10 hours) as compared to Requip IR (median Tmax of approximately 1-2 hours). This slower release rate is expected to result in a better tolerability profile for ropinirole XL 24-Hour compared to IR on a dose-for-dose basis and has been evaluated in the Phase 2 study (Study 164). b(4)

2.2.4.2. Does this drug prolong the QT or QTc interval?

The Sponsor has previously submitted a definitive QT study [Study 902] in support of the sNDA for ropinirole IR for moderate-to-severe primary RLS (NDA20-658/S-013). Study 902 was a steady-state repeat dose study conducted in healthy subjects to evaluate QT at escalating doses of ropinirole IR over the dose range 1- 4 mg once daily. The OCP review of the study report did not find QTcF prolongation in this dose range.

To support the current application and previous application ———— Requip CR-RLS) for the new controlled-release formulations, the Sponsor has performed a meta-analysis of pooled QT data from three Phase 3 studies (Study 168 and Study 169 in patients with Parkinson's disease and Study ROF102100 in patients with fibromyalgia) using extended-release ropinirole XL 24-Hour formulation for Parkinson's disease to support a change in labeling for XL. In these studies, sparse blood samples were collected for the purpose of population PK analysis. The Sponsor's analysis showed an exposure related QT prolongation at higher concentrations even though result of the "thorough QT/QTc study" was negative. b(4)

The pharmacometrics reviewer conducted an independent exposure-response analysis to explore the reason for this discrepancy. Details of the exposure-response re-analysis are available in consultation report from Interdisciplinary Review Team for QT Studies (QT-IRT) ———— The overall review findings are summarized below and are applicable to the current submission for XL 24-Hour tablets: b(4)

Overall summary of findings:

- The sponsor's exposure-response analysis of pooled concentration and QT data collected in studies 168, 169 and ROF102100 was inconclusive because the analysis did not take into account the placebo time-course. Sensitivity analysis of the model using the concentration-QTc data collected in the TQT study (902) illustrated the importance of incorporating the placebo time course into the model: ignoring placebo data resulted in a positive C-QTc relationship over the dose range of 1 to 4 mg when in fact the TQT study was negative.
- The effects of higher ropinirole concentrations on the QTc interval should be evaluated in a thorough QT study.
- No change should be made to the current label.

b(4)

2.2.4.3. Are the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dose regimen are properly selected from a clinical pharmacology and biopharmaceutics perspective. Please refer to Section 2.2.4.1.

2.2.5. What are the pharmacokinetic characteristics of the drug and its major metabolite?

The general ADME characteristics of ropinirole were described in detail in the ropinirole NDA for the treatment of Parkinson's disease (NDA 20-658) and in label for approved Requip® Tablets (IR). Therefore, the general ADME characteristics provided by the Sponsor in the current application, as well as new findings for proposed XL formulation, are summarized in the following sections.

2.2.5.1. What are the single dose and multiple dose PK parameters?

The single- and multiple-dose pharmacokinetics of 1 mg ropinirole XL tablets in healthy subjects were compared in Study 163. Study 163 was a double-blind, two-way crossover, placebo-controlled, randomized single- and repeat-dose study in healthy subjects. Subjects were randomized to receive ropinirole 1 mg XL tablets od (with concomitant domperidone 20 mg tid) or placebo for 9 days. Blood samples for PK evaluation were collected up to 48 hours following the single dose and up to 24 hours on Day 9 of multiple dosing. Trough samples were collected on Days 4- 8 of the repeat dose phase.

The pharmacokinetic properties and systemic exposure to ropinirole were generally similar following single and multiple doses of XL tablet. Mean ropinirole plasma concentration-time profiles following single and multiple doses in Study 163 are shown in Figure 7. The

mean PK parameters of ropinirole and point estimates are summarized in Tables 5-6. More details are available in the Individual Review section (Section 4.2).

Figure 7. Mean ropinirole plasma concentration-time profiles following single and repeated dose administration of ropinirole 1 mg XL od (Study 163)

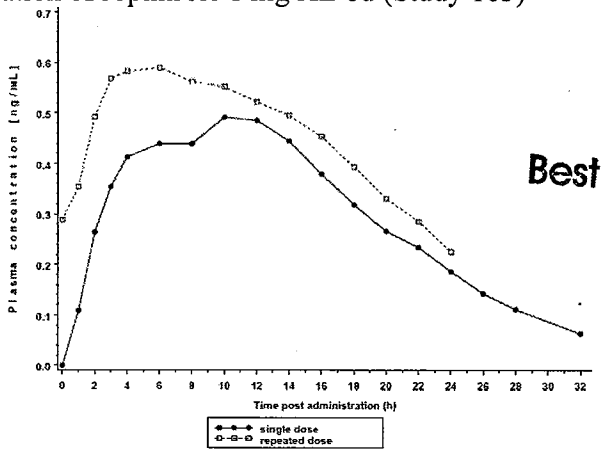


Table 5. Comparison of the single- and multiple-dose ropinirole PK parameters

Parameter	Single Dose	Repeat Dose
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 6. Summary of the statistical analysis for ropinirole (Day 9 : Day 1)

Parameter	Point Estimate
Cmax (Repeat:Single)	1.24
Repeat AUC(0–24) : Single AUC(0-24) (Ro)	1.26
Repeat AUC(0–24) : Single AUC(0–∞) (Rs)	1.13
Cmin (Repeat:Single)	1.27

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

state of ropinirole (and the inactive metabolite) was observed by Day 4 of dosing. There were no marked changes in metabolite-parent ratios after multiple doses.

2.2.5.2. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

As described in (NDA 20-658) and as presented in Phase 1 and 2 studies in the current application for XL formulations, the pharmacokinetics of ropinirole and major metabolites are similar in healthy subjects and patients with Parkinson's disease. The basic pharmacokinetic properties are available in approved label for Requip IR.

2.2.5.3. What are the characteristics of drug absorption?

The absolute bioavailability of ropinirole given as a solution or as an immediate release (IR) tablet was approximately 40~50%. The bioavailability of ropinirole based on steady-state AUC(0-24) was similar for ropinirole XL and ropinirole IR, suggesting similar bioavailability (~40~50%) of ropinirole from XL formulations. When ropinirole is administered as a solution or IR tablet, absorption of ropinirole is rapid with maximal plasma concentrations being attained within 2 hours after dosing. Mass-balance study shows 87.7% urinary recovery of drug-related material following oral administration, suggesting a near complete absorption (except that we don't know if drug degrades in GIT before absorption).

2.2.5.4. What are the characteristics of drug distribution?

According to the approved label for Requip IR, after intravenous administration, ropinirole was rapidly and extensively distributed out of the vascular compartment, with a volume of distribution of approximately 7.7 L/kg. The plasma protein binding of ropinirole is low (range 10-39%) and was independent of concentration over the range 0.03~3940 ng/mL. The blood to plasma ratio of 1.2 suggests that ropinirole was associated to some extent with blood cells.

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Following oral administration of [^{14}C]ropinirole (as a solution) to healthy subjects, absorption of drug-related material was rapid with maximal plasma concentrations of radioactivity seen within 2 hours after dosing. Approximately 87.7% of the administered drug was recovered in urine as drug related material. Ropinirole is primarily cleared by hepatic metabolism with minimal renal excretion, as indicated by less than 10-12% of ropinirole being excreted unchanged into urine. The Tmax for each of the metabolites is similar to that of ropinirole. The half-life of SKF-89124 and ropinirole are similar (~5 – 6 hours), whereas the half-life of SKF-104557 is slightly longer (~8 – 9 hours).

2.2.5.6. What are the characteristics of drug metabolism?

According to the approved label for Requip IR, ropinirole is primarily cleared by hepatic metabolism via the CYP1A2 enzyme to form two circulating metabolites (SKF-104557 and SKF-89124) which are both renally cleared. SKF-104557 is approximately 100 times less potent at the D2 receptor than ropinirole in animal models of dopaminergic function. SKF-89124 possesses pharmacological activity similar to ropinirole at the D2 receptor. The steady-state systemic exposure to SKF-104557 following once daily administration of ropinirole is approximately 1.1- to 1.2 fold higher than the exposure to ropinirole. However, the systemic exposure to SKF-89124 is generally <5% of the systemic exposure to ropinirole and therefore its overall contribution to activity is limited.

The ratio of metabolite:parent systemic exposures were similar following administration of ropinirole IR tablets and ropinirole XL tablets (Study 161, 163 and 164). Following single dose administration of ropinirole XL (0.75–3.0 mg) to healthy subjects, systemic exposure to SKF-104557 was approximately 1.4~1.8-fold higher than the exposure to ropinirole, and systemic exposure to SKF-89124 was approximately 1% to 4% of exposure to ropinirole (Study 161 and Study 163). In patients with Parkinson's disease at steady state, systemic exposure to SKF-104557 was approximately 1.1~1.2-fold higher than the exposure to ropinirole, and systemic exposure to SKF-89124 was approximately 4-5 % that of ropinirole (Study 164).

2.2.5.7. What are the characteristics of drug excretion?

After attainment of Cmax, plasma concentrations of ropinirole decline in a mono-exponential manner with a half-life of ~6 hours. Ropinirole is primarily cleared by hepatic metabolism with minimal renal excretion, as indicated by less than 12% of the drug-related material in urine being unchanged ropinirole. Also see above Section 2.2.5.5.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose proportionality of ropinirole XL was investigated (1) in patients with Parkinson's disease (Study 165 and population PK analysis conducted in the Phase 3 clinical studies 168 and 169) and (2) in healthy subjects (Studies 162 and 219).

Study 165:
This study evaluated the dose proportionality of ropinirole XL investigated at steady-state across the available tablet strength range of 2 - 8 mg (1 x 2 mg, 1 x 4 mg, 4 x 2 mg, and 1 x 8 mg) in patients with Parkinson's disease. The ropinirole XL tablets were administrated after a standard meal. The median steady state concentration-time profiles, including an outlier, for ropinirole following 4 XL dosing regimens are presented in Figure 7. A summary (geometric mean (CVb%)) of the PK parameters following administration of ropinirole XL are presented in Table 7. The statistical summary for the dose proportionality assessment using power model are shown in Table 8.

Figure 8. Median steady state ropinirole plasma concentrations-time profiles by treatments (N=22)

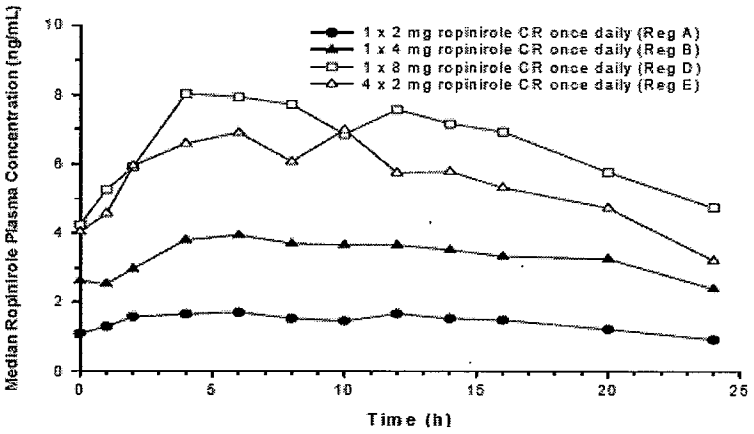


Table 7. Summary of ropinirole PK parameters following administration of ropinirole XL

Parameter	2 mg (n=22)	4 mg (n=22)	8 mg (n=22)
AUC(0-24) (ng.h/mL)	37.9 (56.7%)	76.3 (54.7%)	168 (69.1%)
Cmax (ng/mL)	2.16 (50.6%)	4.19 (50.7%)	9.30 (67.2%)
Cmin (ng/mL)	1.13 (76.5%)	2.36 (65.8%)	4.74 (88.0%)
Tmax (h)[a]	7.00 (1.00-20.0)	6.00 (4.00-24.0)	6.00 (2.00-20.0)

a. Median (range)

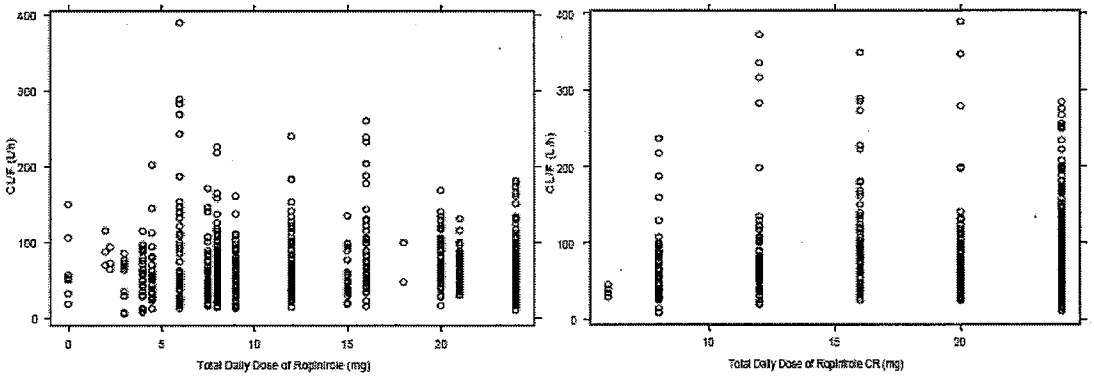
Table 8. Summary of statistical analysis using Power Model (with and without the outlier)

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)

The estimated slopes obtained from the power models for AUC(0-24), Cmax, and Cmin were close to unity, indicating the dose proportionality and linearity for ropinirole over the XL dose range 2 to 8 mg at steady state.

Population PK analysis:
The linearity of ropinirole was assessed at doses of up to 24 mg/day as part of the population PK analysis conducted in the Phase 3 clinical studies 168 and 169. Results show linear Pharmacokinetic property without dose-dependent change in CL/F over the dose range studied (2-24mg). Results of post-hoc estimates of CL/F are presented in Figure 9.

Figure 9. Post-hoc estimates of CL/F vs. total daily dose of ropinirole for patients in Study 168 (Left) and 169 (Right)



Study 162:
The dose proportionality was assessed following single oral doses in healthy subjects over the dose range 0.75 to 3 mg ropinirole XL in Study 162. Subjects were randomized to receive either single doses of ropinirole 0.75 mg XL, ropinirole 3.0 mg XL or placebo, or three, 8-hourly doses of open-label ropinirole 0.25 mg IR, in each of four study periods. Summaries of dose-normalized geometric mean (CVb%) PK parameters and statistical analysis are presented in Table 9 and Table 10. Point estimates and the 90%CI for the dose-normalized exposure measures meet the BE acceptance criteria.

Table 9. Summary of ropinirole dose-normalized PK results (geometric mean (CV%))

Parameter (unit)	XL 0.75 mg (n = 30)	XL 3 mg (n = 31)
AUC(0-∞) (ng·h/mL)	6.87 (61.3)	6.92 (51.7)
Cmax (ng/mL)	0.34 (50.4)	0.36 (45.0)
Cmin (ng/mL)	0.14 (78.8)	0.14 (80.7)
DF	0.61 (66.0)	0.59 (106)
Tmax (h)	8.00 (3.0 – 16.0)	10.0 (3.0 – 18.0)
t½ (h)	4.92 (25.0)	4.53 (19.4)

Table 10. Statistical analysis for assessing the dose proportionality between 3 mg and 0.75 mg of XL formulation

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

Study 219:
The dose proportionality was assessed following single oral doses in healthy subjects over the dose range 1 to 3 mg ropinirole XL (1+1mg, 2mg, 1+1+1mg and 3 mg) in Study 219. Statistical analysis for the dose proportionality assessment using Power Model are presented in Table 11. The dose proportionality for ropinirole exposure from XL formulations across the dose range of 1-3 mg can be concluded, based on visual assessments and the point estimate of the slope (i.e., close to unity) for each parameter.

Table 11. 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)

2.2.5.9. How do the PK parameters change with time following chronic dosing?

As seen in the single- and multiple-dose PK results presented above in Section 2.2.5.1, the PK parameters of the ropinirole remained similar across single-dose and multiple-dose dose ranges studied during the study periods. Results seem to suggest a lack of autoinduction for CYP1A2.

2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Two population PK analyses have been conducted in support of the ropinirole IR and ropinirole XL clinical programs for the use of ropinirole in the treatment of Parkinson's disease. See Section 2.2.4.1 for population mean PK estimates for ropinirole XL.

Age was identified as a source of variability for oral clearance (CL/F) for ropinirole XL. The population PK analysis for the ropinirole XL showed a small (13%) but statistically significant difference between CL/F in older subjects ≥65 years compared with younger subjects (<65 years). The inter-individual variability for CL/F in the current analysis (47%) was similar to that observed in the IR population PK analysis (46%). Co-administration of HRT was identified as an influential covariate on CL/F in the population PK analysis for ropinirole IR but not in the analysis for ropinirole XL (due to <5% of patients taking HRT). For V/F, inter-individual variability for ropinirole XL is 41%, slightly higher than that (33%) for ropinirole IR.

Based on pharmacokinetic data from studies 164 and 165, the intra-subject variability of Cmax and AUC is generally <30%, whereas the inter-subject variability is generally 50 – 60%.

As described in label of the approved IR tablets, the potential sources of the variability may include food, factors affecting CYP1A2 metabolism for ropinirole, and age and hormone replacement therapy (HRT).

2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence the exposure and/or response?

No formal studies were conducted to assess the effects of general intrinsic factors (e.g., race, sex, age, or hepatic or renal impairment) on the pharmacokinetics of ropinirole in this NDA. Therefore, the information and relevant dosage adjustments can be referenced to label for the approved Requip IR Tablet (NDA 20-658).

2.3.2. What dosage regimen adjustments, if any, are recommended for each of these groups based on the known exposure-response relationships or alternative basis?

Because therapy with REQUIP XL 24 HOUR is initiated at a low dose and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary.

2.3.2.1. What is the effect of Age (elderly)?

Based on the population PK analyses conducted for ropinirole IR and XL 24h for Parkinson's disease, CL/F for ropinirole was slightly lower (~13-15%) in patients who were ≥65 years of age compared to patients who were <65 years of age. This slightly lower clearance in patients ≥65 years of age would translate in to slightly higher exposure to ropinirole (~13-15%) in the elderly. Dose adjustment is not recommended.

2.3.2.2. What is the effect of Gender?

Based on the population PK analysis conducted for ropinirole IR, there was no observable difference in the clearance of ropinirole between males and female subjects (not receiving HRT).

2.3.2.3. What is the effect of Race?

The effect of race has not been systematically evaluated, since the majority of the patient populations have been Caucasian in the studies.

2.3.2.4. What is the effect of Body Weight?

The effect of body weight on the PK property of ropinirole was not evaluated.

2.3.2.5. What is the effect of Hepatic Impairment?

The pharmacokinetics of ropinirole has not been studied in patients with hepatic impairment. See approved IR label for additional information.

2.3.2.6. What is the effect of Renal Impairment?

A population PK analysis conducted for Requip IR in Parkinson's disease patients found no change of ropinirole pharmacokinetics in patients with moderate renal impairment (defined as creatinine clearance between 30 to 50 mL/min) compared to an age-matched population with creatinine clearance above 50 mL/min. No specific recommendation was made for dose adjustment in patients with moderate renal impairment. See approved IR label for additional information.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors influence the exposure and/or response?

The influence of extrinsic factors on the pharmacokinetics of ropinirole was described in detail in the ropinirole IR NDA for the treatment of Parkinson's disease (NDA 20-658). Therefore, a brief summary of the influence of extrinsic factors on the pharmacokinetics of ropinirole is provided in the current application.

The main extrinsic factors that influence systemic exposure to ropinirole are inhibitors or inducers of CYP1A2 metabolism. Therefore, it is recommended that when therapy with a drug known to be an inhibitor of CYP1A2 (e.g., ciprofloxacin, fluvoxamine, HRT (Section 2.4.2.3.)) or an inducer of CYP1A2 (e.g., omeprazole, smoking) is stopped or started during treatment with ropinirole, adjustment of the dose of ropinirole may be required.

Thus, when patients introduce an inhibitor of CYP1A2 or stop treatment with an inducer of CYP1A2, the systemic exposure to ropinirole is likely to be increased and may result in an increase in the dopaminergic side effects associated with ropinirole. Conversely, when patients stop treatment with an inhibitor of CYP1A2 or start treatment with an inducer, the systemic exposure to ropinirole is likely to be reduced and may result in a decrease in efficacy.

2.4.2. Drug-drug interaction

2.4.2.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?

Drug interaction involving metabolic enzyme for ropinirole:
According to the approved Requip IR label, in vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. The potential exists for inducers or inhibitors of this enzyme to alter the clearance of ropinirole. Therefore, if therapy with a drug known to be a potent inducer or inhibitor of CYP1A2 is stopped or started during treatment with ropinirole, adjustment of the dose of ropinirole may be required.

Ropinirole as inhibitor of CYP isozymes:
In-vitro data in literature showed that ropinirole and its circulating metabolites do not inhibit most CYP450 enzymes in vitro (including 1A2, 2A6, 2C8, 2C9, 2C19, 2E1, and 3A) and have only a weak potential for inhibiting CYP2D6. Therefore, ropinirole was concluded as unlikely to affect the pharmacokinetics of other medicinal products via a CYP450 mechanism.

Ropinirole as inducer of CYP isozymes:
Some induction of CYP activity was observed in animals at a dose level much higher than the maximum clinical therapeutic dose (6 mg/day), which was considerably less than that of classic CYP inducers. However, information pertaining to induction potential of ropinirole for major CYPs in humans is not available. Following repeated doses of ropinirole, no changes in PK indicates a lack of CYP1A2 induction.

Drug interaction based on protein binding:
Plasma protein binding of ropinirole is low (10-40%) and independent of concentration. Drug interactions due to displacement of drug from plasma proteins, and alterations in the pharmacokinetics of ropinirole as a result of changes in binding proteins in disease states would, therefore, not be expected.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

In vitro studies indicate that CYP1A2 is the primary hepatic enzyme responsible for the extensive hepatic metabolism of ropinirole. Influence of genetic polymorphism for its role in ropinirole metabolism has not been evaluated.

2.4.2.3. Are there major drug-drug interactions and are dosage adjustments required?

In vivo drug interactions:
According to the approved IR label, no clinically relevant pharmacokinetic interactions have been observed with ropinirole, except that concomitant administration of a potent inhibitor of CYP1A2 (ciprofloxacin) led to higher systemic exposure of ropinirole (<2-fold). CYP1A2 is known to be induced by smoking and omeprazole, and inhibited by CYP1A2 inhibitors, such as fluvoxamine, mexiletine, and the older fluoroquinolones such as ciprofloxacin and norfloxacin. Cigarette smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking. In one study in patients with RLS, cigarette smokers had an approximate 30% lower Cmax and a 38% lower AUC of ropinirole than did nonsmokers, when those parameters were normalized for dose.

Co-administration of hormone replacement therapy (HRT) was identified as an influential covariate in the population PK analysis for ropinirole IR. There was a 33% decrease in CL/F in patients taking hormone replacement treatment (HRT).

There is no evidence of a pharmacokinetic interaction between ropinirole and other substrates of CYP1A2. Coadministration of theophylline with ropinirole did not alter the pharmacokinetics of ropinirole, and ropinirole did not alter the pharmacokinetics of theophylline.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No pertinent information is available as to whether ropinirole is a substrate and/or an inducer of P-glycoprotein. Available information regarding the lack of effect on the steady-state pharmacokinetics of digoxin (0.125 to 0.25 mg once daily) in 10 patients with

coadministration of ropinirole (2 mg 3 times daily) in the approved Requip IR label indicates the lack of inhibitory effect on P-glycoprotein by ropinirole in vivo. b(4)

[redacted]

2.4.2.5. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

According to the label, since ropinirole is a dopamine agonist, it is possible that dopamine antagonists such as neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide may diminish the effectiveness of ropinirole. Therefore, patients with a history or presence of major psychotic disorders should be treated with dopamine agonists only if the potential benefits outweigh the risks.

2.5. General Biopharmaceutics

The Biopharmaceutic program was designed to evaluate the relative bioavailability of proposed film-coated XL formulation to the IR tablets, the potential food effects (with the highest strength), potential dose-dumping in the presence of alcohol, and the dosage strength equivalence, with supporting data from IVIVC model and prediction and in vitro dissolution test.

2.5.1. What is the BCS classification of this drug?

According to the Sponsor, ropinirole can be considered as BCS Class 1 based on the following factors. However, this has not been evaluated in detail by the FDA.

- Ropinirole hydrochloride is highly soluble in water (133 mg/mL at 25°C)). [redacted] This meets the FDA "highly soluble" criteria whereby the highest tablet strength (8 mg XL) is soluble in 250 mL or less of aqueous media over the pH range of 1-7.5. b(4)
- The mass balance study showed [redacted] urinary recovery of drug related material following oral administration, suggesting near complete absorption which is close to the >90% FDA criteria for a high permeability drug. (FDA comment: %urinary recovery is [redacted] cut off. In addition, stability data in GI is not available).
- Ropinirole can be considered as fast dissolving since ropinirole IR releases [redacted] of drug over minutes. This is [redacted] than the FDA criteria of 85%, or more dissolving within 30 minutes.

In any case, BCS based waivers are not applicable to MR products.

2.5.2. What is the proposed formulation of the drug product?

Ropinirole XL 24-Hour tablets of all four strengths consist of 3-layer core in which the central, active-containing, slow-release layer is sandwiched between two [redacted] inactive barrier layers. Control of drug release from the formulation is achieved using b(4)

Geomatrix® technology developed by SkyePharma plc, London. The barrier layers, providing additional control over, serve to restrict the surface area available for release. The proposed formulation is designed to have approximately zero order in release and is released over a time period of approximately 24 hours.

During Phase 1 study (Study 161), the pharmacokinetics of three prototype formulations with different in vitro release profiles were evaluated. These three formulations (A705, A703 and A701) delivered greater than — release over 14, 16 and 20 hours, respectively, and the one with the slowest dissolution profile provided the desired *in vivo* PK profile and was selected for all subsequent studies. Tablets with uncoated round shape were used in early clinical studies (phase 1/2), however for late Phase 2 and subsequent pivotal studies, the tablet image was modified to the capsule shape proposed for the commercial product.

All proposed strengths are biconvex capsule-shaped tablets (approximately 12.6 mm x 6.9 mm). Different debossings and film coat colors are used to aid identification, as described below. Each biconvex film-coated tablet contains ropinirole hydrochloride equivalent to ropinirole 2, 3, 4, or 8 mg.

Table 12. Descriptions of proposed commercial Requip XL 24-Hour tablets

2 mg	Pink tablets debossed GS on the upper side and 3V2 on the lower side
3 mg	Purple tablets debossed GS on the upper side and TYH on the lower side
4 mg	Light brown tablets debossed GS on the upper side and WXG on the lower side
8 mg	Red tablets debossed GS on the upper side and 5CC on the lower side

The to-be-marketed (TBM) formulations of different strengths are proportionally similar in composition. The quantitative composition of the TBM ropinirole XL formulations is shown in Table 13. —

b(4)

Table 13. Composition of the to-be-marketed ropinirole XL 24-Hour tablets

Appears This Way
On Original

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								

b(4)

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								

b(4)

Comment:
The active moiety, ropinirole, and the inactive excipients are proportionally similar across different strengths. In vivo bioequivalence study is not necessary and demonstration of the similarity through in vitro dissolution profiles will be adequate to bridge different strengths. However, the sponsor has conducted steady state relative bioavailability and dosage strength equivalence studies to demonstrated BE between various strengths of XL tablets.

2.5.3. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

A relative bioavailability of the to-be-marketed formulations and those used in the clinical trials was not conducted and is not considered necessary for the following reasons: same manufacturing site and equipment, identical core composition, size and shape, with the exception of coating color and debossings.

2.5.4. What is the relative bioavailability of the proposed to-be-marketed formulation to the reference Requip IR Tablets?

The relative bioavailability of ropinirole XL formulation compared to that of ropinirole IR was evaluated in Study 162 in healthy subjects and in Study 164 in patients with Parkinson's disease.

Study 162:
The dose proportionality was assessed following single oral doses in healthy subjects over the dose range 0.75 to 3 mg ropinirole XL (0.75 and 3 mg XL od vs. 0.25 mg IR tid) in Study 162. Summaries of dose-normalized PK parameters and statistical analysis for exposure are presented in Tables 14 and 15.

Table 14. Dose-normalized geometric mean (CVb) of PK Parameters

Parameter (unit)	IR 3 x 0.25 mg (n = 33)	XL 0.75 mg (n = 30)
AUC(0-∞) (ng·h/mL)	7.59 (68.1)	6.87 (61.3)
Cmax (ng/mL)	0.51 (55.3)	0.34 (50.4)
Cmin (ng/mL)	0.15 (89.1)	0.14 (78.8)
DF	1.16 (38.3)	0.61 (66.0)
Tmax (h)	1.50 (0.5 – 4.0)	8.00 (3.0 – 16.0)
t½ (h)	4.23 (20.9)	4.92 (25.0)

Table 15. Statistical analysis for assessing the relative bioavailability of 0.75 mg of ropinirole XL od vs. IR 0.25 mg tid

Parameter	Comparison	Point Estimate	95% CI
AUC(0-∞)	XL 0.75mg : IR 0.75mg	0.958	(0.84, 1.10)
Cmax	XL 0.75mg : IR 0.75mg	0.693	(0.60, 0.80)

The AUC(0-∞) 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.

Study 164:
The steady-state relative bioavailability of the ropinirole XL formulations (8.0 mg od) was compared with that of steady-state IR tablets (2.5 mg IR tid or 7.5 mg/day) in patients with Parkinson's disease in Study 164. This was an open-label, randomized study conducted in two parts to investigate the relative bioavailability and the effects of food on proposed XL formulation. All patients had to have received a dose of 8 mg od ropinirole CR for at least 3 days. Mean dose normalized concentration-time profiles for ropinirole CR and IR are presented in Figure 10. Summaries of PK parameters and statistical analysis are presented in Tables 16 and 17.

Figure 10. Mean ropinirole plasma concentrations-time profiles (8-mg od CR vs. 7.5-mg IR (2.5 mg tid))

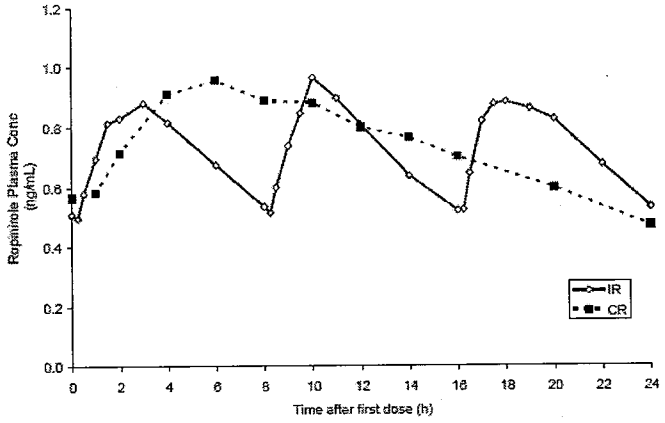


Table 16. Summary (geometric mean (CVb%)) of steady-state dose normalized (to 1 mg) PK parameters

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)	6.05 (3.98 -20.0)	11.0 (0.55 -19.0)
DF	0.70 (0.34 – 1.19)	0.79 (0.40 – 2.52)

Table 17. Summary of the statistical analysis for dose-normalized PK Parameters of ropinirole XL vs. IR

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

Statistical analysis of PK data from this study showed that on a dose-for-dose basis the AUC(0-24) and Cmin of ropinirole XL at steady state were similar to that of ropinirole IR, whereas Cmax was ~12% lower compared with that of ropinirole IR.

For ratios of dose-normalized AUC(0-24) and Cmin between 8 mg XL and 2.5 mg IR tid, point estimates and 90% CIs indicate that equivalence was established based on the 80-125% BE range. The 90% CI for Cmax ratio fell slightly outside of the lower BE limit, however, this reviewer agrees that the difference is unlikely to be clinically significant.

2.5.5. What data support or do not support a waiver of in vivo BE study for the lower strengths of the TBM formulation?

A biowaiver of in vivo BE study for lower strength of the TBM formulation is not necessary because the Sponsor has evaluated and demonstrated BE or dose proportionality using all available strengths. Otherwise, supporting evidence for a biowaiver can be obtained from the following:

- Same film-coated tablet dosage form for all TBM strengths with proportionally similar active and inactive ingredients between different strengths
- All strengths have been used in PK and clinical trials.
- All strengths have the same release mechanism.
- Similar dissolution profiles of all strengths of TBM tablets in multiple pH media
- The kinetics of ropinirole from XL formulations appear to be linear and approximately dose-proportional over the dose range studied. In addition, the linearity has been shown previously for the IR tablets in PD patients up to 8 mg tid.

2.5.6. What is the relative bioavailability of the ropinirole from XL tablets among various dosage strengths?

The dosage strength equivalence was investigated in both patients (Study 165) and in healthy subjects (Study 219). See Section 2.2.5.8 for additional study information.

Study 165:
The dosage strength equivalence of 1 x 8.0 mg (Regimen D) vs. 4 x 2.0 mg (Regimen E) ropinirole XL tablets was examined at steady-state in patients with Parkinson's disease because of the concern for safety and the need for dose titration. Median steady state ropinirole plasma concentration-time profiles following administration of the 1 x 8 mg and the 4 x 2 mg tablets are presented in Figure 11. Summaries of the geometric mean (CVb%) PK parameters and results of the statistical analysis are presented in Tables 18 and 19.

Figure 11. Median ropinirole plasma concentration–time profiles following multiple dose administration of 1 x 8mg and 4 x 2 mg ropinirole XL

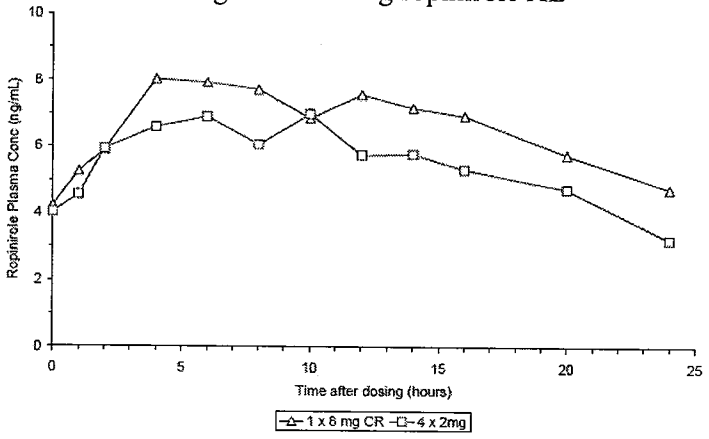


Table 18. Summary of steady-state ropinirole pharmacokinetic parameters (geometric mean (CVb%)) following administration of 1 x 8.0 mg or 4 x 2.0 mg XL tablets

XL Regimen	AUC(0-24) (ng·h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax (h)
1 x 8.0 mg	168 (69.1)	9.30 (67.2)	4.74 (88.0)	6.00 (2.00 - 20.0)
4 x 2.0 mg	152 (56.8)	8.50 (49.2)	4.49 (66.1)	10.0 (2.00 - 20.0)

Data include outlier

Table 19. Summary of statistical analyses of ropinirole XL PK parameters

Parameter	**Comparison**	**Ratio**	**90% CI**	**CVw%**
AUC(0-24) (ng·h/mL)	1 x 8.0 mg: 4 x 2.0 mg	1.10 1.05[a]	(0.95, 1.26) (0.93, 1.18)[a]	27.5 22.2[a]
Cmax (ng/mL)	1 x 8.0 mg: 4 x 2.0 mg	1.09 1.03[a]	(0.93, 1.27) (0.90, 1.18)[a]	31.1 25.4[a]
Cmin (ng/mL)	1 x 8.0 mg: 4 x 2.0 mg	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

When including data of an outlier, 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. After excluding the outlier, dosage strength equivalence of ropinirole 1 x 8 mg vs. 4 x 2 mg XL formulations was demonstrated in patients with Parkinson's disease, since the 90% CIs for AUC(0-24), Cmax, and Cmin were all completely contained within the range of 0.80-1.25.

Study 219:
The dosage strength equivalence of 2 x 1.0 mg (Regimen B) vs. 1 x 2.0 mg (Regimen C) ropinirole XL and 3 x 1.0 mg (Regimen D) vs. 1 x 3.0 mg (Regimen E) ropinirole XL were examined following single oral doses of ropinirole XL tablets in healthy subjects as part of 5-way cross-over study design.

Mean ropinirole plasma concentration-time profiles by regimens are presented in Figure 11. Summaries of the geometric mean (CVb%) PK parameters and results of the statistical analysis are presented in Tables 20 and 21.

Figure 11. Mean ropinirole plasma concentration–time profiles following multiple dose administration of 1 x 8mg and 4 x 2 mg ropinirole XL

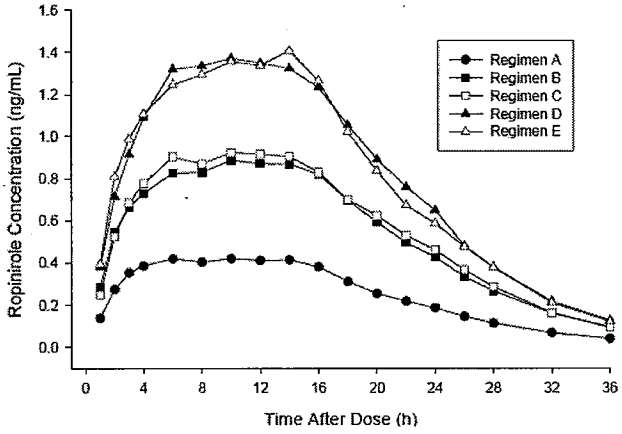


Table 20. Summary of ropinirole PK parameters (geometric mean (CVb%))

Regimen	**2 x 1mg (B)**	**1 x 2mg (C)**	**3 x 1mg (D)**	**1 x 3mg (E)**
N	33	33	33	31
AUC(0-∞)[1] (ng.hr/mL)	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)	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)	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)	0.996 (0.477-2.17)	1.07 (0.562-2.03)	1.49 (0.760-3.04)	1.58 (0.691-2.83)
Tmax (h)	10.0 (3.00-18.0)	10.0 (3.00-24.0)	10.0 (4.00-18.0)	12.0 (3.00-26.0)
t½ (h)	4.74 (3.35-7.26)	4.69 (2.79-8.32),	4.67 (3.01-7.89)	4.71 (3.42-6.76)

Table 21. Summary of statistical analyses of ropinirole XL PK parameters

Parameter (unit)	Comparison	Ratio	90% CI
AUC(0-∞) (ng.hr/mL)	2 x 1.0 mg : 1 x 2.0 mg	1.01	(0.92, 1.11)
	3 x 1.0 mg : 1 x 3.0 mg	0.99	(0.90, 1.08)
AUC(0-t) (ng.hr/mL)	2 x 1.0 mg : 1 x 2.0 mg	0.97	(0.89, 1.06)
	3 x 1.0 mg : 1 x 3.0 mg	1.01	(0.92, 1.10)
Cmax (ng/mL)	2 x 1.0 mg : 1 x 2.0 mg	0.94	(0.87, 1.03)
	3 x 1.0 mg : 1 x 3.0 mg	0.94	(0.86, 1.02)

Since 90% CIs for AUC(0-∞), AUC(0-t) and Cmax for the comparisons were contained within the BE range (0.80, 1.25), dosage strength equivalence was demonstrated for ropinirole XL up to 3 mg strength in healthy subjects.

2.5.7. What is the effect of food on the bioavailability (BA) of the drug from the Requip XL tablet and what dosing recommendation should be made, if any? Does food affect the bioavailability of Requip XL tablet formulation?

The food effect was evaluated both in healthy subjects (Study 161) and in patients (Study 164)

Study 161:
This was a study designed to select an appropriate test formulation to bring forth to the clinical development (Part I) and investigate the effect of high-fat food on the selected single-dose 0.75-mg Tablet C (Part II). Summary of statistical analysis for ropinirole PK parameters for investigating the food effect on selected test formulation is presented in Table 22.

Table 22. Summary of statistical analysis for ropinirole PK parameters for investigating the food effect following single dose of Tablet C in healthy subjects

Parameter	Geometric mean (CVb%)		Fed : Fasted	95% CI
	Fasted (n = 14)	Fed (n=13)		
AUC(0-∞) (ng.h/mL)	5.95 (46.7%)	7.86 (47.0%)	1.30	(1.06, 1.60)
Cmax (ng/mL)	0.280 (50.7%)	0.414 (49.8%)	1.44	(1.24, 1.68)

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

Study 164:
This was an open-label, randomized study conducted to evaluate the definitive food effect on the PK of ropinirole following multiple doses of 8-mg XL tablets in patients in Part B of the study. Patients received a single steady-state dose of ropinirole 8.0 mg XL in either the fed or fasted state, and repeated the study after crossing over to the alternate state after a 3-days period between treatments.

Mean ropinirole plasma concentration-time profiles by regimens are presented in Figure 13. Summaries of the geometric mean (CVb%) PK parameters and results of the statistical analysis are presented in Tables 23 and 24.

Figure 13. Mean ropinirole plasma concentration–time profiles following steady-state dose 1 x 8 mg ropinirole XL

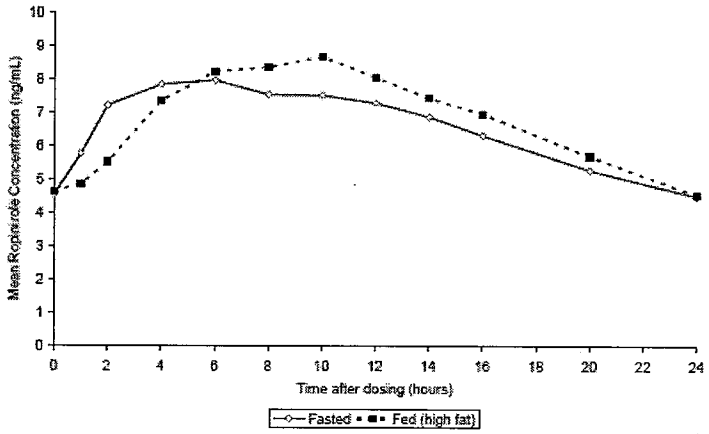


Table 23. Summary of ropinirole PK parameters (geometric mean (CVb%))

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)	7.59 (6.01 - 9.58)
Cmin (ng/mL)	3.77 (2.72 - 5.24)	3.94 (3.03 - 5.11)
Tmax (hours)	10.00 (4.00 - 14.00)	6.00 (2.00 - 14.00)
DF	0.74 (0.28 - 1.72)	0.58 (0.27 - 1.46)

Table 24. Summary of statistical analyses of ropinirole XL PK parameters

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)	

- 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 XL at 1 x 8 mg appeared to be prolonged, as reflected by median prolonged Tmax by 2 hours, following a high fat breakfast compared to fasted state. The extents 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 in this study because of food.

Reviewer's comments:

- 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

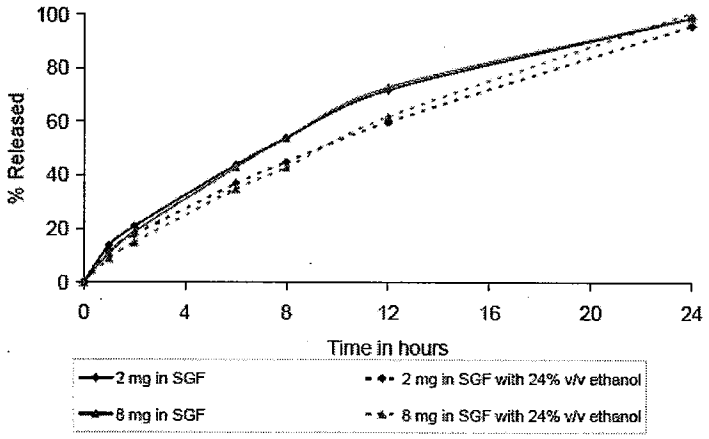
marketed. The definitive food effect was studied at steady-state of the highest 8-mg/day dose level, instead of on a single 8-mg dose. The study design is considered acceptable in view of the tolerability reasons and the up-titration dosing regimen.

- 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.

2.5.8. What is the effect of ethanol on the bioavailability (BA) of the drug from the Requip XL tablet? Is there concern for potential dose-dumping in the presence of alcohol?

The Sponsor investigated the potential for dosing dumping using simulated gastric fluid (SGF) containing 24% v/v ethanol as dissolution medium, with the highest 8-mg and the lowest 2-mg strengths. Data generated in Simulated Gastric Fluid (SGF) with pepsin both with ethanol (24 % v/v) and without ethanol. As shown in the Figure 14 below, slightly slower release is observed in the presence of 24% ethanol, which could be attributed to the lower solubility of ropinirole in ethanol ——— than in aqueous media (133 mg/mL). b(4)

Figure 14. Dissolution of ropinirole XL tablets 2 and 8 mg in SGF with and without alcohol



Reviewer comment:
Results indicate that the formulation is resistant to dose dumping under the test conditions. Even though pepsin was used in the testing, since no increases in dissolution was observed these results are acceptable.

2.5.9. Was an IVIVC established for this extended-release formulation?

Yes. However, the external validation was inconclusive for the highest 8-mg strength. Since the model development, and internal and external validations for ropinirole XL 24-Hour have been previously reviewed in detail for ——— Requip CR for RLS). Details of the review for IVIVC are also available in Individual Study Review in Section 4.2, so only pertinent comments will be provide below. b(4)

IVIVC model development:

The Sponsor developed a Level A in vitro-in vivo correlation (IVIVC) model based on three ropinirole controlled release formulations (XL 24-Hour) of fast, standard, and slow release characters developed for Parkinson's disease. However, the mean dissolution data of fast vs. standard release and of standard vs. slow release pass the f2 test for similarity (calculated by this reviewer), and only the fast vs. slow release profiles differed from each other. Based on the Agency's Guidance that IVIVC model should be developed using a minimum of two formulations with different release characteristics. Since at least two formulations (the fastest and the slowest) showed different release characteristics based on similarity testing (f2), the sponsor's approach for the establishment of the IVIVC model is acceptable and can be used to predict in vivo concentration-time profile of ropinirole XL based on in vivo dissolution data.

Internal validation for IVIVC model:
The IVIVC model was developed and internally validated using the PK data from Part I of the Study 161. Results of the internal validation for the IVIVC model is presented in Table 25. For AUC, the absolute %PE values were no greater than 13.31% for the XL Slow (A701) formulation and the MAPPE was 5.14 %. For Cmax, the absolute %PE values were no greater than 11.79 % for the XL Standard (A703) formulation and the MAPPE was 4.84 %. All the prediction errors fell within the acceptance criteria (MAPPE <10%) for internal validation of an IVIVC according to the Agency's Guidance.

Table 25. Internal validation statistics for the deconvolution-based IVIVC model

Treatment	C_{max} (ng/mL)				AUC_{0-last} (ng·h/mL)			
	Obs.	Pred.	Ratio	|%PE|	Obs.	Pred.	Ratio	|%PE|
CR Fast (A705)	0.397	0.392	0.988	1.216	6.997	7.128	1.019	1.883
CR Standard (A703)	0.364	0.321	0.882	11.786	7.254	7.271	1.002	0.226
CR Slow (A701)	0.280	0.275	0.985	1.511	6.249	7.081	1.133	13.311
MAPPE				4.838				5.140

External validation for IVIVC model:
External validation on the IVIVC was performed using data from Study 162 and Study 164. Results of the external validation for the IVIVC model is presented in Table 26. Per the Agency's Guidance, results of the external validation (i.e., %PE) indicate that external predictability of the established IVIVC model was valid up to 3 mg. However, results suggest that the external validation was inconclusive for 8 mg strength (i.e., absolute %PE values >10% for Cmax and AUC)

Table 26. External validation statistics for the deconvolution-based mean IVIVC model: Study 162 (0.75 mg, 3 mg) and Study 164 (8 mg).

Treatment	C_{max} (ng/mL)				AUC_{0-last} (ng·h/mL)			
	Obs.	Pred.	Ratio	|%PE|	Obs.	Pred.	Ratio	|%PE|
CR A701 (0.75 mg)	0.343	0.326	0.951	4.90	7.49	8.22	1.10	9.78
CR B581 (3 mg)	1.36	1.27	.938	6.23	29.9	33.1	1.11	10.6
CR N02045 (8.0 mg)[a]	7.98	6.67	0.836	16.4	158	135	0.856	14.4

[a] Administered at fasted condition

Reviewer comment:
Since external predictability is inconclusive for 8 mg, we recommend additional evaluation of predictability with other strengths and data sets and submitted prior to full application of this IVIVC for biowaiver. The sponsor is using study specific UIR. While acceptable for this development and predictability, the sponsor should come up with reasonable estimates of UIR that can be used for future biowaiver.

2.5.10. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The proposed dissolution method is acceptable but not ideal, more specifically, a lower paddle speed of 50 rpm is preferred. The proposed dissolution specifications are acceptable.

In vitro dissolution test for the ropinirole XL tablets is performed using dissolution USP Apparatus 2 with paddles. Test medium is a citrate buffer solution, 500 mL, at a pH value of 4.0. Rotation speed is 100 rpm. The same dissolution medium and methods were also used for the approved Requip Tablets (IR). The range of in vitro specifications proposed by the Sponsor is defined as follows: [redacted] for mean release data at 2, 12 and 24 hours, respectively. Proposed dissolution method and specifications proposed by the sponsor for ropinirole XL tablets of available strengths, as well as justifications and dissolution results, are shown as follows:

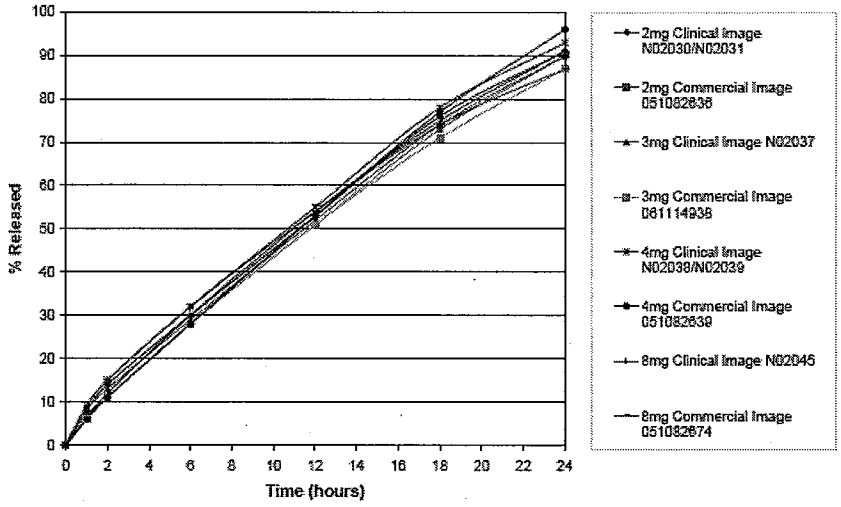
Apparatus:	USP Apparatus II (paddles)
Speed:	100 rpm
Medium:	pH 4.0 Citrate Buffer
Volume:	500 mL
Temperature:	37 ± 0.5 °C
Specifications:	

Time	% Dissolved
2 hour	
12 hours	
24 hours	

Justification for Dissolution Specifications:
The same dissolution medium was also used for Requip IR Tablets. The same method was used for routine testing and for development of IVIVC model developed for Ropinirole XL-24 Hour Tablets (for Parkinson's disease). The proposed dissolution method utilizes USP Apparatus II (paddles) at a speed of 100 rpm with pH 4 citrate buffer as the medium.

These specifications for in vitro dissolution were proposed based on dissolution profiles, as shown in Figure below, from clinical and commercial batches of ropinirole XL tablets of 2, 3, 4, and 8 mg strengths. Results demonstrate that in vitro release is consistent across tablet strengths in various media.

Figure 15. Mean dissolution profiles for clinical and commercial batches of ropinirole XL Tablets of all strengths



Effects of dissolution media:

Dissolution testing was conducted in media covering a range of physiologically relevant pH values, including 0.1 M hydrochloric acid, pH 6.8 citrate buffer (for 2 mg and 8 mg strengths only) and pH 7.5 citrate buffer. Dissolution profiles of different strengths in various media, as shown in Figures below, appear to be generally similar, though with slightly faster release at 0.1M HCl due to slightly impaired gelling of hypromellose in acidic media.

Figure 16. Dissolution of ropinirole XL tablets 2, 3, 4 and 8 mg in 0.1M HCl

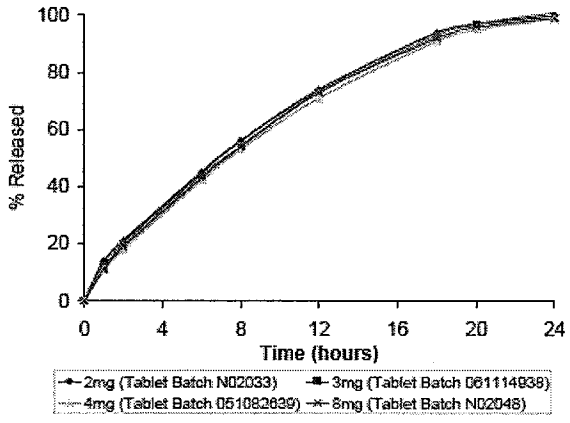


Figure 17. Dissolution of ropinirole XL tablets 2 and 8 mg in pH 6.8 citrate buffer

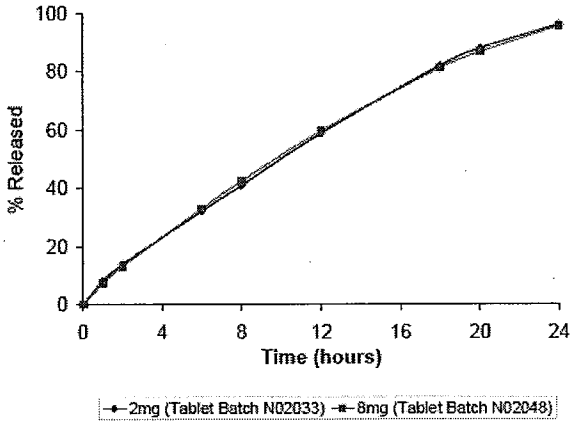
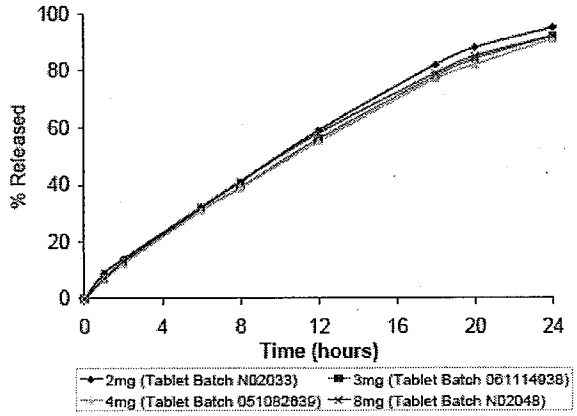


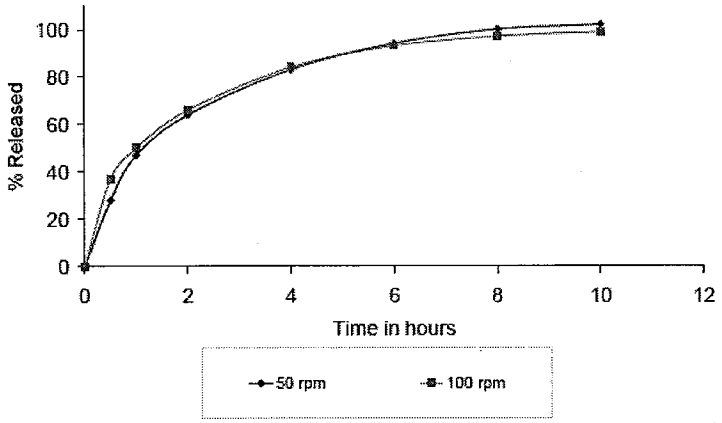
Figure 18. Dissolution of ropinirole XL tablets 2 and 8 mg in pH 7.5 citrate buffer



Effects of paddle speed:
The impact of paddle rotation speed (50, 100 and 150 rpm) has been evaluated for ropinirole XL tablets with the highest 8-mg strength in pH4 citrate buffer. As shown in the figure below, all paddle speeds tested generated similar dissolution profiles, indicating the lack of significant effect of paddle speed over the range covered on the in-vitro dissolution profile of XL tablets. Based on this result the Sponsor selected the 100 rpm paddle speed.

As provided in this submission, a paddle speed of 50 rpm, as selected for the IR tablets, was originally utilized. However, the paddle speed for the ropinirole XL was increased to 100 rpm, since the Sponsor considered that the formulation was sufficiently challenged at this speed to ensure that the tablet matrix system is adequately performing to provide controlled release of the drug.

Figure 19. Effect of paddle speed on drug release from 8 mg ropinirole XL tablets (batch 051082674)



Comment:
The justification of the choice of speed seems reasonable. However, from a regulatory perspective, the slower 50 rpm is preferred as the choice of paddle speed and should be used in future drug development programs.

2.6. Analytical Section

b(4)

The bioanalytical methods have been employed for analysis for ropinirole for approved Requip IR (NDA 20-658), and has been reviewed in detail as part of ——— submission for Ropinirole CR for RLS. The OCP finds the bioanalytical methods adequate and justified.

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Concentrations of ropinirole and its two metabolites, SKF-89124 and SFK-104557, in human plasma were analyzed using a validated ——— b(4)
——— and high performance liquid chromatography (HPLC) is performed using a ——— Extracts are analyzed by tandem mass spectrometry using an ———
Sample analyses were conducted by ———

2.6.2. Which metabolites have been selected for analysis and why?

Both SKF-89124 and SFK-104557 were analyzed because they are the major circulating metabolites of ropinirole, even though neither contributes significantly to the pharmacological activity of ropinirole.

2.6.3. Is free, bound, or total of the moieties measured?

The total drug was measured for ropinirole (and its metabolites) and the method is considered appropriate since ropinirole is only 40% plasma protein bound.

2.6.4. What bioanalytical methods are used to assess drug concentrations and are they validated and acceptable?

Summaries of the bioanalytical validation using high performance liquid chromatography – mass spectrometry/mass spectrometry (HPLC-MS/MS) method are provided in the following tables:

Table 27. Summary of ———— analytical method (SKF-101468/ ———— b(4)

Parameter	Ropinirole	SKF-89124	SKF-104557
Method	LC/MS/MS		
LLOQ	20 pg/mL	20 pg/mL	50 pg/mL
Linear range	20 – 5000 pg/mL	20 – 5000 pg/mL	50 – 5000 pg/mL
QC samples	20, 50, 1000, 5000 pg/mL	20, 50, 1000, 5000 pg/mL	50, 100, 1000, 5000 pg/mL
Inter-day accuracy Inter-day precision	-4.7% ~ -0.92% ≤ 6.6%	-1.5% ~ 3.9% ≤ 9.7%	-4.7% ~ -0.9% ≤ 7.6%
Intra-day accuracy Intra-day precision	-7.4% ~ 2.3% ≤ 9.1%	-6.8% ~ 9.9% ≤ 10.6%	-10.6% ~ 4.7% ≤ 9.6%
Recovery	~95% (at 50, 1000 and 5000 pg/mL)	~85% (at 50, 1000 and 5000 pg/mL)	~95% (at 100, 1000 and 5000 pg/mL)

Table 28. Summary of the short-term and long-term stability data for ropinirole

Parameter	Results
Freeze-thaw stability	At least 3 Freeze/thaw cycles at -20°C
Plasma extract stability	At least 3 days at 4°C
Short term stability in plasma	At least 4 hours at room temperature
Long-term stability in plasma	At least 507 days at -20°C
Stability in whole blood	At least 5 hours at room temperature (followed by centrifugation at 4°C or room temperature)
Short term stability in plasma	At least 24 hours at room temperature

The sponsor provided data for within-study analytical performance. The summarized precision and accuracy results for QC samples used in each of the clinical studies to assess the day-to-day performance of the method and provide concurrent storage stability of the analyte in human plasma are listed in Table 26.

Table 26. Between-run accuracy and precision of study quality control samples

Protocol	Analyte	Number	Precision (%CV) (≤)	Accuracy (%bias, range)
101468/161	Ropinirole	38	3.5	-0.25 to 2.0
	SKF-89124	38	8.2	0.25 to 3.0
	SKF-104557	38	4.9	-1.75 to 0

101468/162	Ropinirole SKF-89124 SKF-104557	99 99 99	5.0 11.1 5.8	-0.8 to 1.6 0.1 to 2.3 -1.1 to 2.0
101468/163	Ropinirole SKF-89124 SKF-104557	48 48 48	4.6 8.7 11.1	-3.1 to 0.9 -1.5 to 4.1 0.3 to 3.3
101468/164	Ropinirole SKF-89124 SKF-104557	72 72 75	6.0 11.3 9.9	-0.3 to 2.9 2.8 to 6.5 -1.2 to 0.1
101468/165	Ropinirole SKF-89124 SKF-104557	34 32 34	4.8 10.3 12.5	-6.0 to -0.3 -6.6 to 1.4 -4.2 to 0.4
101468/168	Ropinirole SKF-89124 SKF-104557	54 54 54	8.1 9.7 7.4	5.6 to 9.2 -2.2 to 6.4 -2.2 to 5.1
101468/169	Ropinirole SKF-89124 SKF-104557	34 36 34	7.6 8.8 6.8	3.8 to 6.9 -2.7 to 5.0 -1.7 to 2.0
101468/219	Ropinirole SKF-89124 SKF-104557	102 98 101	5.4 6.6 5.2	-2.5 to 0.8 -5.1 to 4.8 -4.3 to 4.9

3. DETAILED LABELING RECOMMENDATIONS

Office of Clinical Pharmacology has reviewed the proposed labeling for Requip® XL 24-Hour tablet for Parkinson's disease and found it acceptable provided that revision is made to the labeling language.

Labeling recommendation to be sent to the Sponsor:
The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~strikethrough~~ is recommendation for deletion from the perspective of OCP.

4. APPENDICES

4.1. Package Insert (proposed and annotated with agency recommendation)

26 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio-2

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

Note: The "CR" in individual study review section, as denoted in the current submission by the sponsor, is referred to the "XL 24-Hour" for the proposed indication.

Study SK&F-101468/161

A single dose study to compare the pharmacokinetics of ropinirole from three controlled release (CR) test formulations with the immediate release (IR) reference formulation in healthy male volunteers and to assess the influence of food and domperidone on one of the test formulations

Principal Investigator: [redacted]

b(4)

Study Center: [redacted]

Study Period: 12 January 2000 - 20 March 2000

Objectives:

Part I:

- Primary: To compare the pharmacokinetic profile of ropinirole from each test formulation and the reference formulation
- Secondary: (1) To compare the tolerability of ropinirole from the test formulations and the reference formulation; (2) To compare the extent of metabolite formation from each test formulation with the reference formulation

Part II:

- Primary: (1) To assess the effect of domperidone on the pharmacokinetic profile of the selected test formulation; (2) To assess the influence of food on the selected test formulation
- Secondary: To assess the extent of metabolite formation from the test formulation

Study Design:

This was an open-label study in 16 healthy, non-smoking, non-vegetarian males, aged 30-50 years and weighed > 50 kg, who were eligible to be enrolled in the study. Treatment administration is shown in the following table (Table 1):

Treatment	Product	Batch no.
1	Ropinirole 0.25 mg Tiltab IR tablet (three consecutive doses at 8-hour intervals)	N98217
2	Ropinirole Geomatrix® 0.75 mg tablet A	A705
3	Ropinirole Geomatrix® 0.75 mg tablet B	A703

4	Ropinirole Geomatrix® 0.75 mg tablet C	A701
5	Ropinirole Geomatrix 0.75 mg tablet C with domperidone (Motilium®, batch no. 199281, three consecutive doses of two 10mg tablets at 8-hour intervals)	A701
6	Ropinirole Geomatrix 0.75 mg tablet C administered with food	A701

Part I: (Study Periods 1 - 4) randomized, 4-way, crossover, single oral CR doses and IR t.i.d.

Subjects were randomly administered three consecutive 0.25mg ropinirole Tiltab immediate release (IR) tablets at 8-h intervals (reference) or a single dose of 0.75mg of one of three controlled release (CR) test formulations (tablets A, B or C) during study periods 1 to 4. Treatments were separated by a washout period of 7 days. At the end of Part I, ropinirole pharmacokinetics and tolerability were analyzed in order to select a CR test formulation for Part II. Part I and Part II were separated by a wash-out of 14 days.

Part II: (Study Periods 5 and 6) non-randomized, single oral CR doses in presence of domperidone or food.

Subjects in Study Period 5 were given the selected 0.75mg test CR formulation, i.e., tablet C, and three consecutive doses of two 10mg tablets of domperidone at 8-h intervals (1 hour before the selected CR formulation, and 7 and 15h thereafter). In study period 6, subjects received tablet C at 30 min after the start of a high-fat breakfast. Subjects remained in-house from the evening before each dosing until 36h after dosing during all 6 study periods. Before each dosing, subjects were required to have fasted for at least 10h except for period 6.

None of the subjects had any prior or concomitant medication before starting this study or concomitant medication for the duration of this study.

Safety Assessments:

Safety assessments included Medical History, physical examination, vital signs (supine and standing blood pressure and heart rate), clinical chemistry, haematology and urinalysis, AE monitoring, and 12-lead ECG (at pre-dose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 22, 24, 26 and 32 h after each test formulation and 1, 2, 4, 6, 8, 9, 10, 12, 14, 16, 17, 18, 20, 22, 24, 25, 26, 28, 30, 32 and 36 h after the morning dose of the reference formulation).

Pharmacokinetics Assessments:

Blood samples for plasma concentrations of ropinirole and its two metabolites (SKF 104557 and SKF 89124) were collected from each subject at pre-dose, 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 36h after the morning dose of the reference formulation (Study Periods 1-4 only) and pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 32 and 36h after dosing of the CR formulations.

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). A batch of QC (n=6) was analyzed each day of the assay with the biological samples collected during the study. 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.

b(4)

Table 2. Assay validation for Study SK&F-101468/161

			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:	0.93~3.21 %	2.73~7.19 %	1.95~4.58 %
		Accuracy:	-1.40~2.60 %	-4.8~4.6 %	-2.40~1.6 %
	Linearity:		$r^2 = 0.9993$	$r^2 = 0.9959$	$r^2 = 0.9984$
LOQ	LLOQ:		20 pg/mL	20 pg/mL	50 pg/mL
QC	Low:		50 pg/mL	50 pg/mL	100 pg/mL
		Precision:	3.53 %	5.97 %	4.94 %
		Accuracy:	0.80 %	3.60 %	0.00 %
	Med:		1000 pg/mL	1000 pg/mL	1000 pg/mL
		Precision:	1.75 %	6.39 %	3.92 %
		Accuracy:	-2.00 %	1.00 %	-0.90 %
	High:		4000 pg/mL	4000 pg/mL	4000 pg/mL
		Precision:	1.74 %	5.51 %	2.25 %
		Accuracy:	-0.25 %	0.25 %	-1.75 %

Reviewer comment:
The same bioanalytical methods have been reviewed in ——— submission for Ropinirole CR-RLS and were found acceptable. Inter-day and intra-day accuracy and precision were <10%.

Pharmacokinetic Analysis:
The following pharmacokinetic parameters for ropinirole were estimated by standard non-compartmental methods:
Part I:

- Primary: AUC(0-∞) for ropinirole.

- Secondary: Degree of fluctuation [(Cmax-Cmin)/Cavg], Cmax and Cmin for ropinirole.
- Tertiary: tmax, Frel (test vs. ref), kel and t1/2 for ropinirole and metabolite/parent AUC(0-t) ratio for both metabolites

Part II:

- Primary: AUC(0-∞) and Cmax for ropinirole.
- Secondary: Degree of fluctuation [(Cmax-Cmin)/Cavg], Cmax and Cmin, tmax, kel and t1/2 for ropinirole and metabolite/parent AUC0-t ratio for both metabolites

For Part I, ropinirole AUC(0-∞), Cmax, Cmin and degree of fluctuation, analyzed by ANOVA, for the 3 CR formulations vs. reference formulation were examined. For Part II, the ratios for ropinirole Cmax and AUC(0-∞), analyzed by ANOVA, for the selected CR formulation from Part I with and without domperidone and the selected CR formulation with food vs. fasted CR formulation were examined. Point estimates and 95% confidence intervals (CI) for the geometric mean differences between test and reference regimens were evaluated.

Note: Due to the low ropinirole dose (i.e., 0.75 mg) used in this study, plasma concentrations of the metabolite SKF 89124 were below limit of quantification (<20 pg/mL) for most time points and thus no PK and/or statistical analyses were therefore performed.

RESULTS

Demographics of Subjects: (Table 3)

		All Subjects (N=16)
Race, n (%)	Caucasian	16 (100)
Sex, n (%)	Male	16 (100)
Age, years	Mean (Range)	37.3 (31.0-49.0)
Weight (kg)	Mean (Range)	71.3 (60.0-81.8)
Height (cm)	Mean (Range)	177 (167-187)
BMI (kg/m2)	Mean (Range)	22.9 (19.5-26.6)

All 16 subjects dosed were evaluable for safety, with 13~15 subjects being available for different PK evaluations. Subjects # 02, 11 and 13 withdrew from study, did not participate in Part II of the study, and therefore were not included in the statistical analyses (except for tablet A vs. IR reference).

Pharmacokinetic Summary:

The mean plasma ropinirole concentration-time profiles for all treatments are shown in Figure 1. The summary of pharmacokinetic parameters and statistics for Part I of the

Parameter unit	Reference	Tablet A	Tablet B	Tablet C
$AUC_{(0-\infty)}$ ng*h/mL				
N	14	15	13	14
Geometric Mean	6.82	6.46	6.74	5.95
CV_b (%)	50.0	51.9	52.3	46.7
Comparison:		Tablet	Tablet	Tablet
Point Estimate		A/Reference	B/Reference	C/Reference
		0.954	0.996	0.881
95% C.I.		(0.84, 1.09)	(0.87, 1.14)	(0.77, 1.01)
DF (Degree of Fluctuation) [1]				
N	14	15	13	14
Geometric Mean	1.29	1.04	0.835	0.516
CV_b (%)	33.8	29.9	47.9	62.0
Comparison:		Tablet	Tablet	Tablet
Point Estimate		A/Reference	B/Reference	C/Reference
		0.794	0.660	0.430
95% C.I.		(0.61, 1.03)	(0.51, 0.86)	(0.33, 0.56)
C_{max} [2] ng/mL				
N	14	15	13	14
Geometric Mean	0.483	0.389	0.374	0.280
CV_b (%)	40.0	48.3	51.9	50.7
Comparison:		Tablet	Tablet	Tablet
Point Estimate		A/Reference	B/Reference	C/Reference
		0.807	0.789	0.599
95% C.I.		(0.73, 0.89)	(0.71, 0.87)	(0.54, 0.66)
C_{min} [3] ng/mL				
N	14	15	13	14
Geometric Mean	0.111	0.100	0.115	0.130
CV_b (%)	58.6	62.6	85.0	60.3
Comparison:		Tablet	Tablet	Tablet
Point Estimate		A/Reference	B/Reference	C/Reference
		0.925	1.02	1.11
95% C.I.		(0.70, 1.22)	(0.76, 1.35)	(0.84, 1.48)

Note: For the reference formulation the highest of the three Cmax values is used. For the reference formulation the lowest of the three Cmin values is used.

Reference = Ropinirole Tiltab 0.25 mg tablet t.i.d

Tablet A = Ropinirole Geomatrix 0.75 mg

Tablet B = Ropinirole Geomatrix 0.75 mg

Tablet C = Ropinirole Geomatrix 0.75 mg

Note: Point estimate and 95% C.I. are derived from ANOVA

Table 5. Summary of ropinirole tertiary PK parameters (Part I)

study are shown in Tables 4-5. The summary of pharmacokinetic parameters and statistics for Part II of the study are shown in Tables 6-7.

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

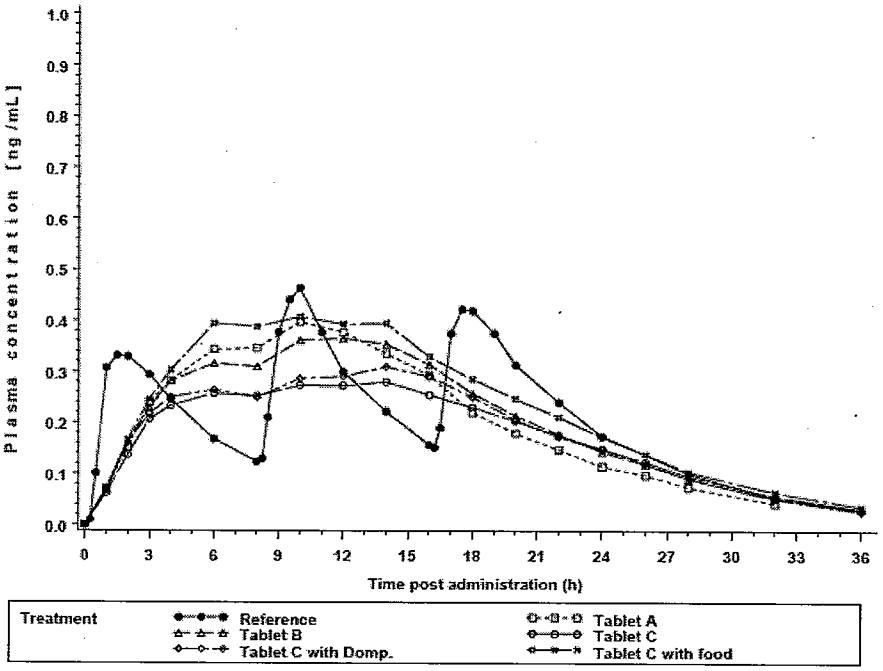


Table 4. Summary of ropinirole primary and secondary PK parameters (Part I)

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