

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-421**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

Pramipexole Dihydrochloride

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

NDA:	22-421	Submission Date(s): October 23, 2008
Generic Name:	Pramipexole Dihydrochloride	
Brand Name:	Mirapex® ER™ Tablets	
Sponsor:	Boehringer Ingelheim	
Dosage Strengths:	Extended Release Tablets (0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, and 4.5 mg)	
Indication:	Treatment of Parkinson's Disease	
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**I. EXECUTIVE SUMMARY**

Boehringer Ingelheim is seeking approval for Mirapex® 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, and 4.5 mg extended-release tablets [ER] for the treatment of adult patients with idiopathic Parkinson's disease. The ER tablet is designed to be administered once a day and offers an alternative formulation to the approved Mirapex® IR tablet (NDA 20-667) currently marketed by the sponsor in the US. All relevant non-clinical and clinical safety and efficacy data for the approved IR tablet will be incorporated by reference. In support of the Clinical Pharmacology portion of the application, the Sponsor has included four BA/BE studies:

1. A pilot study [Study 248.529] which evaluated PK profiles of prototype formulations
2. A relative bioavailability study [Study 248.530] in healthy Caucasian male subjects with an uptitration period of increasing doses (0.375 to 4.5 mg qd) of pramipexole ER q.d which evaluated the dose-proportionality, the relative bioavailability of the ER tablet relative to the IR formulation and food effect
3. A relative bioavailability study [Study 248.607] with multiple ascending doses (0.375 to 1.5 mg qd) which evaluated the dose-proportionality and relative bioavailability of the ER tablet compared to the IR formulation in healthy Japanese males.
4. A single dose study [Study 248.560] in healthy subjects which examined the possibility of an in vitro/in vivo correlation and food effect.
5. An in vitro study to determine the effect of alcohol on the release of pramipexole from the extended release tablet.

The sponsor also submitted three additional studies:

1. A pharmacokinetic and tolerability study [Study M/2730/0060] in renally impaired subjects
2. A population PK study [Study 248.524]
3. A multiple dose study [248.545] which thoroughly evaluated QT/QTc of the highest ER dose(4.5 mg qd)

The results of the population PK will be discussed and the review is attached [Pop PK]

**1.1 Recommendation**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 has reviewed the information submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 22-421 and finds the data acceptable. OCP supports the approval of the Pramipexole ER 0.375, 0.75 mg, 1.5 mg, 3.0 mg, and 4.5 mg tablets provided an agreement can be made regarding changes in the proposed labeling [Shown by track changes in Attachment VI] including the recommendation that patients with moderate renal impairment (a creatinine clearance between 30 and 50 mL/min) (b) (4)

**1.2 Phase IV Commitments**

There are no Phase IV commitments.

**1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

## Pramipexole Dihydrochloride

**Background:** This NDA is submitted in accordance with section 505b(1) of the Federal Food, Drug and Cosmetic Act, referencing the safety and efficacy information for Mirapex® immediate-release (IR) tablets (NDA 20-667) approved July 1, 1997. Mirapex® IR is currently marketed by the sponsor in the US as immediate-release (IR) 0.125mg tid to 1.5 mg tid tablets (NDA 20-667) and in the European Union (EU), Norway, Switzerland, Canada and South America as well as in countries in Eastern Europe, Near East and Asia (Sifrol®/Mirapexin®). Pramipexole IR tablets are indicated in the EU and US for the treatment of signs and symptoms of either early Parkinson's disease or advanced Parkinson's disease in combination with levodopa as well as for Restless Legs Syndrome (RLS)

**Proposed Therapeutic Indication and Dosage Regimen:** Mirapex® (pramipexole dihydrochloride monohydrate) is a dopamine D2 receptor agonist. The sponsor is seeking approval for the treatment of idiopathic Parkinson's disease which is one of the indications approved for the IR tablet. The usual treatment consists of an up-titration phase starting at the lowest dosage strength, 0.375 mg, given once per day. Based on efficacy and tolerability, dosages may be increased gradually, but not more frequently than every 5 to 7 days, first to 0.75 mg per day and then by increments of 0.75 mg up to a maximum recommended dose of 4.5 mg per day. Patients should be assessed for therapeutic response and tolerability at a minimum interval of 5 days after each dose increment. Caution should be exercised during dose titration because too rapid a rate of titration may lead to dose selection that may not provide additional benefit, but that may increase the risk of adverse reactions.

**Bioavailability and Bioequivalence of Pramipexole Extended Release and Mirapex® IR tablets:**

**Single Dose:** The PK parameters of the to-be-marketed pramipexole ER formulation and the 0.125 mg IR dose following a single daily dose of 0.375 mg, (Study 248.560) are given in the following table.

Parameter	0.125 mg IR Tablet	0.375 mg C2 ER Tablet
AUC 0-24[ ng*h/mL]	2.10 [10.9]	4.63 [19.7]
C <sub>max</sub> [ng/mL]	0.218 [16.3]	0.268 [10.9]
T <sub>max</sub> [h]	0.983 [0.2-2.0]	0.998 [3.0-14.1]

**Multiple-dose:** The multiple-dose steady-state pharmacokinetics of all strengths of pramipexole ER tablets, and IR reference are shown in the following table:

Parameter	0.375 mg	0.75 mg	1.5 mg	3.0 mg	4.5 mg	1.5 mg tid (IR)
C <sub>max, ss</sub>	0.42	0.79	1.71	3.61	4.89	5.26
AUC <sub>0-24,ss</sub>	7.79	14.60	31.20	67.60	91.70	94.40
T <sub>max,ss</sub>	6.00	3.50	9.00	7.07	6.00	1.00
AUC <sub>0-24, ss norm</sub>	29.7	27.9	29.7	32.2	29.2	
C <sub>max,ss norm</sub>	1.62	1.51	1.62	1.72	1.56	

Summary statistics are given in the following table for the highest strength daily dose of 4.5 mg given either as the ER or the IR formulation [Study 248.530]. The rate and extent of absorption at steady state were equivalent after administration of a 4.5 mg daily dose of either the ER or IR formulation.

## Pramipexole Dihydrochloride

Parameter	gMean %	gMean %	Ratio (ER/IR)	intra-indiv. % gCV	90% Confidence Intervals	
	IR	ER			lower limit	upper limit
C <sub>max,ss</sub> ng/mL	5.18	4.94	95.38	10.9	90.4	100.6
AUC <sub>0-24,ss</sub> [ng*h/mL]	92.27	92.83	100.61	14.6	93.7	108.0

**Accumulation:** The accumulation was approximated by comparing the results from the single dose study 248.560 with results from the multiple dose study 248.530 on the lowest dose strength of 0.375 mg pramipexole ER. As shown in the following table, the accumulation factor (RA) was 1.68 and 1.58 for AUC and C<sub>max</sub>, respectively. The accumulation is most likely due to slow, rate limiting release from the extended release formulation.

Parameter	SD 0.375 (Study 560)	MD 0.375 qd (Study 530)
AUC 0-24 (ng*h/mL)	4.63	7.79
C <sub>max</sub> (ng/mL)	0.268	0.423
T <sub>max</sub> (h)	9.98	6.00
Accumulation Ratio		
RA AUC		1.68
RAC <sub>max</sub>		1.58

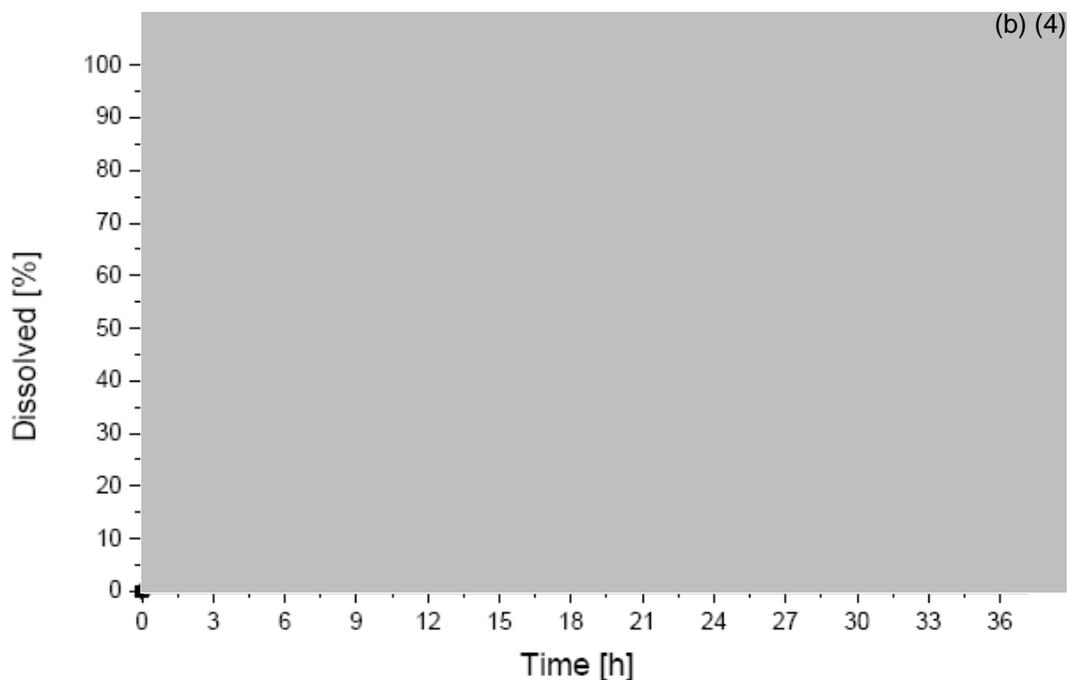
***Effect of Food on the Pharmacokinetics of Pramipexole after administration of 4.5 mg ER:***

Following administration of 4.5 mg of pramipexole ER under fed conditions (Study 248.530), the AUC<sub>τ,ss</sub> for fed/fasted ER formulation was within the 90% confidence intervals (105.8 to 122.1%). C<sub>max,ss</sub> was higher by about 20% under fed conditions and the 90% CI was slightly outside the boundaries of 80 to 125% with an upper 90% CI of 126.8%. The t<sub>max,ss</sub> was slightly prolonged from (median) 6.0 h to 7.92 h under fed conditions. AUC<sub>0-6,ss</sub> and AUC<sub>0-4,ss</sub> never exceeded 30% of AUC<sub>τ,ss</sub> excluding the possibility of dose dumping when taken with food.

Parameter	gMean %	gMean %	Ratio (FED/FASTED)	intra-indiv. % gCV	90% Confidence Intervals	
	ER FED	ER FASTED			lower limit	upper limit
C <sub>max,ss</sub> ng/mL	5.94	4.94	120.19	10.9	113.92	126.80
AUC <sub>0-24,ss</sub> [ng*h/mL]	105.51	92.83	113.65	14.6	105.83	122.06
AUC <sub>0-6,ss</sub> [ng*h/mL]	27.86	24.62	113.17	13.8	105.53	121.36
AUC <sub>0-4,ss</sub> [ng*h/mL]	17.31	15.79	109.67	15.9	101.18	118.88
T <sub>max,ss</sub> [h]	7.92 [2.5-12.0]	6.00 [1.5-16.0]				

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**Effect of Alcohol:** To evaluate the potential effect of dose dumping when pramipexole ER tablets are taken in the presence of alcohol, the sponsor conducted *in vitro* drug release tests using the approved dissolution method with increasing amounts of ethanol in the media. The results are shown in the following figure.



The amounts of pramipexole released at the early 2 hours time point shows a slight decrease by increasing the concentrations of ethanol (e.g. 5% ethanol = (b) dissolved, 10% ethanol (b) (4) dissolved and 40% ethanol = (b) dissolved). These results indicate that there is a low probability of the ER tablets “dose dumping” pramipexole *in vivo* when taken with alcohol.

**Dose Proportionality:** Dose proportionality was assessed using a power model. Dose proportional increases of  $C_{max,ss}$  and  $AUC_{\tau,ss}$  as well as  $C_{pre,ss}$  were demonstrated over the dose range between 0.375 and 4.5 mg of the pramipexole ER formulation.

Table 6. Power Model Assessment of Dose Proportionality Analysis of PK Parameters of Pramipexole ER tablets (0.375mg -4.5 mg qd)				
			95% Confident Limits	
Parameter	SE for $\beta$	Slope $\beta$	Lower Limit	Upper Limit
$C_{max,ss}$	0.042	1.007	0.978	1.036
$AUC_{0-24,ss}$	0.016	1.012	0.980	1.045
$C_{pre,ss}$	0.031	1.039	0.977	1.101

Dose proportionality was also supported by comparing dose normalized [to 4.5 mg]  $AUC_{ss,norm}$  and  $C_{max,ss,norm}$  between different ascending dose strengths from 0.375 to 3.0 mg q.d. to the 4.5 mg qd in the fasted state. The results were between 92-108% for dose normalized  $AUC_{ss}$  and 90-104% for  $C_{max,ss}$ .

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Parameter	TEST				REFERENCE
	0.375 mg	0.75 mg	1.5 mg	3.0 mg	4.5 mg
AUC <sub>0-24, ss norm</sub>	29.7	27.9	29.7	32.2	29.2
% AUC <sub>ss TEST/REFERENCE</sub>	101.7%	95.5%	101.7%	110.3%	
C <sub>max,ss norm</sub>	1.62	1.51	1.62	1.72	1.56
% C <sub>max,ss TEST/REFERENCE</sub>	103.9%	96.8%	103.8%	110.3%	

**Attainment of Steady-State:** In order to confirm that steady state conditions were attained in the study, trough concentrations after multiple dosing of ER were compared on day 5. Two trough concentrations were obtained one hour before drug administration (C<sub>pre,ss</sub>) and 23 hours thereafter (C<sub>23,ss</sub>) on day 5. An estimate of the ratio of C<sub>23,ss</sub>/C<sub>pre,ss</sub> was 109.2 with a 95% confidence interval of 101.9-117.1%. Steady-state conditions were assumed, although C<sub>23,ss</sub> was higher than C<sub>pre,ss</sub> levels.

Dose Levels	LS mean ratio C <sub>23,ss</sub> /C <sub>pre,ss</sub>	95% Confidence Intervals	
Overall	109.2	101.9	117.1
0.375	108.2	98.0	119.6
0.750	109.4	95.9	124.7
1.500	115.7	101.8	131.5
3.000	111.8	95.3	131.2
4.500	104.0	89.3	121.1

**Ethnic Influences:** To determine the BA/BE in the Japanese population, the sponsor conducted a multiple dose study [Study 248.607] of pramipexole with increasing doses (0.375 mg to 1.5 mg q.d.) of extended release (ER) tablets with a two-way crossover comparison of 0.375 mg pramipexole ER q.d. versus 0.125 mg immediate release (IR) tablet t.i.d. The 1.5 mg ER tablet q.d was also compared to the 0.5 mg IR tablet t.i.d. in Japanese healthy male volunteers. The study concluded that the ER tablets met the BE criteria for both the 0.375 mg/day and the 1.5 mg/day.

Parameters	Daily dose (mg)	ER (Test)	IR (Reference)	Ratio	90% CI	
					Lower	Upper
AUC <sub>0-24,ss</sub> ng*h/mL	<b>0.375</b>	8.86	10.02	88.4	83.33	93.88
	<b>1.5</b>	34.87	39.06	89.3	86.72	94.77
C <sub>max,ss</sub> ng/mL	<b>0.375</b>	0.626	0.554	113.2	107.48	119.15
	<b>1.5</b>	2.363	2.139	110.5	106.69	114.43
Ae <sub>0-24,ss</sub> [μg]	<b>0.375</b>	226.20	244.42	93.6	86.23	99.33
	<b>1.5</b>	851.02	961.16	88.6	82.72	94.77

## Pramipexole Dihydrochloride

Compared to Caucasians from Study 248.530, the C<sub>max</sub> was approximately 40-50% higher and the AUC was approximately 12-22% in Japanese volunteers from Study 248.607.

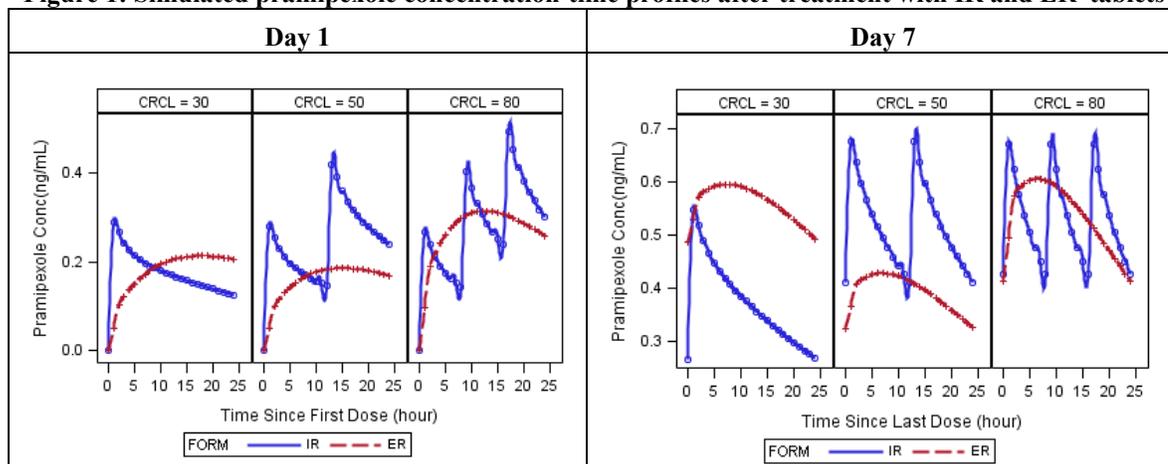
**Effect of Renal Impairment:** To determine the effect of renal impairment on the PK of pramipexole released from the extended-release tablets, the sponsor conducted a population PK study. A model was developed to simulate the pharmacokinetics of pramipexole in patients with mild, moderate and severe renal impairment.

The labeling from the Mirapex IR tablets makes the following dosing recommendations for patients with renal impairment:

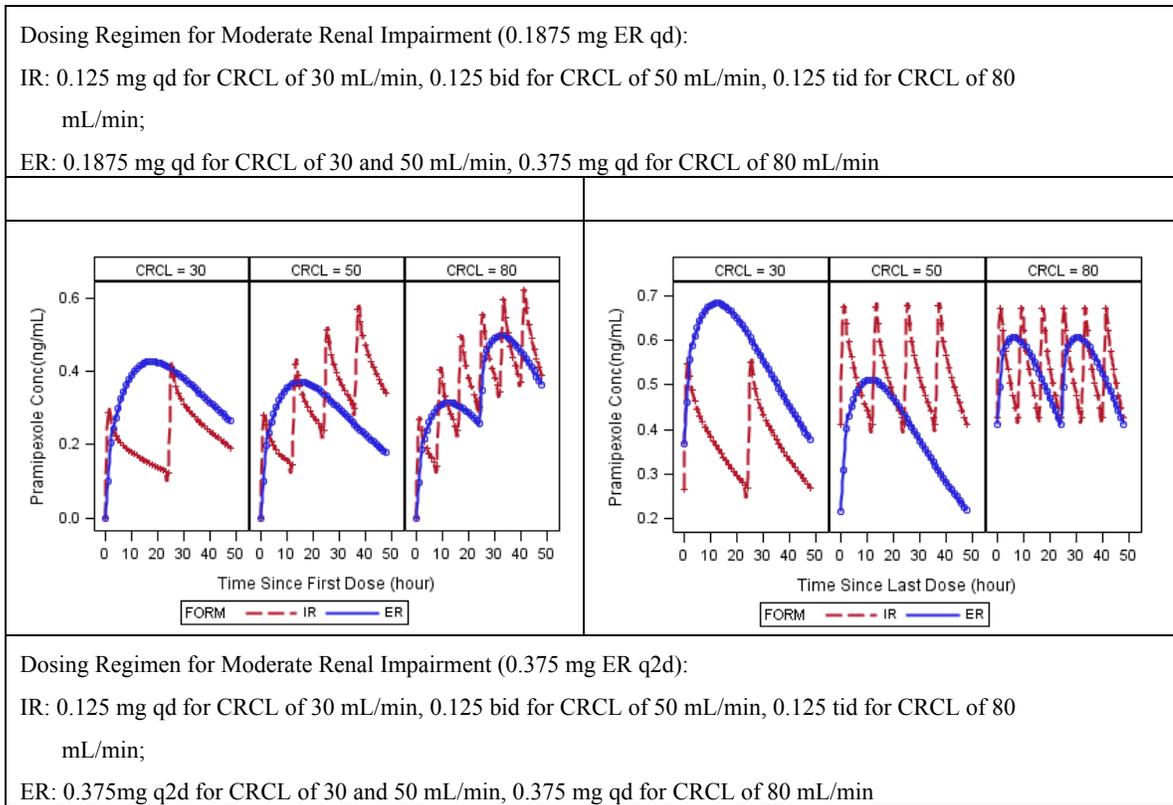
Category	Initial Dosage	Maximum Dosage
Mild	0.125 mg tid	1.5 mg tid
Moderate	0.125 mg bid	1.5 mg bid
Severe	0.125 mg qd	1.5 mg qd

The following simulations were conducted by the pharmacometric reviewer based on the proposed dosing regimen with body weight fixed at 75 kg and with initial dose of 0.375 mg Q2D for patients with creatinine clearance of 30 and 50 mL/min, 0.375 mg QD for patients with creatinine clearance of 80 mL/min. The pramipexole plasma concentration-time profiles at day 1 and day 7 are shown in Figure 1 (bottom). The steady-state (day 7) AUC<sub>0-48,ss</sub> for creatinine clearance of 30, 50 and 80 mL/min after ER tablets are 27.12, 18.88 and 25.78 ng.h/mL, respectively. In addition, we conducted simulations with a lower dose of 0.1875 mg qd for patients with creatinine clearance of 30 and 50 mL/min and compared with 0.375 mg qd in patients with creatinine clearance of 80 mL/min. The simulated pramipexole plasma concentration-time profiles at day 1 and day 7 are shown in Figure 1 (top). The steady-state AUC<sub>0-24,ss</sub> (Day 7) for creatinine clearance of 30, 50 and 80 mL/min after ER tablets are 13.46, 9.43 and 12.89 ng.h/mL, respectively. At steady state (Day 7), patients with creatinine clearance of 50 mL/min following ER tablets have significant lower exposure in either dosing regimens of 0.375 mg ER q2d or 0.1875 mg ER qd than patients with IR tablets. Based on the results of these simulations, it appears that it is not appropriate to treat patients with moderate renal impairment with ER tablets.

**Figure 1: Simulated pramipexole concentration-time profiles after treatment with IR and ER tablets**



Pramipexole Dihydrochloride



Based on these simulations, OCP recommends the following statement for the dosing of Mirapex ER in patients with moderate renal impairment:

(b) (4)

[Redacted text block]

Mirapex ER is not recommended in patients with severe renal impairment.

**1.4. Signatures**

Reviewer: Carol Noory  
 Team Leader: Raman Baweja, Ph.D.

cc list:

DFS: NDA 22-241  
 HFD-860: (NooryC, BawejaR, UppoorR, MehtaM, WangY, BhattramA, LiF)  
 HFD-120: (KatzR, ConnorB, JillapalliD, FeeneyJ, PodskalnyG, BergmannK, BrounsteinD, WilsonW)

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## II. QUESTION BASED REVIEW

### 2.1. General Attributes of the Drug

#### 2.1.1. What pertinent regulatory background contributes to the current assessments of this drug?

Pramipexole was first approved in 1997 in the USA. Boehringer Ingelheim, the sponsor of this NDA, is the current holder of NDA 20-667 for Mirapex® IR tablets. The immediate-release (IR) 0.125mg to 1.5 mg tablets are taken 3-times a day. All information for pramipexole drug substance is incorporated by cross reference to the approved NDA 20-667 for Mirapex® IR tablet. Pramipexole is also marketed as Sifrol® and Mirapexin®

#### 2.1.2 What are the highlights of the chemical and physical-chemical properties of the drug substance and the drug product as they relate to clinical pharmacology and biopharmaceutics review?

*Drug Substance:* The dose of pramipexole is always given as the dihydrochloride monohydrate salt (MW = 302.28) while the plasma concentrations are given as free base concentration (MW = 211.28). For calculation of dose normalized PK parameters or the CL/F, the free base dose was determined as the pramipexole dihydrochloride monohydrate dose divided by a factor of 1.431.

Solubility: water : freely soluble  
methanol : soluble  
ethanol (96%) : slightly soluble

*Drug Product:* The extended-release formulation incorporates a swelling matrix system which erodes to release the drug over time.

#### 2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mirapex® is seeking approval as 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, and 4.5 mg extended-release tablets [ER] for the treatment of adult patients with idiopathic Parkinson's disease. Animal studies have shown that pramipexole inhibits dopamine synthesis, release and turnover. Pramipexole protects dopamine neurons from degeneration in response to ischemia or methamphetamine neurotoxicity. In vitro studies showed that pramipexole protects neurons from levodopa neurotoxicity.

#### 2.1.4. Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Dose proportional increases in  $C_{max,ss}$  and  $AUC_{0-24,ss}$  over the dosing range from 0.375 and 4.5 mg of pramipexole ER were demonstrated in healthy Caucasian subjects. From analysis of co-variance (power model) linearity could be concluded because the slope  $\beta$  was not significantly different from 1 for those parameters (Table 1).

		95% Confident Limits		
Parameter	SE for $\beta$	Slope $\beta$	Lower Limit	Upper Limit
$C_{max, ss}$	0.042	1.007	0.978	1.036
$AUC_{0-24,ss}$	0.016	1.012	0.980	1.045

#### 2.1.5. What are the proposed dosage(s) and route(s) of administration?

Mirapex® ER Tablets, available in 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, and 4.5 mg strengths, are intended to be administered orally (b) (4). The dose range for Parkinson's Disease is .375 mg to 4.5 mg daily.

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## 2.2. General Clinical Pharmacology

### 2.2.1. What are the design features of the Clinical Pharmacology Studies used to Support the Dosing Regimen?

The pivotal clinical pharmacology study (Study 248.530) with an uptitration period was designed to demonstrate the steady-state bioequivalence of the highest strength (4.5 mg) Mirapex® ER tablet to the 1.5 mg IR tablet dosed 3 times/day. By meeting the 90% CI demonstrating bioequivalence, the ER tablet is able to use the Agency's finding of efficacy and safety for the reference IR tablet. The study also determined the effect of dosing the ER tablet with a high fat meal (Effect of Food). In general, therapy with pramipexole is initiated at a low dosage and gradually titrated upward to achieve a maximum therapeutic effect, balanced against the principal side effects.

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

Yes, the parent compound was measured using a validated bioanalytical method.

### 2.2.3. Does Pramipexole affect the QT or QTc interval?

According to the sponsor, the results of a thorough QT trial 248.545 [U08-1652-01] demonstrated that pramipexole did not prolong the individually heart rate corrected QT (QTcI) interval at both doses investigated (2.25 mg and 4.5 mg daily). This study was not addressed in the current review.

## 2.3. Pharmacokinetic Characteristics

### 2.3.1. What are the single-and multiple dose pharmacokinetic characteristics of the drug?

Linearity and the accumulation comparing single and multiple dosing were approximated by comparing the results from the single dose study 248.560 with results from the multiple dose study 248.530 on the lowest dose strength of 0.375 mg pramipexole ER [Table 11]. The accumulation is most likely due to slow, rate limiting release from the extended release formulation.

Parameter	SD 0.375 (Study 560)	MD 0.375 qd (Study 530)
AUC 0-24 (ng*h/mL)	4.63	7.79
Cmax (ng/mL)	0.268	0.423
Tmax (h)	9.98	6.00
Accumulation Ratio		
RA AUC	1.68	
RACmax	1.58	

The multiple-dose steady-state pharmacokinetics of all strengths of pramipexole ER tablets are shown in the following table:

Parameter	0.375 mg	0.75 mg	1.5 mg	3.0 mg	4.5 mg	1.5 mg tid (IR)
Cmax, ss	0.42	0.79	1.71	3.61	4.89	5.26
AUC0-24,ss	7.79	14.60	31.20	67.60	91.70	94.40
Cpre,ss	0.201	0.411	0.779	1.77	2.71	2.80
Tmax,ss	6.00	3.50	9.00	7.07	6.00	1.00
AUC0-24, ss norm	29.7	27.9	29.7	32.2	29.2	

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### 2.3.2 General ADME Characteristics of the Drug

After pramipexole dihydrochloride monohydrate is absorbed it is expected to have the same distribution, protein binding, metabolism, and elimination as the currently approved formulations. According to the reference label, the PK of pramipexole dihydrochloride monohydrate displays linear pharmacokinetics over the clinical dosage range. This has been verified for the ER tablet in Study 0248.530. Pramipexole has a terminal half-life of about 8 hours in young, healthy volunteers. Changes reflecting the PK parameters of the ER product include:

#### *Absorption:*

Pramipexole is rapidly and almost completely absorbed reaching peak concentrations in approximately 4-9 hours. In humans, the absolute bioavailability after oral administration as tablet exceeded 90%. Food did not affect the extent of absorption, although the time of maximum plasma concentration was delayed by approximately 2 hour indicating a reduction in the absorption rate. Independent of the dose, steady-state concentrations were achieved within two days.

### 2.3.3 What is the inter-subject variability in PK parameters?

In the current submission, the inter-subject %CV from the statistical analysis were approximately 30% for both C<sub>max,ss</sub> and AUC<sub>0-24,ss</sub>.

## 2.4 Intrinsic Factors

***What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?***

The influence of age, sex/gender and body weight (BW) on the PK of pramipexole ER was assessed in the Population PK analysis based on data from study 248.524. The OCP Pharmacometric Staff evaluated the results of this model simulation and the review is Attachment V [Pharmacometric Review]. In Study 248.524, CL/F and V<sub>3</sub>/F were compared between White, all Asian (except Japanese) and Japanese subjects. There was no statistically significant difference in CL/F.

### ***Race-Japanese***

Pramipexole has been marketed in Japan since 2003 with eight dose levels available for up-titration, i.e., 0.25, 0.5, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.5 mg per day. The ER therapy will also be initiated at the lowest dose and gradually titrated upward to achieve a maximum therapeutic effect and to balance against the principal side effects. Based on what is known about exposure-response relationships, and the current market potential in Japan, the sponsor decided to develop two pramipexole ER tablets (0.375 mg and 1.5 mg). These two dose levels (0.375 mg daily and 1.5 mg daily) of ER tablets were chosen for the evaluation of the relative BA compared with the IR tablets (0.125 and 0.5mg tid) in Japanese healthy male volunteers. The BA in Japanese patients indicates that the ER tablets are bioequivalent to IR tablets (Table 13).

Parameters	Daily dose (mg)	ER (Test)	IR (Reference)	Ratio	90% CI	
					Lower	Upper
AUC <sub>0-24,ss</sub> ng*h/mL	0.375	8.86	10.02	88.4	83.33	93.88
	1.5	34.87	39.06	89.3	86.72	94.77

## Pramipexole Dihydrochloride

C <sub>max,ss</sub> ng/mL	<b>0.375</b>	0.626	0.554	113.2	107.48	119.15
	<b>1.5</b>	2.363	2.139	110.5	106.69	114.43
Ae <sub>0-24,ss</sub> [μg]	<b>0.375</b>	226.20	244.42	93.6	86.23	99.33
	<b>1.5</b>	851.02	961.16	88.6	82.72	94.77

An assessment was made of dose proportionality for the ER tablets in Japanese patients. The increases of AUC<sub>τ,ss</sub>, C<sub>max,ss</sub> and Ae<sub>0-24,ss</sub> were proportional to the dose over the whole dose range between 0.375 mg and 1.5 mg of the pramipexole ER tablets. There was no deviation from linearity, since the 95% CI of the slope  $\beta$  included 1 for the parameters AUC<sub>τ,ss</sub>, C<sub>max,ss</sub> and Ae<sub>0-24,ss</sub> as determined by analysis of covariance (ANCOVA) using the power model (Table 14).

			90% Confidence Intervals	
Parameter	Estimate of $\beta$	Standard Error	Lower Limit	Upper Limit
AUC <sub>τ,ss</sub> (ng*h/mL)	0.9886	0.0257	93.68	104.03
C <sub>max, ss</sub> (ng/mL)	0.9578	0.0249	90.76	100.80
Ae <sub>0-24,ss</sub> (μ)	0.9558	0.0322	89.10	102.06

When compared to healthy male Caucasians, the pramipexole peak exposure (C<sub>max</sub>) at a given pramipexole ER dose was approximately 40-50% higher in healthy male Japanese subjects compared to healthy male Caucasians. The effect was much less pronounced in the AUC (12-22% higher). The difference in peak exposure is most likely caused by the difference in body weight (BW), the mean BW being 60.2 kg in Japanese vs. 79.3 kg in Caucasians.

Parameter	Japanese	Caucasians	Japanese/Caucasian ratio		Difference after BWI Adjustment
0.375 mg ER	mean BW 60.2 kg	mean BW 79.3 kg	not adjusted	adjusted for BW	
gAUC <sub>ss</sub> (ng*hg/mL)	8.86	7.79	113.4	86.2	14% ↓
g C <sub>max,ss</sub> ng/mL	0.626	0.423	148.0	113.0	13% ↑
T <sub>max</sub> (H)	4 (2.0-8.0)	6 (0.5-16)	Study 607 and Study 530		

## 2.5 Extrinsic Factors

Drug interactions related to metabolism and transport of pramipexole, either as the IR or ER formulation, should be the same. No additional studies were done to explore these extrinsic factors. The influences of drugs affecting gastro-intestinal motility or increasing gastric pH were assessed by covariate screening in the PopPK analysis from study 248.524. No significant effect on the PK of pramipexole ER was observed for tested drug: propulsives, antacids, H<sub>2</sub>-blockers, proton-pump inhibitors or anticholinergics.

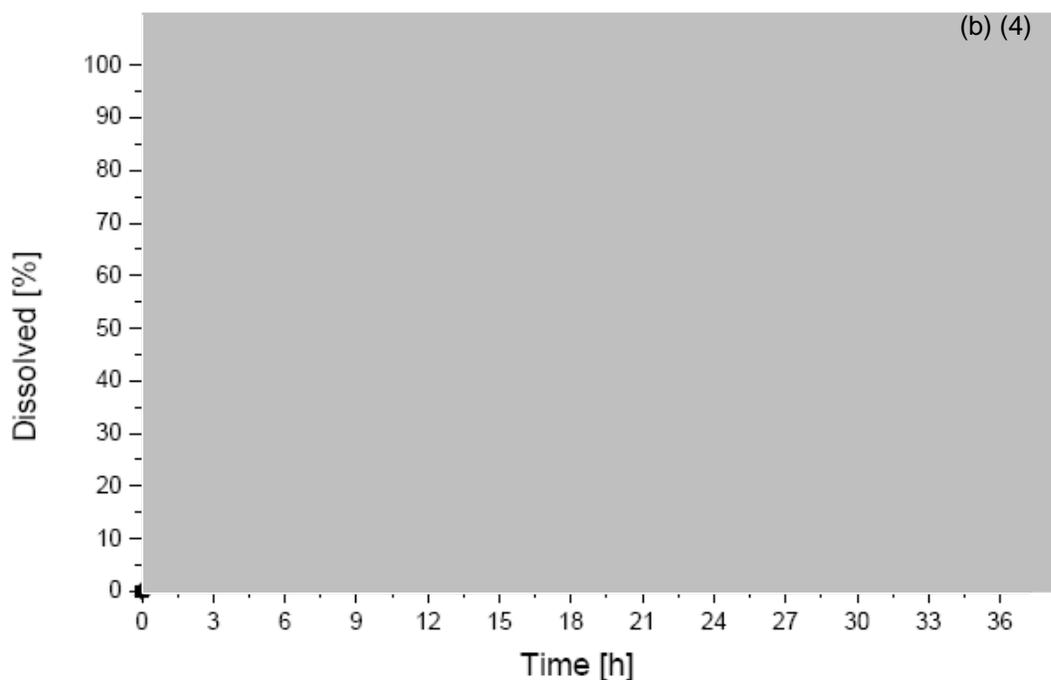
### 2.5.1 What the potential effect of alcohol use on the release of the drug from the dosage form?

In order to evaluate the potential of dose dumping when pramipexole ER tablets are taken in the presence of ethanol, in vitro dissolution experiments using the highest (4.5 mg) dosage strength were conducted. The experiments used Ph.Eur./USP/JP apparatus 1 [Basket Method] at 100 rpm. The dissolution medium

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consisted of 0.05 M phosphate buffer pH 6.8 with varying amounts of ethanol added [5, 10, 20 and 40 % w/w]. The sponsor selected the highest strength tablet since the % of hypromellose (relative to the total weight of the tablet) (b) (4). The results of these experiments using the highest strength [4.5 mg ER tablet] are shown in Figure 2.

**Figure 2. The Influence of Different Amounts of Ethanol on the Dissolution Profile of Pramipexole Dihydrochloride Monohydrate 4.5 mg ER Tablets.**



The amounts of pramipexole released at the early 2 hours time point, the indicator of dose dumping, are gradually reduced by increasing the concentrations of ethanol (e.g. 5% ethanol= (b) (4) dissolved, 10% ethanol (b) (4) dissolved and 40% ethanol (b) (4) dissolved). These results indicate that there is a low probability of the ER tablets “dose dumping” pramipexole *in vivo* when taken with alcohol.

## 2.6. General Biopharmaceutics

The Biopharmaceutics’ program was designed to address the performance of the proposed ER tablet formulation compared to the approved IR tablet reference product under fasted conditions and the effect of taking the ER tablet with food.

### 2.6.1. What is the proposed formulation of the drug product?

The ER tablets are manufactured by (b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4) maize starch was selected (b) (4), Hypromellose (b) (4) and carbomer (b) (4) (b) (4). The formulation for all strength appears in the following table (Table 15).

**Table 16. Qualitative and Quantitative Composition of Pramipexole Dihydrochloride Monohydrate ER tablets**

Dosage strength	0.375 mg	0.75 mg	1.5 mg	3.0 mg	4.5 mg		
Ingredient	[mg/tablet]	[mg/tablet]	[mg/tablet]	[mg/tablet]	[mg/tablet]	Function	Reference to Standards
Pramipexole dihydrochloride monohydrate, (b) (4) (Pramipexole free base)	0.375 (b) (4)	0.750 (b) (4)	1.500 (b) (4)	3.000 (b) (4)	4.500 (b) (4)	Active ingredient	Company standard
Hypromellose (b) (4)						(b) (4)	USP
Corn starch							NF
Carbomer homopolymer, (b) (4)							NF
Colloidal silicon dioxide							NF
Magnesium stearate							NF
<b>Total weight</b>	<b>250.000</b>	<b>330.000</b>	<b>350.000</b>	<b>425.000</b>	<b>500.000</b>		

The ER tablets are manufactured using pramipexole dihydrochloride monohydrate drug substance that has (b) (4). The various strengths are differentiated by size, shape and debossed code. Pramipexole dihydrochloride monohydrate has one chiral center and is present as the S-enantiomer.

**2.6.2. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?**

The formulation, the manufacturing site and the manufacturing process used in the pivotal phase III clinical trials are identical to those proposed for commercial supply. The to-be-marketed formulation was used in the BA/BE pivotal study.

**2.6.3. Is the to-be-marketed extended-release tablet formulation bioequivalent to the RLD formulation given at the same dose?**

Yes, the bioequivalence of the 4.5 mg ER tablet formulation was established in a multiple-dose, cross-over study (Study 248.0530) conducted in 36 healthy male volunteers. The highest strength, 4.5 mg, pramipexole ER tablet formulation was bioequivalent under fasted conditions relative to the currently approved Mirapex® 1.5 mg IR tablet dosed tid for both AUC<sub>ss(0-24h)</sub> [100.6%] and C<sub>max,ss</sub> [95.4%]. The 90% CI of the ratio 4.5 mg pramipexole ER tablet: IR tablet at steady-state were within the equivalence range of 80.0% to 125.0% for AUC, C<sub>max</sub> and C<sub>min</sub>.

**2.6.4. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

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For the highest strength ER tablet (4.5 mg), no food effect was demonstrated with respect to AUC<sub>τ,ss</sub>. C<sub>max,ss</sub> was higher on average by about 20% under fed conditions and the 90% CI was slightly outside the boundaries of 80 to 125%. The median t<sub>max,ss</sub> was slightly prolonged from 6.0 h to 7.92 h under fed conditions. AUC<sub>0-6,ss</sub> and AUC<sub>0-4,ss</sub> never exceeded 30% of AUC<sub>τ,ss</sub>. Irregular release leading to dose dumping under food intake could be excluded (Table 17).

<b>Table 17. Relative Bioavailability of Pramipexole after Multiple Administration of 4.5 mg ER QD in Fasted or Fed State [n=24]</b>						
Parameter	gMean %	gMean %	Ratio	intra-indiv.	90% Confidence Intervals	
	fed	fasted	(fed/fast)	% gCV	Lower Limit	Upper Limit
C <sub>max,ss</sub> ng/mL	5.94	4.94	120.19	10.9	113.92	126.80
AUC <sub>0-24,ss</sub> [ng*h/mL]	105.51	92.83	113.65	14.6	105.83	122.06
AUC <sub>0-6,ss</sub> [ng*h/mL]	27.86	24.62	113.17	13.8	105.53	121.36
AUC <sub>0-4,ss</sub> [ng*h/mL]	17.31	15.79	109.67	15.9	101.18	118.88
T <sub>max,ss</sub> [h]	7.92 [2.5-12.0]	6.00 [1.5-16.0]				

For the lowest strength, 0.375 mg qd, no food effect was demonstrated for single-dose administration when comparing AUC<sub>0-30</sub> of pramipexole ER (0.375 mg to-be-marketed formulation) given either fasted or after a high fat meal. The gMean ratio fed/fast of AUC<sub>0-30h</sub> was 110.3% and the 90% confidence interval (90%CI) ranged from 101.5 to 119.8%. Food did affect the C<sub>max</sub> [mean ratio 124%]; the upper limit of the 90% CI was 134.1%, outside the bioequivalence boundary of 125%. The mean T<sub>max,ss</sub> was shortened by 3 hours for fed (6.05 h) versus T<sub>max</sub> for fasted (9.98 h) conditions for the lowest strength dose.

<b>Table 18. Relative Bioavailability of Pramipexole after Single-Dose Administration of 0.375 mg ER Tablet in the Fed or Fasted State [Study 248.560]</b>						
Parameters n=15	gMean	gMean	Mean Ratio	Intra-indiv.	90% Confidence Intervals	
	FED	FASTED	[Fed/Fasted]	gCV	Lower Limit	Upper Limit
C <sub>max</sub> [ng/mL]	0.33	0.27	124.1	12.5	115.1	134.1
AUC <sub>0-30 h</sub> [ng*h/mL]	5.80	5.28	110.3	13.6	101.5	119.8

The current studies showed that there was no effect of food on pramipexole 4.5 mg or 0.375 mg ER tablet for AUC<sub>ss</sub>. C<sub>max,ss</sub> was 20-25% higher fed/fast. The steady-state T<sub>max</sub> was approximately 2 hours longer for the highest strength (4.5 mg) under steady-state conditions. The T<sub>max</sub> for the lowest strength (0.375 mg) single-dose is approximately 3 hours shorter in the fed vs. fasted state. Since the exposure is similar for the ER tablet taken with or without food, the ER tablet can be dosed without regard to food.

### 2.6.5 Was an IVIVC explored?

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An IVIVC was explored at the lowest dose strength since dosing of higher strengths to healthy subjects is not recommended due to tolerability. The IVIVC is being reviewed by the Office of Pharmaceutical Sciences. The BA/BE portion was examined in Study 248.560, a single-center, active controlled, five-treatment, five-period, five-way cross-over study comparing 4 different extended-release pramipexole formulations (C, C2 [targeted to-be-marketed formulation with (b) (4)], C2A, and C2B) under fasted conditions to the commercial IR tablet. The extended-release to-be-marketed pramipexole ER C2 formulation was also evaluated in a two-way crossover treatment in the fed versus fasted state.

## 2.7. Analytical

### 2.7.1. Were the correct moieties identified and properly measured?

Yes, the parent compound was measured.

### 2.7.2. What bioanalytical methods are used to assess concentrations?

A validated HPLC-MS/MS was used to assess the concentrations of pramipexole in human plasma.

### 2.7.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The HPLC-MS/MS method was validated over the range 0.05 to 15.0 ng/mL. The pivotal study C<sub>max</sub> was approximately 5 ng/mL. The regression model used peak signal ratios with 1/x<sup>2</sup> weighted linear regression.

### 2.7.4 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The method was validated between 0.05 ng/mL and 15.0 ng/mL.

### 2.7.5 What are the inaccuracy and imprecision at these limits?

The % inaccuracy and % imprecision of pramipexole in human EDTA plasma is given in the following table.

Extracted Recovery	51% for pramipexole		53% for IS	
Calibration Standards	0.050 to 15.0 ng/mL		8 calibration standards	
Internal Standard	D7-pramipexole dihydrochloride		Batch AGS 337/10	
Correlation Coefficient r <sup>2</sup>	0.998892			
Inter-batch	0.05 ng/mL	1.5 ng/mL	2.0 ng/mL	12 ng/mL
Imprecision	4.88%	4.76%	1.71%	0.95%
Inaccuracy	7.80%	1.33%	2.50%	2.50%
Quality Control Samples	0.05 ng/mL	0.15 ng/mL	2.0 ng/mL	12 ng/mL
Imprecision	12.93%	7.87%	2.80%	2.07%
Inaccuracy	13.80%	0.00%	1.50%	0.83%

The selectivity of the method was established by the analysis of samples of control human plasma. HPLC-MS/MS chromatograms of the blanks and validation samples were visually examined and compared for chromatographic integrity and potential interferences. Representative chromatograms at the LLQ and HLQ showed no unacceptable interferences at the retention times of pramipexole and its internal standard.

### 2.7.6 What is the sample stability under the conditions used in the study?

The stability of pramipexole in spiked human plasma samples stored at room temperature was assessed at 0.05 ng/mL and 15.00 ng/mL by comparing the mean concentrations of samples extracted after storage for 24 hours against those of the samples extracted immediately upon spiking. The difference is less than 15%, and indicates that pramipexole is stable in human plasma stored at room temperature for at least 24 hours.

(b) (4)

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*The remainder of the labeling is acceptable.*

## IV. INDIVIDUAL STUDY REVIEWS

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### 4.1. STUDY NUMBER: 248.530; Phase 1 [PIVOTAL STUDY]

**TITLE:** A multiple dose study with increasing pramipexole doses (0.375 mg to 4.5 mg q.d.) of oral extended release (ER) tablets with a three-way cross comparison of 4.5 mg pramipexole ER q.d. fed versus 4.5 mg pramipexole ER fasted q.d. versus 1.5 mg pramipexole immediate release tablets t.i.d. fasted in healthy male volunteers

**DATES OF STUDY:** 26 April 2006 to 21 July 2006

**LOCATION OF STUDY:** [REDACTED] (b) (4)

#### **OBJECTIVE:**

Food Effect: determine total exposure between pramipexole ER fasted and fed after multiple administration of the highest daily dose of 4.5 mg q.d.

Relative Bioavailability: determine the relative bioavailability of the ER-formulation of pramipexole in comparison to the IR-formulation at the highest daily dose of 4.5 mg after multiple dosing.

Dose Proportionality: demonstrate dose proportionality between the pramipexole ER formulation, 0.375, 0.75, 1.5, 3.0, and 4.5 mg, after multiple daily (q.d.) dosing.

#### **STUDY DESIGN:**

Double-blind, double placebo (with regard to IR or ER tablets), randomized, three-way, multiple-dose crossover bioequivalence and food effect trial with an open label up-titration period (0.375 mg to 3.75 mg) and down-titration period in 36 healthy male volunteers. Dose was administered with 230 mL of non-sparkling water by authorized staff:

- Up-titration: six dose levels, 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg of pramipexole ER formulations (visits 2 to 7)
- Three-way cross-over (visits 8 to 10) with the following treatments:
  - A. 1.5 mg pramipexole immediate release tablets t.i.d. fasted
  - B. 4.5 mg pramipexole ER q.d. fasted

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C. 4.5 mg pramipexole ER q.d. fed (with a high-fat meal 30 min before drug administration)

- Down-titration (visit 11): six dose levels of pramipexole oral ER formulations (3.75 mg, 3 mg, 2.25 mg, 1.5 mg, 0.75 mg, 0.375 mg)
- An end-of-study examination was performed at visit 12 (4 to 7 days after last administration).

All subjects underwent ten treatment visits of 3 to 6 days duration without wash-out, adding up to 47 to 49 subsequent days of dosing. The seven dose levels corresponded to the dose levels used for up-titration of the IR formulation. The highest dose of 4.5 mg daily was chosen for the investigation of the food effect and the relative bioavailability versus the IR formulation. The dose levels and treatment schedule are described in the following table.

Visit	Dose level	Duration	Tablet strength and posology (q.d. once daily, t.i.d. three times daily)
2	0.375 mg	5 days	0.375 mg q.d. fed on day 1, fasted on other days
3	0.75 mg	5 days	0.75 mg q.d. fed on day 1, fasted on other days
4	1.5 mg	5 days	1.5 mg q.d. fed on day 1, fasted on other days
5	2.25 mg	3-4 days	1.5 mg q.d. + 0.75 mg q.d. fed on day 1, fasted on other days
6	3.0 mg	5 days	3.0 mg q.d. fed on day 1, fasted on other days
7	3.75 mg	3-4 days	3.0 mg q.d. + 0.75 mg q.d. fed on day 1, fasted on other days
8 to 10	4.5 mg	5 days each	(A) 4.5 mg ER placebo q.d. + 1.5 mg IR active t.i.d. fed on day 1, fasted for morning dose on other days (B) 4.5 mg ER active q.d. + 1.5 mg IR placebo t.i.d. fed on day 1, fasted for morning dose on other days (C) 4.5 mg ER active q.d fed on days 1 and 5, fasted for morning dose on other days
11	3.75 mg, 3.0 mg, 2.25 mg, 1.5 mg, 0.75 mg, 0.375 mg	6 days (one day each level)	Tablet strength as on the respective dose level in visits 2 to 7, q.d., fed

On days 5 of Treatment C the following breakfast was given, starting 30 min before dosing.

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t: 2 Composition of a standard high-fat breakfast

	Amount	kcal	kJ
2 eggs	120 g	184.0	772.0
2 strips of bacon	30 g	160.0	672.0
Butter	30 g	225.0	945.0
2 toast bread slices	60 g	140.0	588.0
Hash brown potatoes	120 g	84.0	352.0
Whole milk	240 mL	152.0	640.0
Sum		945.0	3969.0

(i.e., approximately 150 protein calories, 250 carbohydrate calories, 500-600 fat calories).

**Protocol Deviations**

Several protocol violations were identified in 8 subjects including missing blood and urine samples; missing and/or delayed drug administration; and hypertension which lead to premature discontinuation. These deviations resulted in exclusion of some data but did not have a major impact on the statistical analyses.

**SUBJECT AND TREATMENT INFORMATION****Subject Demographic Characteristics**

The study population consisted of healthy male volunteers, age 21 to 50 years, BMI: 18.5 to 29.9 kg/m<sup>2</sup>;

**Dose Proportionality Portion:** 33 subjects completed the titration phase; median age 36.0 (21-50); BMI (kg/m<sup>2</sup>) 25.7 (19.0-29.70); **Three-way Crossover Portion:** 25 subjects completed the cross-over phase; median age 40.0 (21-49); BMI 26 (19.6-29.7).

SUBJECT DISPOSITION FOR PRAMIPEXOLE ER DOSES DURING UP-TITRATION						
Subjects Disposition	ER 0.375 mg	ER 0.75 mg	ER 1.5 mg	ER 2.25 mg	ER 3.0 mg	ER 3.75 mg
Treated	39	33	32	31	28	26
Discontinued	6	1	1	0	2	0
Completed	33	32	31	31	26	26

**Population Size Determination**

The size of the study was based on a previous trial performed with sustained release forms of pramipexole (Study No.: 248.529).

**Study drugs**

Test product: Pramipexole ER tablets: 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, 4.5 mg

Dose: Seven dose levels: 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, 4.5 mg q.d.

**Batch nos.:**

PO06/10180 (Bulk Batch No.: B061000242) (0.375 mg)

PO06/10181 (Bulk Batch No.: B061000243) (0.75 mg)

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PO06/10182 (Bulk Batch No.: B061000244) (1.5 mg)

PO06/10184 (Bulk Batch No.: B061000245) (3.0 mg)

PR06/10027 (Bulk Batch No.: B061000246) (4.5 mg)

### **Other products:**

Placebo matching Pramipexole ER tablets 4.5 mg : PR06/10027 (Bulk Batch No.: B061000382)

Placebo matching Pramipexole IR tablets 1.5 mg : PR06/10027 (Bulk Batch No.: B051000953)

### **Sample Collection and Handling**

#### *Plasma Sampling:*

Blood samples for pharmacokinetic measurements of pramipexole were taken before first administration on day 1 of visit 2 (blank sample) and:

before, 00:30 h, 01:00 h, 01:30 h, 02:00 h, 02:30 h, 03:00 h, 04:00 h, 06:00 h, 08:00 h, 09:00 h, 10:00 h, 12:00 h, 16:00 h, and 23:00 h

After drug application of 5 days on visits 2, 6, 8, 9 and 10 (Planned times: 95:00 h, 96:30 h, 97:00 h, 97:30 h, 98:00 h, 98:30 h, 99:00 h, 100:00 h, 102:00 h, 104:00 h, 105:00 h, 106:00 h, 108:00 h, 112:00 h, and 119:00 h)

For each one half of the subjects on day 5 of visits 3 and 4, respectively (odd numbers on visit 3 and even numbers on visit 4) at the times as above (for visits 2, 6, 8, 9 and 10)

23:00 h after drug application of 5 days on visits 3 and 4 also for all other subjects (Planned time: 119:00 h)

The total amount of blood collected during the trial (including laboratory) was approximately 400 mL (450 mL maximum).

#### *Urine sampling*

Urine samples for pharmacokinetic measurements of pramipexole were taken before first dose on Day 1 of visit 2 (blank sample) and in the following collection periods: from (morning) dosing (00:00 h) to 08:00 h, and from 08:00 h to 24:00 h after the morning dose of day 5 on visits 8, 9 and 10. Urine was collected quantitatively. In cases of low (less than 1000 mL for 24 h intervals) urine volumes, water was added in order to avoid precipitation of solids when freezing.

### **ANALYTICAL PROCEDURES**

*Pramipexol in Plasma:* Samples were tested at (b) (4).

Pramipexole was extracted using a (b) (4) and determined using a validated HPLC-MS/MS assay. In-study assay performance was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of quality control (QC) samples. The accuracy of individual analyses met the acceptance criteria. A total of 5240 study samples were analyzed between 27-Jul-2006 to 08-Sep-2006. The table below shows in-study accuracy and precision data obtained.

IN STUDY ACCURACY AND PRECISION OF BIOANALYSIS OF PRAMIPEXOLE IN PLASMA
---

## Pramipexole Dihydrochloride

<b>Study Drug</b>	Pramipexiole Dihydrochloride		Batch 0006; exp. 28-Feb-2010	
<b>Internal Standard</b>	D7-pramipexole		Batch AGS337/10; exp. 03-May-2008	
<b>Test site</b>	(b) (4)			
<b>Matrix</b>	EDTA Plasma			
<b>Calibration Standard</b>	0.05 to 15.00 ng/mL (8 point curve)			
<b>Regression Method</b>	Weighted linear least-squares regression ( $1/x^2$ )			
<b>% CV (Precision)</b>	5.83 LLOQ; 2.42 ULOQ			
<b>Accuracy (%)</b>	-0.20% LLOQ; -1.70% ULOQ			
<b>Calibration Curve n=3</b>	<b>r2= 0.998827</b>			
<b>QC samples (n=56)</b>	0.05 ng/mL	0.15 ng/mL	2.00 ng/mL	12.00 ng/mL
<b>Inter-run Precision %CV</b>	1.31	5.16	4.54	2.81
<b>Inter-run Accuracy</b>	5.20	5.33	2.50	-.83

*Pramipexole Concentration in Urine:* Pramipexole in urine samples was determined using a validated HPLC-MS/MS assay. Linear calibration curves were obtained over the range from 0.1 to 100 ng/mL pramipexole using 0.2 mL urine. Assay performance was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of QC samples. The accuracy of individual analyses met the acceptance criteria. A total of 372 samples were analyzed between 09 and 19 September 2006. The table below shows the in-study accuracy and precision data.

IN STUDY ACCURACY AND PRECISION OF BIOANALYSIS OF PRAMIPEXOLE IN URINE				
<b>Study Drug</b>	Pramipexiole Dihydrochloride		Batch 0006; exp. 28-Feb-2010	
<b>Internal Standard</b>	D7-pramipexole		Batch AGS337/10; exp. 03-May-2008	
<b>Test site</b>	(b) (4)			
<b>Matrix</b>	Human Urine			
<b>Calibration Standard</b>	0.1 to 100 ng/mL (8 point curve)			
<b>Regression Method</b>	Weighted linear least-squares regression ( $1/x^2$ )			
<b>% CV (Precision)</b>	8.03 LLOQ; 3.42 ULOQ			
<b>Accuracy (%)</b>	1.20% LLOQ; 2.70% ULOQ			
<b>Calibration Curve n=3</b>	<b>r2= 0.995297</b>			
<b>QC samples (n=6)</b>	0.2 ng/mL	3.00 ng/mL	80 ng/mL	500 ng/mL
<b>Inter-run Precision %CV</b>	7.94	5.66	5.23	6.88
<b>Inter-run Accuracy</b>	2.00	1.33	1.63	-.80

**PHARMACOKINETICS****Assessment of dose proportionality**

Dose proportionality was explored based on the following regression model:

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$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^\beta * \varepsilon'_{ij}$$

Together with  $\alpha' = \exp(\alpha)$  and  $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$ , taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

$Y_{ij}$  logarithm of the pharmacokinetic endpoint (AUC<sub>0-24,ss</sub>, C<sub>max,ss</sub>, or C<sub>pre,ss</sub>) for subject j at dose level i; where i = 1, 2, ..., 7, j = 1, 2, ..., N;

$\alpha$  intercept parameter;

$\beta$  slope parameter;

$X_i$  logarithm of dose i;

$\varepsilon_{ij}$  random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

The slope  $\beta$  of the regression line was estimated and a 95% confidence interval was calculated. Dose proportional increases of C<sub>max,ss</sub> and AUC<sub>0-24,ss</sub> (AUC <sub>$\tau$ ,ss</sub>) as well as C<sub>pre,ss</sub> over the whole dose range between 0.375 and 4.5 mg of pramipexole ER formulation were demonstrated. The slope  $\beta$  was not significantly different from 1 for parameters C<sub>max,ss</sub> and AUC <sub>$\tau$ ,ss</sub> using analysis of co-variance (power model) indicating linearity.

Dose Proportionality Analysis of PK Parameters of Pramipexole ER tablets (0.375mg -4.5 mg qd) using the Power Model				
			95% Confident Limits	
Parameter	SE for $\beta$	Slope $\beta$	Lower Limit	Upper Limit
C <sub>max, ss</sub>	0.042	1.007	0.978	1.036
AUC <sub>0-24,ss</sub>	0.016	1.012	0.980	1.045
C <sub>pre,ss</sub>	0.031	1.039	0.977	1.101

Dose normalized C<sub>pre,ss,norm</sub> and C<sub>max,ss,norm</sub> were compared between different ascending dose strengths from 0.375 to 4.5 mg q.d. in the fasted state. The gMean C<sub>pre,ss,norm</sub> and C<sub>max,ss,norm</sub> ranged between 0.742 ng/mL/mg and 0.865 ng/mL/mg and 1.51 and 1.72 ng/mL/mg, respectively. The half value duration (HVD), the time at which the concentration is above 50% of the maximum concentration, ranged between 20.8 and 22.2 h for all dose strengths. A comparison of the dose normalized AUC<sub>ss</sub> and C<sub>max,ss</sub> over the dosing range vs. the normalized 4.5 mg dose is given in the following table.

Dose Normalized AUC and C <sub>max</sub> Comparisons Over the Dosage Range					
Parameter	TEST				REFERENCE
	0.375 mg	0.75 mg	1.5 mg	3.0 mg	4.5 mg
AUC <sub>0-24, ss norm</sub>	29.7	27.9	29.7	32.2	29.2

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% AUC <sub>ss</sub> TEST/REFERENCE	101.7%	95.5%	101.7%	110.3%	
C <sub>max,ss</sub> norm	1.62	1.51	1.62	1.72	1.56
% C <sub>max,ss</sub> TEST/REFERENCE	103.9%	96.8%	103.8%	110.3%	

**PHARMACOKINETIC RESULTS**

Pramipexole was given as the pramipexole dihydrochloride monohydrate. Therefore, dose divided by a factor of 1.431 yields the respective amount of pramipexole base. This adjusted dose was used for the calculation of pharmacokinetic parameters involving a dose term. The PK parameters for all dose strengths and conditions are summarized in Tables 11.5.2.2: 1 to 2.

gMean (gCV) Noncompartmental Pharmacokinetic Parameters of Pramipexole after Multiple Oral Administration of either 1.5 mg IR tid or 4.5 mg ER qd.														
The Dose of 4.5 mg ER Was Also Given Under Fed as Well as Fasted Conditions														
Pramipexole	1.5 mg IR tablet		4.5 mg ER tablet		4.5 mg ER tablet		0.375 mg ER		0.75 mg ER		1.5 mg ER		3.0 mg ER	
	tid		FASTED		FED		tablet		tablet		tablet		tablet	
	gMean	CV	gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV
		[%]		[%]		[%]		[%]	n	[%]		[%]		[%]
AUC <sub>0-24,ss</sub> [ng-h/mL]	94.4	21.4	91.7	30.1	105	29.6	7.79	20.8	14.6	18.6	31.2	29.0	67.6	22.1
AUC <sub>0-6,ss</sub> [ng-h/mL]	---	---	24.4	23.9	27.6	31.4	2.10	20.0	4.02	17.2	7.90	28.9	17.5	29.7
AUC <sub>T,ss,norm</sub> [ng-h/mL/mg]	---	---	29.2	30.1	33.5	29.6	29.7	20.8	27.9	18.6	29.7	29.0	32.2	22.1
C <sub>max,ss</sub> [ng/mL]	5.26	19.0	4.89	22.3	5.94	24.7	0.423	19.1	0.792	16.2	1.71	24.7	3.61	23.8
C <sub>max,ss,norm</sub> [ng/mL/mg]	---	---	1.56	22.3	1.89	24.7	1.62	19.1	1.51	16.2	1.62	24.7	1.72	23.8
C <sub>pre,ss</sub> [ng/mL]	2.80	27.7	2.71	31.1	2.56	58.4	0.201	38.0	0.411	28.8	0.779	42.0	1.77	53.0
C <sub>pre,ss,norm</sub> [ng/mL/mg]	---	---	0.865	31.1	0.814	58.4	0.767	38.0	0.785	28.8	0.742	42.0	0.842	53.0
t <sub>max,ss 2</sub> [h]	1.00	0.50	6.00	1.50- 16.0	7.92	2.50	6.00	0.51	3.50	2.00	9.00	2.50	7.07	2.00
		- 3.02				- 12.0		7- 16.1		- 12.0		- 16.1		- 16.0
C <sub>avg</sub> [ng/mL]	3.93	21.4	3.82	30.1	4.38	29.6	0.325	20.8	0.609	18.6	1.30	29.0	2.82	22.1
C <sub>23,ss</sub>	3.08	24.1	2.82	43.0	2.76	43.1	0.218	28.5	0.450	22.4	0.901	41.1	1.98	24.1

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gMean (gCV) Noncompartmental Pharmacokinetic Parameters of Pramipexole after Multiple Oral Administration of either 1.5 mg IR tid or 4.5 mg ER qd.														
The Dose of 4.5 mg ER Was Also Given Under Fed as Well as Fasted Conditions														
Pramipexole	1.5 mg IR tablet		4.5 mg ER tablet		4.5 mg ER tablet		0.375 mg ER		0.75 mg ER		1.5 mg ER		3.0 mg ER	
	tid		FASTED		FED		tablet		tablet		tablet		tablet	
	gMean	CV	gMean	gCV	gMean	gCV	gMean	gCV	gMea	gCV	gMean	gCV	gMean	gCV
		[%]		[%]		[%]		[%]	n	[%]		[%]		[%]
[ng/mL]														
PTF	54.9	35.1	55.1	33.4	73.1	30.1	65.3	31.1	57.0	28.6	68.0	19.6	59.8	36.4
[%]														
HVD	----	----	22.2	13.4	20.8	13.0	21.5	13.0	22.1	10.5	21.8	8.36	22.2	6.00
[h]														
Ae0-24,ss	1080	66.8	1140	58.6	1330	104								
[µg]														

The statistical analysis of steady-state Pramipexole ER compared to the IR tablet of the same daily concentration given tid is shown in the following table.

RELATIVE BA OF PRAMIPEXOLE AFTER MULTIPLE ADMINISTRATION OF 1.5 MG IR [TID] OR 4.5 MG ER QD [N=24]						
Parameter	gMean %	gMean %	Ratio	intra-indiv.	90% Confidence Intervals	
	IR	ER	(ER/IR)	% gCV	lower limit	upper limit
Cmax,ss ng/mL	5.18	4.94	95.38	10.9	90.4	100.6
AUC0-24,ss [ng*h/mL]	92.27	92.83	100.61	14.6	93.7	108.0
Cpre,ss [ng/mL]	2.74	2.74	100.20	27.8	87.7	114.5

**Summary of Relative Bioavailability:**

- The relative bioavailability of the ER 4.5 mg formulation compared to the IR 1.5 mg tablet tid was 100.6% for AUC(0-24,ss).
- The inter-subject variation was 14.6 [AUC0-24,ss]; 10.9 [Cmax,ss] and 27.8 [Cpre,ss]. The intersubject variability was about the same for the IR and the ER formulation.
- Tmax: In comparison to the immediate-release formulation, the ER tablets had a longer tmax,ss. The median tmax,ss after 1.5 mg pramipexole IR t.i.d. was 1.00 h in the fasted state, while median tmax,ss for 4.5 mg q.d. of the ER-formulation was 6.0 h in the fasted.

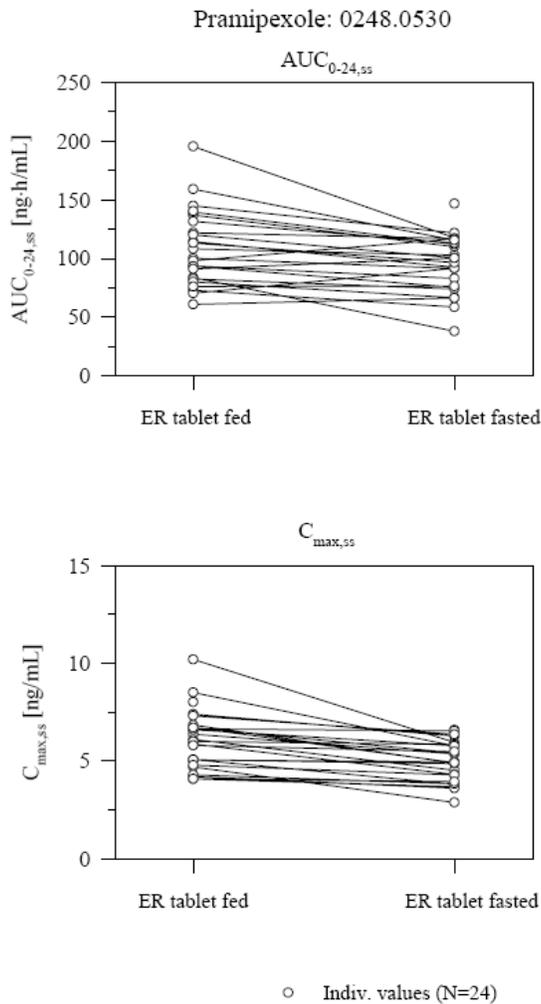
**Results of Food Effect:**

The results of the statistical analysis of the effect of food on the bioavailability of the 4.5 mg ER strength given qd under fed and fasted conditions is shown in the following table.

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RELATIVE BIOAVAILABILITY OF PRAMIPEXOLE AFTER MULTIPLE ADMINISTRATION OF 4.5 MG ER QD IN FASTED OR FED STATE [N=24]						
Parameter	gMean %	gMean %	Ratio	intra-indiv.	90% Confidence Intervals	
	FED	FASTED	FED/FASTED	% gCV	lower limit	upper limit
C <sub>max,ss</sub> ng/mL	5.94	4.94	120.19	10.9	113.92	126.80
AUC <sub>0-24,ss</sub> [ng*h/mL]	105.51	92.83	113.65	14.6	105.83	122.06
AUC <sub>0-6,ss</sub> [ng*h/mL]	27.86	24.62	113.17	13.8	105.53	121.36
AUC <sub>0-4,ss</sub> [ng*h/mL]	17.31	15.79	109.67	15.9	101.18	118.88
T <sub>max,ss</sub> [h]	7.92 [2.5-12.0]	6.00 [1.5-16.0]				

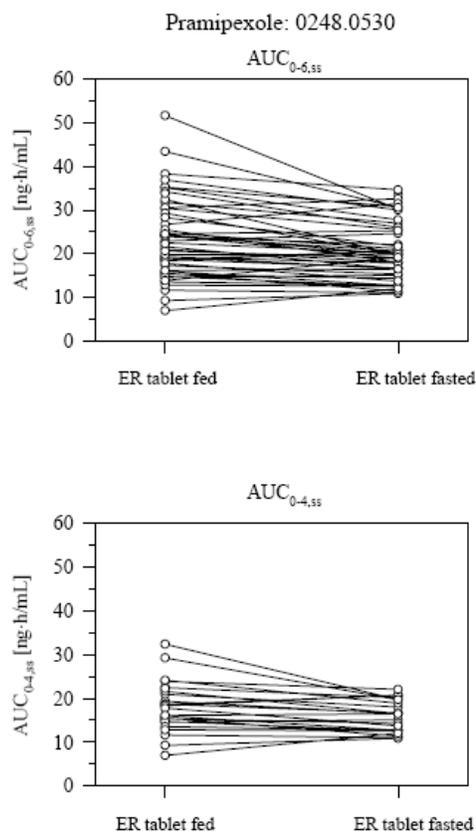
Intra-subject comparison of AUC<sub>0-24,ss</sub> and C<sub>max,ss</sub> of pramipexole after multiple oral administration of 4.5 mg pramipexole ER given either fasted or fed after a high fat meal are shown in the following figure.



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**Lack of Dose Dumping**

To illustrate a lack of dose-dumping, the sponsor compared the AUC<sub>0-4,ss</sub> and the AUC<sub>0-6,ss</sub> with and without food. The intra-subject comparison of AUC<sub>0-6h,ss</sub> and AUC<sub>0-4h,ss</sub> of pramipexole after multiple doses of 4.5 mg ER tablet given either fasted or fed are shown in the following figure.

**Summary of Food Effect Study:**

- **AUC:** No food effect was shown with respect to AUC<sub>τ,ss</sub> [113.7% (105.8-122.1)].
- **C<sub>max</sub>:** C<sub>max,ss</sub> was higher on average by about 20% under fed conditions [120.2%] and the 90% CI was slightly outside the boundaries of 80 to 125% [113.9-126.8].
- **T<sub>max</sub>:** The median t<sub>max,ss</sub> was slightly prolonged by 2 hours from 6.0 h to 7.92 h under fed conditions.
- **Dose-Dumping:** AUC<sub>0-6,ss</sub> and AUC<sub>0-4,ss</sub> never exceeded 30% of AUC<sub>τ,ss</sub>. The possibility of dose dumping under food intake could be excluded.

**Drug urine concentration-time profiles of pramipexole**

The amount excreted over a time interval from drug administration to 24h (Ae<sub>0-24,ss</sub>) was comparable between the IR formulation given 1.5 mg t.i.d. or 4.5 mg ER-formulation qd in the fasted state as well as under fed conditions. It ranged from 459 to 2480 μg for the IR formulation and from 342 to 2720 μg for

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ER formulation under fasted conditions. When the ER formulation was given with food, A<sub>e0-24,ss</sub> ranged from 101 to 3640 µg.

### ***Analysis of steady state condition of the ER formulation***

Steady state conditions were demonstrated by two trough concentrations, one hour before drug administration (C<sub>pre,ss</sub>) and 23 hours after dosing (C<sub>23,ss</sub>) on day 5. Comparison of the trough levels is shown in the following table.

<b>Comparison of Trough Levels C<sub>23,ss</sub>/C<sub>pre,ss</sub>: Adjusted Mean Ratio and 95% Confidence Interval (4.5 mg Pramipexole ER Formulations)</b>			
Dose Levels	LS mean ratio C <sub>23,ss</sub> /C <sub>pre,ss</sub>	95% Confidence Intervals	
Overall	109.2	101.9	117.1
0.375	108.2	98.0	119.6
0.750	109.4	95.9	124.7
1.500	115.7	101.8	131.5
3.000	111.8	95.3	131.2
4.500	104.0	89.3	121.1

The estimate of the ratio C<sub>23,ss</sub>/C<sub>pre,ss</sub> of 109.2% with a 95% confidence interval of [101.9, 117.1%] Since this ratio is within the interval 80% to 125% steady state conditions can be assumed. However, C<sub>23,ss</sub> levels are higher than those of C<sub>pre,ss</sub>. For dose levels of 1.5 mg and 3 mg the upper limits of the 95% confidence interval are greater than 125%. The sponsor speculated that this is due to the conservative type of analysis by dose level (as compared to the analysis including all doses) and is only to be interpreted in a descriptive sense.

### **EXTENT OF EXPOSURE**

39 subjects entered the up-titration phase of the study and received daily doses of pramipexole increasing from 0.375 mg/day to 3.75 mg/day. 25 entered into the cross-over phase and received all scheduled doses, i.e., 1.5 mg IR t.i.d for 5 days (A), 4.5 mg ER q.d. fed and fasted for 5 days (B, C).

### **SAFETY EVALUATIONS**

All 39 subjects were included into the safety set. Safety was evaluated based on adverse events; clinical laboratory tests and alcohol tests; 12-Lead ECG; vital sign measurements; and physical and neurological examination. Adverse events were observed in 32 of the 39 subjects (82.1%) who had received at least one dose of pramipexole. Fatigue (69.2%), headache (48.7%), dizziness (23.0%), nausea (17.9%), insomnia (17.9%), decreased interest (15.4%), dry mouth (15.4%), and vomiting (10.3%) constituted the most frequently observed adverse events. The highest frequency of drug-related adverse events was observed under treatment with ER 3.0 (75.0%), the frequency of drug-related adverse events under the other dose levels ranged from 35.5% (ER 2.25) to 56.3% (ER 1.5).

All adverse events observed in the course of this trial were of mild or moderate intensity, apart from 3 adverse events which were classified as severe. Only one of them (vomiting on treatment with

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pramipexole 3.0 mg/day) was considered as drug-related. Three subjects were withdrawn due to study drug related adverse events: one subject reported tremor under 0.375 mg pramipexole, one subject experienced headache and nausea under 3.0 mg pramipexole, and one subject experienced auditory and visual hallucinations under treatment with 3.75 mg pramipexole. In summary, no relevant differences in the frequency and intensity of adverse events could be observed between the different dose levels, and between the three cross-over treatments at the highest dose level.

Only slight changes of vital signs were observed for vital signs in supine position or standing position, except for day 5 of the treatment ER 4.5 mg fed. No dose-related effect on safety laboratory parameters or ECG was observed. During both the up-titration phase and the cross-over phase, tolerability was assessed by the investigator as good. Of the 14 subjects who withdrew from the study, all withdrew during the up-titration phase, and only 3 of these were due to study drug related adverse events.

**CONCLUSION:**

**Relative Bioavailability:** The pramipexole 4.5 mg ER tablet given q.d. resulted in about the same 24h-exposure compared as the 1.5 mg IR tablet given t.i.d [100.6% (93.7-108.0%)] with about the same inter-individual variability. The  $C_{max,ss}$  [95.4% (90.4-100.6)] and  $C_{pre,ss}$  [100.2% (87.7-114.5%)] were also comparable.

**Effect of Food:** No food effect was shown with respect to  $AUC_{0-24h,ss}$  [113.7% (105.8-122.1)].  $C_{max,ss}$  was higher on average by about 20% under fed conditions [120.2%] and the 90% CI was slightly outside the boundaries of 80 to 125% [113.9-126.8]. The median  $t_{max,ss}$  was slightly prolonged from 6.0 h to 7.92 h under fed conditions.

**Lack of Dose Dumping:** Concomitant food intake did not result in any irregular release of pramipexole from the matrix tablet formulation.  $AUC_{0-6,ss}$  and  $AUC_{0-4,ss}$  never exceeded 30% of  $AUC_{\tau,ss}$  excluding dose dumping when taken with food.

**Dose Proportionality:** Dose proportional exposure was observed between the lowest strength [0.375 mg] and the highest strength [4.5 mg] using a power model and by comparing dose normalized [normalized to 4.5 mg]  $C_{pre,ss}$  norm [Predose concentration] and  $C_{max,ss}$  norm for all strengths.

**Safety:** The step-wise up-titration scheme applied in this trial lead to satisfactory tolerability.

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**4.2 STUDY NUMBER: 248.560; Phase 1**

**TITLE:** A single dose five-way cross over study to establish an in vitro/in vivo correlation (IVIVC) for oral slow release (ER) tablets with 0.375 mg pramipexole in healthy male volunteers

**DATES OF STUDY:** 20 October 2005 to 19 December 2005

**LOCATION OF STUDY:** Clinical Research

Pramipexole Dihydrochloride

Boehringer Ingelheim Pharma GmbH & Co. KG  
Biberach, Germany

**OBJECTIVE**

- **Primary:** Determine if a correlation exists to predict in vivo bioavailability (AUC<sub>0-30</sub>, C<sub>max</sub>) by means of in vitro dissolution data (IVIVC).
- **Secondary:** to investigate the effect of the intake of food 30 minutes prior to drug administration on pramipexole ER C2.

**STUDY DESIGN:**

This was an open-label, single-center, randomized, active controlled, five-treatment, five-period, five-way cross-over study to evaluate the IR tablet and 4 different extended-release pramipexole formulations (ER C, ER C2, ER C2A, and ER C2B) under fasted conditions and pramipexole ER C2 in the fed state. There was a washout period of ~118 h between treatment periods. Formulation ER C2 was given in two cross-over periods: fasted state; and with a high-fat meal (composition below) 30 minutes prior to the administration.

COMPOSITION OF THE HIGH FAT, HIGH CALORIES MEAL ACCORDING TO THE FDA GUIDANCE "FOOD-EFFECT BIOAVAILABILITY AND FED BIOEQUIVALENCE STUDIES"			
	Amount	Energy [calories]	Energy [kJ]
2 Eggs	120 g	184	772
2 Strips of Bacon	30 g	160	672
Butter	30 g	225	945
2 Slices of Toast	60 g	140	588
Hash Brown Potatoes	120 g	84	352
Whole Milk	240 g	152	640
Sum		945*	3969

\*Approximately 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat

In vitro dissolution profiles were determined for all ER formulations and compared with the respective plasma profiles to evaluate an in vitro/in vivo correlation (IVIVC). This will be reviewed by the Office of Pharmaceutical Sciences. No important protocol violations occurred during the study.

**SUBJECT AND TREATMENT INFORMATION*****Subject Demographic Characteristics***

The study population consisted only of 15 healthy male volunteers, age 18 to 50 years, BMI: 18.5 to 29.9 kg/m<sup>2</sup>.

***Population Size Determination***

Based on publications, a sample size of 15 subjects was considered sufficient for applying an IVIVC.

The small sample size does not allow for any conclusion on differences between treatments.

***Study drugs***

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**Test product:** All four different pramipexole ER tablets contained 0.375 mg of Pramipexole dihydrochloride monohydrate:

- Treatment B: ER C2: Batch B050612- (b) (4) (target formulation) FASTED
- Treatment C: ER C2A: Batch B050606- (b) (4) (20% faster release than target formulation) FASTED
- Treatment D: ER C2B: Batch B050607- (b) (4) (20% slower release than target formulation) FASTED
- Treatment E: ER C: Batch B050509- (b) (4) (previous target formulation, trial BI 248.529) FASTED
- Treatment F: ER C2: Batch B050612- (b) (4) (target formulation) FED

**Reference Product:**

- Treatment A: Pramipexole IR tablets, 0.125 mg Batch 503806

**Sample Collection and Handling**

**Plasma Sampling:** 2.7 mL of blood were taken in an EDTA-anticoagulant tube. Sampling times are given below.

BLOOD SAMPLING TIME POINTS RELATIVE TO DRUG ADMINISTRATION		
Formulation	Visit	Time Points
C, C2, C2A, C2B	3 to 7	-1.0, 0.3, 1.0, 1.3, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 14.0, 22.0, 26.0, and 30.0
IR	2	-1.0, 0.15, 0.3, 1.0, 1.3, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 14.0

**Urine sampling:** Urine was collected up to 30 hours for all treatments in the fed state. Urine was collected over 5 days following administration of ER C2 in the fasted state.

**ANALYTICAL PROCEDURES**

**Pramipexol in Plasma:** Pramipexole was determined by (b) (4) using a validated HPLC-MS/MS assay. Assay performance was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of quality control (QC) samples. 4 of the 6 QC samples had to be within  $\pm 15\%$  of their respective nominal values (2, not at the same concentration, could be outside  $\pm 15\%$ ). The accuracy met the acceptance criteria. Samples were analyzed between 27 December 2005 and 19 January 2006.

A single dose five-way, cross-over study to establish an in-vitro/in-vivo correlation (IVIVC) for oral slow release (ER) tablets with 0.375 mg pramipexole in healthy male volunteers.			
<b>Study Drug</b>	Pramipexole		
<b>Internal Standard</b>	D7-pramipexole		
<b>Test site</b>	(b) (4)		
<b>Calibration Standard</b>	0.05 to 15.00 ng/mL (8 point curve)		
<b>Regression Method</b>	Weighted linear least-squares regression ( $1/x^2$ )		
<b>% CV (Precision)</b>	5.71 LLOQ; 2.88 ULOQ		
<b>Accuracy (%Nominal)</b>	114.2% LLOQ; 102.05% ULOQ		
<b>Calibration Curve n=16</b>	r2= 0.996555		
<b>QC samples (n=32)</b>	0.150 ng/mL	2.00 ng/mL	12.00 ng/mL
<b>Inter-run Precision %CV</b>	5.09	3.31	3.16

## Pramipexole Dihydrochloride

<b>Inter-run Accuracy</b>	4.00	5.00	4.17
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*Pramipexole Concentration in Urine:* Pramipexole in urine samples was determined using a validated HPLC-MS/MS assay. Assay performance was assessed by backcalculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of QC samples. 4 of the 6 QC samples had to be within  $\pm 15\%$  of their respective nominal values (2, not at the same concentration, could be outside the  $\pm 15\%$ ). All QC samples were within  $\pm 13\%$  of their respective nominal values. Samples were analyzed between 25 January 2006 and 27 January 2006.

<b>A single dose five-way, cross-over study to establish an in-vitro/in-vivo correlation (IVIVC) for oral slow release (ER) tablets with 0.375 mg pramipexole in healthy male volunteers. Urine</b>			
<b>Study Drug</b>	Pramipexole		
<b>Internal Standard</b>	D7-pramipexole		
<b>Test site</b>	(b) (4)		
<b>Calibration Standard</b>	0.1 to 100 ng/mL (8 point curve)		
<b>Regression Method</b>	Weighted linear least-squares regression ( $1/x^2$ )		
<b>% CV (Precision)</b>	5.51 LLOQ; 2.84 ULOQ		
<b>Accuracy (%Nominal)</b>	110.2% LLOQ; 103.0% ULOQ		
<b>Calibration Curve n=16</b>	<b>r<sup>2</sup>= 0.997513</b>		
<b>QC samples (n=32)</b>	0.20 ng/mL	32.00 ng/mL	80.00 ng/mL
<b>Inter-run Precision %CV</b>	4.88	3.59	3.26
<b>Inter-run Accuracy</b>	6.50	4.00	5.38

**PHARMACOKINETICS**

**Statistical Methodology:** In vitro/in vivo correlation analysis; ANCOVA; 90% two-sided CI for the AUC<sub>0-30</sub> ratio of the test to reference and for C<sub>max</sub>; descriptive statistics.

**Pharmacokinetic Parameters of Pramipexole:** Mean PK parameters for the different formulations and conditions (fed/fasted) are listed in the following tables. All ER formulations had similar (AUC) and maximum (C<sub>max</sub>) exposure. No relevant difference was observed for AUC and C<sub>max</sub> when comparing pramipexole ER C2 in fasted and fed subjects.

GMEAN [GCV] NONCOMPARTMENTAL PK PARAMETERS OF PRAMIPEXOLE AFTER A SINGLE DOSE OF EITHER 0.125 MG IR OR 0.375 MG ER [FORMULATION C2 WAS GIVEN WITH AND WITHOUT FOOD]						
	IR	C2 FASTED	C2 FED	C2A	C2B	C
AUC 0-24 [ng*h/mL]	2.10 [10.9]	4.63 [19.7]	5.23 [14.1]	5.11 [15.9]	4.47 [15.8]	4.93 [14.8]
AUC 0-30 [ng*h/mL]	--	5.29 [22.7]	5.83 [14.2]	5.78 [15.9]	5.18 [15.1]	5.60 [14.8]
AUC 0-inf [ng*h/mL]	2.42 [12.1]	6.61 [31.8]	6.77 [14.8]	6.98 [17.9]	7.04 [34.5]	6.91 [15.0]
%AUC tz-inf *	31.2 [17.5]	19.4 [50.3]	14.0 [14.1]	16.0 [35.8]	20.9 [52.1]	17.8 [39.5]

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C <sub>max</sub> [ng/mL]	0.218 [16.3]	0.268 [10.9]	0.333 [12.0]	0.299 [15.4]	0.254 [20.1]	0.273 [13.0]
T <sub>max</sub> [h]	0.983 [0.2-2.0]	9.98 [3.0-14.1]	6.05 [3.0-14.1]	6.00 [5.0-14.0]	5.02 [3.0-14.0]	9.98 [4.0-14.1]
fe <sub>0-30</sub> %	79.1 [9.32]	64.7 [20.9]	72.0 [16.7]	66.4 [31.8]	63.3 [22.7]	65.0 [17.7]
Ae <sub>0-30</sub> [μg]	69.1 [9.32]	169 [20.9]	189 [16.7]	174 [31.8]	166 [22.7]	65.0 [17.7]
t <sub>1/2</sub> [h]	8.08 [12.9]	9.38 [38.5]	8.40 [9.79]	9.00 [25.2]	11.3 [59.0]	9.67 [27.5]
CL/F [mL/min]	602 [12.1]	661 [31.8]	645 [14.8]	626 [17.9]	620 [34.5]	632 [15.0]
v <sub>z</sub> /F [L]	421 [12.8]	537 [28.0]	469 [16.8]	487 [24.5]	605 [29.9]	529 [29.3]
MRT [h]	12.0 [11.8]	19.5 [27.7]	17.3 [7.02]	18.6 [13.6]	22.3 [47.8]	19.4 [16.0]
*For those individuals the area up to C <sub>30</sub> was extrapolated using C <sub>tz</sub> , the concentration predicted by regression line for the time t <sub>z</sub> and the apparent terminal rate constant $k_z$ .						

All ER formulations (fasted) as well as C2 (fasted and fed) had similar plasma concentration time-profiles; the apparent gMean t<sub>1/2</sub> ranged from 9.00 to 11.3 h. The inter-individual variability was higher for the ER formulations than for the IR.

**Food-Effect**

No food effect was obvious when comparing AUC<sub>0-30h</sub> of pramipexole ER C2 given either fasted or after a high fat meal. The gMean ratio fed/fasted of AUC<sub>0-30h</sub> was 110.3% and the 90% confidence interval (90%CI) ranged from 101.5 to 119.8%. Food did affect the C<sub>max</sub>; the upper limit of the 90% CI was 134.1%, outside the bioequivalence boundary of 125%.

RELATIVE BIOAVAILABILITY OF PRAMIPEXOLE AFTER SINGLE-DOSE ADMINISTRATION OF 0.375 MG ER TABLET IN THE FED OR FASTED STATE [STUDY 248.560]						
Parameters n=15	gMean	gMean	Mean Ratio [Fed/Fasted]	Intra-indiv. gCV	90% Confidence Intervals	
	FED	FASTED			Lower Limit	Upper Limit
C <sub>max</sub> [ng/mL]	0.33	0.27	124.1	12.5	115.1	134.1
AUC <sub>0-30 h</sub> [ng*h/mL]	5.83	5.29	110.3	13.6	101.5	119.8

**Comparison between formulation C2 (new target formulation) and C (previous target formulation)**

Formulation C and the new target formulation C2 were bioequivalent with 90% CI ranging from 97.5 to 115.0 % and 94.3 to 109.8 % for AUC<sub>0-30h</sub> and C<sub>max</sub>, respectively.

COMPARISON OF NEW PRAMIPEXOLE TARGET FORMULATION [C2] AND PREVIOUS TARGET FORMULATION [C] [STUDY 248.560]						
Parameters n=15	C2		C		90% Confidence Intervals	
	gMean	g%CV	gMean Ratio	g%CV	Lower Limit	Upper Limit
C <sub>max</sub> [ng/mL]	0.27	10.9	0.27	13.0	94.3	109.8

## Pramipexole Dihydrochloride

AUC <sub>0-30 h</sub> [ng*h/mL]	5.29	22.7	5.60	14.8	97.5	115.0
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***Drug urine concentration-time profiles of pramipexole***

The amount of pramipexole excreted over the time interval from drug administration to 30 h after drug administration (Ae<sub>0-30</sub>) was similar for all ER formulations under fasted conditions. The gMean Ae<sub>0-30</sub> (%gCV) ranged from 166 µg (22.7%) for formulation C2B to 174 µg (31.8%) for formulation C2A. Between 63.3 (22.7%) and 66.4 (31.8%) percent of the given dose was excreted within 30 h after drug administration (fe<sub>0-30</sub>). In contrast, when the IR formulation was given, 79.1 (9.32%) percent of the dose was excreted in urine within 30 h.

When formulation C2 was given with food, Ae<sub>0-30</sub> increased on average from 169 µg (20.9%) under fasted conditions to 189 µg (16.7%) under fed conditions; fe<sub>0-30</sub> rose from 64.7 (20.9%) to 72.0 (16.7) percent. The urinary excretion of pramipexole after administration of the target formulation C2 was further followed in 24 h intervals up to 120 h after administration. After 120 h, 79.8 (24.2%) percent of the given dose was renally excreted.

**IN VITRO/INVIVO CORRELATION (IVIVC)**

The mean absorption from deconvolution of individual plasma concentration-time profiles after administration of ER formulation C2, C2A, and C2B to fasted subjects was compared with the mean absorption derived from deconvolution of mean concentration time profiles. An IVIVC was developed. This is being reviewed by the Office of Pharmaceutical Sciences.

**EXTENT OF EXPOSURE**

Fifteen subjects were exposed to the 4 different pramipexole 0.375 mg ER formulations.

**SAFETY EVALUATIONS**

Safety and tolerability was assessed by the occurrence of adverse events, measurement of vital signs (pulse rate, systolic, and diastolic blood pressure), laboratory measurements, and physical examinations. All the pramipexole ER formulations studied (C, C2, C2A, C2B in the fasted state and C2 in the fed state) were safe and generally well tolerated at the dose administered (0.375 mg as a single dose). The global tolerability of the ER formulations was good in the vast majority of the subjects.

**CONCLUSIONS:**

***Relative Bioavailability Single-Dose [Fasted]:*** The total exposure was similar among the ER formulations C, C2, C2B, and C2A after single dose in the fasted state [4.63 ng\*h/mL to 5.11 ng\*h/mL]; T<sub>max</sub> varied for the ER formulations from 5.02 hours to 9.98 hours. The T<sub>max</sub> for the IR formulations was 0.983 hours.

***Food Effect:*** The effect of food on the lowest dose strength of the pramipexole ER formulation was regarded as negligible when the target formulation ER C2 was taken after a high fat meal. Mean C<sub>max</sub> increased 24% [90% CI =115.1- 134.1%]; the ratio of gMean between fed and fasted treatments for AUC

## Pramipexole Dihydrochloride

was 110.3 [90% CI=101.5-119.8%] and the Tmax was shortened by approximately 4 hours [9.98 hours fasted -6.05 hours fed].

**Safety:** The analysis of AE data, laboratory values, and vital signs did not raise any concerns regarding the safety and tolerability of the pramipexole ER formulations investigated.

### 4.3 STUDY NUMBER: 248.607; Phase 1

**TITLE:** A multiple dose study of pramipexole with increasing doses (0.375 mg to 1.5 mg q.d.) of oral extended release (ER) tablets with a two-way crossover comparison of 0.375 mg pramipexole ER q.d. versus 0.125 mg immediate release (IR) tablet t.i.d. and 1.5 mg ER tablet q.d versus 0.5 mg IR tablet t.i.d. in Japanese healthy male volunteers.

**DATES OF STUDY:** 09 September 2006 to 21 November 2006

**LOCATION OF STUDY:** [REDACTED] (b) (4)

#### OBJECTIVE

- **Relative Bioavailability:** Determine the relative bioavailability of the 0.375 mg ER tablet q.d versus the pramipexole 0.125 mg IR-tablet tid and the 1.5 mg ER tablet q.d versus the pramipexole 0.5 mg IR-tablet tid after multiple dosing.
- **Dose Proportionality:** Demonstrate dose proportionality between the dose strengths of the pramipexole ER formulation of 0.375, 0.75, and 1.5 mg after multiple daily (q.d.) dosing.

#### STUDY DESIGN:

Two-way crossover study, with an up-titration and down-titration period (0.375 mg to 1.5 mg), in 12 healthy Japanese male subjects. All doses were administered with 230 mL of non-sparkling water, 30 minutes after the start of breakfast or a light meal according to the following schedule. Subjects were randomly assigned to the treatment group A or B and treated for 5 days at each dose. There were no protocol deviations.

- **Treatment A:** ER to IR
- **Treatment B:** IR to ER

DOSE LEVELS, TREATMENT AND POSOLOGY							
Visit	2	3	4	5	6	7	
Treatment	Cross-over	Cross-over	Up-titration	Cross-over	Cross-over	Down-titration	
Daily Dose	0.375 mg	0.375 mg	0.75 mg	1.5 mg	1.5 mg	0.75 mg	0.375 mg
A	0.375 mg ER 1 tablet qd	0.125 mg IR 1 tablet tid	0.375 mg ER 2 tablets	1.5 mg ER 1 tablet qd	0.5 mg IR 1 tablet tid	0.375 mg ER 2 tablets qd	0.375 mg ER 1 tablet qd
B	0.125 mg IR 1 tablet tid	0.375 mg ER 1 tablet qd		0.5 mg IR 1 tablet tid	1.5 mg ER 1 tablet qd		

#### SUBJECT AND TREATMENT INFORMATION

##### *Subject Demographic Characteristics*

Pramipexole Dihydrochloride

24 healthy male Japanese subjects, mean age 24.9 years [20 to 40 years], mean BMI 20.05 kg/m<sup>2</sup> [17.6 to 26.4 kg/m<sup>2</sup>] completed the study. 12 subjects were assigned to each treatment group. There were no withdrawals or drop-outs.

### ***Population Size Determination***

The sample size was not based on a power calculation. A total sample size of 24 evaluable subjects (12 subjects per sequence) was considered as sufficient for comparison of relative BA.

### ***Study drugs***

Test product: Pramipexole ER tablets: 0.375 mg; Batch Number 06067; 1.5 mg; Batch 06068

Reference: Immediate Release Tablet: 0.125 mg; Batch 06069; 0.5 mg; Batch 06070

### ***Sample Collection and Handling***

#### Plasma Sampling:

- Predose, 1, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours (just before next administration) after administration of ER tablets on Day 5 of Visits 2, 3, 4, 5, and 6 (planned times: 96:00, 97:00, 98:00, 98:30, 99:00, 100:00, 102:00, 104:00, 106:00, 108:00, and 119:50)
- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 16 hours (just before next administration) after administration of IR tablets on Day 5 of Visits 2, 3, 5, and 6 (planned times: 96:00, 96:30, 97:00, 97:30, 98:00, 98:30, 99:00, 100:00, 102:00, 104:00, and 112:00)

#### Urine sampling

Urine was collected quantitatively (determination of weight) at predose, 0 to 8 hours, and from 8 to 24 hours after morning administration on Day 5 of Visits 2 through 6

### **ANALYTICAL PROCEDURES**

*Pramipexol in Plasma:* Plasma concentrations of 400  $\mu$ L of pramipexole were analyzed by a validated HPLC tandem mass spectrometry method at (b) (4). Samples were extracted using an (b) (4) A C18 reversed phase HPLC column with isocratic elution and detection by MS/MS using electrospray ionisation in the positive ion mode was used. Assay performance was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of quality control samples. No relevant interference of endogenous compounds was observed in the blank plasma of humans. Samples were analyzed between 08 November and 04 December 2006. The summary of the in-study assay validation is given in the following table.

<b>IN STUDY ACCURACY AND PRECISION OF BIOANALYSIS OF PRAMIPEXOLE IN PLASMA</b>		
<b>Study Drug</b>	Pramipexole Dihydrochloride	Batch 0006; exp. 28-Feb-2010
<b>Internal Standard</b>	D7-pramipexole	Batch AGS337/10; exp. 03-May-2008
<b>Matrix</b>	EDTA Plasma	
<b>Calibration Standard</b>	0.05 to 15.00 ng/mL (8 point curve)	
<b>Regression Method</b>	Weighted linear least-squares regression ( $1/x^2$ )	

## Pramipexole Dihydrochloride

<b>% CV (Precision) n=10/12</b>	4.37 LLOQ; 1.77 ULOQ		
<b>Accuracy (%)</b>	0.20% LLOQ; 0.00% ULOQ		
<b>Calibration Curve n=12</b>	r2= 0.998937		
<b>QC samples (n=56)</b>	0.15 ng/mL	2.00 ng/mL	12.00 ng/mL
<b>Inter-run Precision %CV</b>	5.15	1.58	1.92
<b>Inter-run Accuracy</b>	3.33	0.00	-.83

*Pramipexole Concentration in Urine*

Urine concentrations of pramipexole using 200 µL were analyzed by a validated HPLC-MS/MS method a (b) (4). Samples were cleaned-up with an (b) (4) (b) (4). Chromatography used a C18 reversed phase HPLC column with isocratic elution and detection by MS/MS using electrospray ionisation in the positive ion mode. Assay performance during the study was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of quality control samples. No relevant interference of endogenous compounds was observed in the blank urine of humans. In-study assay validation results are summarized in the following table.

<b>IN STUDY ACCURACY AND PRECISION OF BIOANALYSIS OF PRAMIPEXOLE IN URINE</b>				
<b>Study Drug</b>	Pramipexole Dihydrochloride		Batch 0006; exp. 28-Feb-2010	
<b>Internal Standard</b>	D7-pramipexole		Batch AGS337/10; exp. 03-May-2008	
<b>Matrix</b>	Human Urine			
<b>Calibration Standard</b>	0.1 to 100 ng/mL (8 point curve)			
<b>Regression Method</b>	Weighted linear least-squares regression (1/x <sup>2</sup> )			
<b>% CV (Precision)</b>	1.00 LLOQ; 4.88 ULOQ			
<b>Accuracy (%)</b>	1.00% LLOQ; 4.00% ULOQ			
<b>Calibration Curve n=3</b>	r2= 0.997201			
<b>QC samples (n=11/12)</b>	0.2 ng/mL	3.00 ng/mL	80 ng/mL	2000 ng/mL
<b>Inter-run Precision %CV</b>	13.74	3.55	3.42	4.60
<b>Inter-run Accuracy</b>	1.50	-1.33	-1.25	3.00

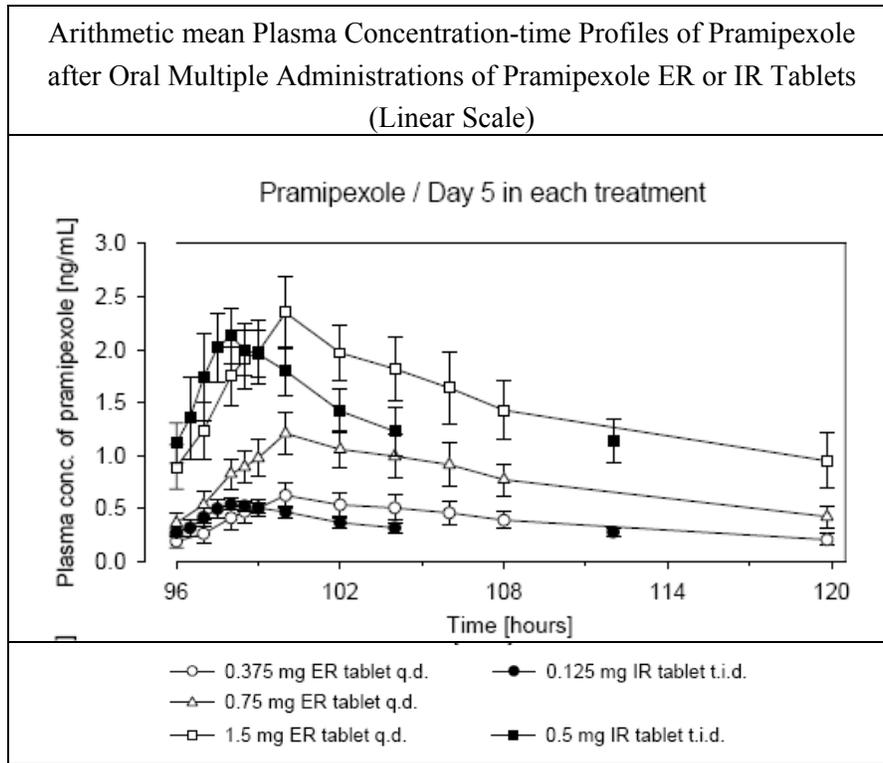
**PHARMACOKINETICS**

Pharmacokinetic parameters of pramipexole were determined by non-compartmental procedures.

***Assessment of Relative BA at steady state:***

The following figure shows the arithmetic mean plasma concentration-time profiles on Day 5 in each treatment period. The shape of the plasma concentration-time profile did not differ between the different doses of ER tablet treatments. The plasma concentrations at pre-dose and 24 hours post dose in ER tablet treatments were comparable. Steady state had been reached within 5 days in each treatment period. The plasma concentrations at pre-dose sampling points with 8-hour intervals (96, 104, and 112 hours) in the IR tablet treatments were also comparable.

Pramipexole Dihydrochloride



The following table summarizes the noncompartmental pharmacokinetic parameters of all treatments. AUC<sub>0-24,ss</sub> in IR tablet treatments was calculated by multiplying AUC<sub>τ,ss</sub> (τ=8 hours) by three. Compared with the IR tablets, the peak concentrations of the ER tablet were slightly higher and the trough concentrations were lower. The peak-to-trough fluctuation [PTF] was larger in the ER tablets than in the IR tablets.

## Pramipexole Dihydrochloride

Table 11.5.2.3: 1 Noncompartmental pharmacokinetic parameters of pramipexole after multiple oral administrations of pramipexole ER or IR tablets

Noncompartmental pharmacokinetic parameters of pramipexole						
		0.375 mg ER q.d.	0.125 mg IR t.i.d.	0.75 mg ER q.d.	1.5 mg ER q.d.	0.5 mg IR t.i.d.
$AUC_{0-24,ss}$ <sup>1)</sup>	[ng·h/mL]	8.86 (20.9)	10.0 (10.9)	17.8 (14.6)	34.9 (15.0)	39.1 (12.6)
$C_{max,ss}$	[ng/mL]	0.626 (16.0)	0.554 (10.6)	1.20 (17.3)	2.36 (12.7)	2.14 (11.3)
$t_{max,ss}$ <sup>2)</sup>	[h]	4.00 (2.00-8.00)	2.00 (1.50-3.00)	4.00 (2.00-8.02)	4.00 (2.50-6.00)	2.00 (0.500-3.00)
$C_{min,ss}$	[ng/mL]	0.182 (39.9)	0.291 (16.2)	0.397 (23.9)	0.909 (29.7)	1.11 (17.4)
PTF	[%]	117 (21.9)	61.7 (20.5)	105 (23.2)	98.0 (18.5)	62.2 (16.5)
$Ae_{0-24,ss}$	[µg]	226 (18.9)	244 (9.29)	441 (13.1)	851 (16.3)	961 (14.1)

N=24

g: Mean (%CV)

1)  $AUC_{0-24,ss}$  for ER.  $AUC_{0-24,ss}$  for IR.

The statistical results are presented in the following table. The 90% confidence intervals for AUC and  $Ae$  met the criterion of bioequivalence (80-125%).

RELATIVE BIOAVAILABILITY OF PRAMIPEXOLE AFTER MULTIPLE ADMINISTRATION OF ER OR IR TABLETS (STUDY 248.607)						
Parameters	Daily dose (mg)	ER (Test)	IR (Reference)	Ratio	90% CI	
					Lower	Upper
$AUC_{0-24,ss}$ ng·h/mL	0.375	8.86	10.02	88.4	83.33	93.88
	1.5	34.87	39.06	89.3	86.72	94.77
$C_{max,ss}$ ng/mL	0.375	0.626	0.554	113.2	107.48	119.15
	1.5	2.363	2.139	110.5	106.69	114.43
$Ae_{0-24,ss}$ [µg]	0.375	226.20	244.42	93.6	86.23	99.33
	1.5	851.02	961.16	88.6	82.72	94.77

**Results of Relative Bioavailability:****0.375 mg daily dose:**

- **AUC:** The  $AUC_{0-24,ss}$  of the ER 0.375 mg formulation compared to the IR 0.125 mg tablet tid for was 88.4% (90 %CI= 83.3-93.9);
- **$C_{max}$ :**  $C_{max,ss}$  of the ER 0.375 mg ER formulation qd compared to the IR 0.125 mg tablet tid was 113.2% (90%CI= 107.5-119.2).
- **$T_{max}$ :**  $T_{max}$  for the 0.375 mg ER formulation was 4 hours vs. 2 hours for the 0.125 mg IR tablet tid.
- **Variability:** The inter-subject variation was 5.2 for  $AUC_{0-24,ss}$  at 0.375 mg/day.

Pramipexole Dihydrochloride

**1.5 mg daily dose:**

- **AUC:** The AUC<sub>0-24,ss</sub> of the ER 1.5 mg formulation compared to the IR 0.5 mg tablet tid was 89.3% (90 %CI= 86.7-94.8%);
- **C<sub>max</sub>:** C<sub>max,ss</sub> of the ER 1.5 mg formulation compared to the IR 0.5 mg tablet tid was 110.5% (90%CI= 106.7-114.4).
- **T<sub>max</sub>:** T<sub>max</sub> for the 1.5 mg ER formulation was 4 hours vs. 2 hours for the 0.5 mg IR tablet tid.
- **Variability:** The inter-subject variation was 7.1 for C<sub>max,ss</sub> at 1.5 mg/day.

**Assessment of Dose proportionality of pharmacokinetic parameters:**

Dose proportionality for pramipexole ER dosages from 0.375 to 1.5 mg q.d was explored using the power model that describes the functional relationship between dose and PK endpoints using the following equation:

$$Y_{ij} = \alpha' + \beta * X_i + s_j + \epsilon_{ij}$$

Y <sub>ij</sub>	logarithm of PK endpoint for subject j at dose level I; where i=1, 2, 3, j=1, 2, ...N
α'	intercept parameter
β	slope parameter
X <sub>i</sub>	logarithm of dose i
s <sub>j</sub>	random effect on subject j
ε <sub>ij</sub>	random error associated with subject j at dose level I (assumed to be independent and identically normally distributed)
equation could be fit as a linear regression model	

For the evaluation of dose proportionality, a two-sided 95% confidence interval of the slope was computed. The confidence interval (CI) had to be interpreted in the perspective of the exploratory character of this study. A dose-proportional increase in exposure was demonstrated over the entire dose range from 0.375 to 1.5 mg pramipexole ER given q.d. over 5 days. There was no deviation from linearity, since the 95% CIs of slope β included 1 for the parameters AUC<sub>τ,ss</sub>, C<sub>max,ss</sub> and Ae<sub>0-24,ss</sub> as determined by analysis of covariance (ANCOVA) using power model.

Results of the Dose-Proportionality Analysis of the Pharmacokinetic Parameters of Pramipexole ER Tablets				
			90% Confidence Intervals	
Parameter	Estimate of β	Standard Error	Lower Limit	Upper Limit
AUC <sub>τ,ss</sub> (ng*h/mL)	0.9886	0.0257	93.68	104.03
C <sub>max, ss</sub> (ng/mL)	0.9578	0.0249	90.76	100.80
Ae <sub>0-24,ss</sub> (μ)	0.9558	0.0322	89.10	102.06

**EXTENT OF EXPOSURE**

## Pramipexole Dihydrochloride

All the 24 subjects completed the treatment as scheduled. Total period of exposure to pramipexole over 27 days was 23.625 mg per subject: 14.25 mg for ER and 9.375 mg for IR.

**SAFETY EVALUATIONS**

Physical examination, blood pressure and pulse rate in supine and sitting positions, laboratory parameters, ECG findings, adverse events, and assessment of global tolerability. Adverse events occurred dose-dependently, but the frequency of adverse events was comparable between ER and IR for the same dose levels. Global tolerability assessed by the investigator was considered as good in 79.2% (ER 1.5 mg q.d.) to 100.0% (ER 0.375 mg q.d.) of subjects. No subjects discontinued the treatment prematurely because of adverse events.

**REVIEWERS COMMENTS**

The study indicated that the ER 0.375 mg and 1.5 mg was comparable to the IR at the same daily dose. When compared to healthy male Caucasians from Study 248.530, , the pramipexole peak exposure (C<sub>max</sub>) at a given pramipexole ER dose was approximately 40-50% higher in healthy male Japanese subjects compared to healthy male Caucasians. The effect was much less pronounced in the AUC (12-22% higher). The difference in peak exposure is most likely caused by the difference in body weight (BW). When normalized for body weight the differences were minimal. The mean BW of Japanese healthy volunteers was 60.2 kg compared to 79.3 kg for the Caucasian healthy volunteers.

Comparison of PK parameters between Healthy Japanese Males and Healthy Caucasian Males							
Strength	Race	AUC <sub>0-24,ss</sub>	C <sub>max,ss</sub>	C <sub>min,ss</sub>	T <sub>max</sub>	PTF	Ae <sub>0-24,ss</sub>
		ng*h/mL	ng/mL	ng/mL	h	%	μ
ER 0.375 mg qd	Japanese	8.86 (20.9)	0.626 (16.0)	0.18 (39.9)	4.0 (2.0-8.0)	117 (21.9)	226 (18.9)
ER 0.375 mg qd	White	7.79 (20.8)	0.423 (19.1)	0.22 (28.5)	6.0 (0.52-16.1)	65.3 (31.1)	
Japanese/White		14% ↑	48% ↑	18% ↓	2 h ↓	51.7 ↑	
ER 0.75 mg qd	Japanese	17.8 (14.6)	1.20 (17.3)	0.40 (23.9)	4.0 (2.0-8.0)	105 (23.2)	441 (13.1)
ER 0.75mg qd	White	14.6 (18.6)	0.79 (16.2)	0.45 (22.4)	3.5 (2.0-12.0)	57.0 (28.6)	
Japanese/White		22% ↑	52% ↑	11% ↓	0.5 h %↑	84% ↑	
ER 1.5 mg qd	Japanese	34.9 (15.0)	2.36 (12.7)	0.91 (29.7)	4.0 (2.5-6.0)	98.0 (18.5)	851 (16.3)
ER 1.5 mg qd	White	31.2 (29.0)	1.71 (24.7)	0.90 (41.1)	9.0 (2.5-16.1)	68.0(19.6)	
Japanese/White		12% ↑	38% ↑	1% ↔	5 h ↓	44% ↑	
IR 0.125 mg tid	Japanese	10.0 (10.9)	0.554 (10.6)	0.291 (16.2)	2.0 (1.5-3.0)	61.7 (20.5)	244 (9.29)
IR 0.5 mg tid	Japanese	39.1 (12.6)	2.14 (11.3)	1.11 (17.4)	2.0 (0.5-3.0)	62.2 (16.5)	961 (14.1)
IR 1.5 mg tid	White	94.4 (21.4)	5.26 (19.0)		1.0 (0.5-3.0)	54.9 (35.1)	1080 (66.8)
ER 3.0 mg qd	White	67.6 (22.1)	3.61 (23.8)	1.98 (24.1)	7.0 (2.0-16.0)	59.8 (36.4)	
ER 4.5 mg qd	White	91.7 (30.1)	4.89 (22.3)		6.0 (1.5-16.0)	55.1 (33.4)	1140 (58.6)

Pramipexole Dihydrochloride

## CONCLUSIONS

- **Relative BA:** The daily exposures to pramipexole following administration of ER tablets and IR tablets were compared.
    - *0.375 mg Daily Dose:* For the 0.375 mg daily dose, the AUC 0-24,ss of the ER 0.375 mg formulation compared to the IR 0.125 mg tablet tid for was 88.4% (90 %CI= 83.3-93.9); Cmax,ss of the ER 0.375 mg ER formulation qd compared to the IR 0.125 mg tablet tid was 113.2% (90%CI= 107.5-119.2; Tmax for the 0.375 mg ER formulation was 4 hours vs. 2 hours for the 0.125 mg IR tablet tid and the inter-subject variation was 5.2 for AUC0-24,ss at 0.375 mg/day.
    - *1.5 mg daily dose:* For the 1.5 mg daily dose, the AUC0-24,ss of the ER 1.5 mg formulation compared to the IR 0.5 mg tablet tid was 89.3% (90 %CI= 86.7-94.8%); Cmax,ss of the ER 1.5 mg formulation compared to the IR 0.5 mg tablet tid was 110.5% (90%CI= 106.7-114.4); Tmax for the 1.5 mg ER formulation was 4 hours vs. 2 hours for the 0.5 mg IR tablet tid; and the inter-subject variation was 7.1 for Cmax,ss.
  - **Dose-proportionality:** In this trial, three dose levels (0.375, 0.75 and 1.5 mg) were administered as ER tablets. The PK parameters, AUC<sub>τ,ss</sub>, Cmax,ss and Ae<sub>0-24,ss</sub>, increased with increasing dose. ANCOVA showed that the estimated slopes for these pharmacokinetic parameters were close to one and their 95% confidence intervals included one, indicating dose-proportionality. The Cmax,ss values were slightly higher (10-13%) and the Cmin,ss values were lower (18-37%).
  - **Safety:** Frequency of events was comparable between ER and IR. Slight decreases of systolic and diastolic blood pressures accompanied by slight increases of pulse rate were observed, but no differences were found in the changes between the treatments with ER and IR.
- 

## 4.4 STUDY NUMBER: 248.529; Phase 1

### TITLE:

A multiple dose seven-way cross-over formulation-finding study comparing the oral bioavailability of seven prototype slow-release formulations with 0.75 mg pramipexole (four days each) to immediate-release tablets at steady state in healthy male volunteers

**DATES OF STUDY:** 24 June 2004 to 21 September 2004

**LOCATION OF STUDY:** Human Pharmacology Centre,  
Boehringer Ingelheim Pharma GmbH & Co. KG,  
Germany Clinical Research

### OBJECTIVE

Compare the oral bioavailability of seven prototype slow-release formulations containing 0.75 mg of pramipexole to the immediate-release tablets at steady-state in healthy subjects.

### STUDY DESIGN:

Pramipexole Dihydrochloride

This was an open-label, single-center, randomized, seven-way cross-over study to evaluate the IR tablet and 7 different extended-release pramipexole formulations (B, C, D, E, F, G and H) under fasted conditions. A 7-day uptitration period with increasing doses of the IR tablet preceded the start of ER dosing. Each ER formulation was given for four days. There was no washout period between treatment periods. No important protocol violations occurred during the study.

**SUBJECT AND TREATMENT INFORMATION**

***Subject Demographic Characteristics***

Out of 18 healthy male white subjects enrolled in the study, 14 subjects, age 21 to 50 years, BMI: 18.5 to 29.9 kg/m<sup>2</sup>, received the ER-formulations B to H.

***Population Size Determination***

Based on publications, a sample size of 14 subjects was considered sufficient for the exploratory comparison of the relative bioavailability of the different formulations.

***Study drugs***

***Test products:***

All pramipexole SR tablets (b) (4) contained 0.75 mg of pramipexole dihydrochloride monohydrate:

- Treatment B: formulation B: Batch B0405-09 (b) (4)<sub>r</sub>
- Treatment C: formulation C: Batch B0405-10- (b) (4)
- Treatment D: formulation D: Batch B0405-04- (b) (4)
- Treatment E: formulation E: Batch B0404-09- (b) (4)
- Treatment F: formulation F: Batch B0404-10- (b) (4)
- Treatment G: formulation G: Batch B0405-01- (b) (4)
- Treatment H: formulation H: Batch B0405-02- (b) (4)

***Reference Product:***

- Uptitration Phase: Pramipexole IR tablets, 0.125 mg Batch 402083A

Subjects were randomized to 14 sequences each including all seven test treatments. The set of these sequences were composed of two Latin 7×7 squares building a Williams design. Williams designs are a particular subgroup of Latin squares with the property that every treatment follows every other once. The treatment schedules were balanced using the following Latin square design.

B H C G D F E	E F D G C H B
C B D H E G F	F G E H D B C
D C E B F H G	G H F B E C D
E D F C G B H	H B G C F D E
F E G D H C B	B C H D G E F
G F H E B D C	C D B E H F G
H G B F C E D	D E C F B G H

Pramipexole Dihydrochloride

### ***Sample Collection and Handling***

#### *Plasma Sampling:*

Blood samples (2.7 mL) for pharmacokinetic measurements of pramipexole were taken at:

- screening (blank sample)

#### *Run-in-phase (Uptitration)*

- on day 7 of visit 2: before the morning dose (referred to as planned time 144:00); before noon doses, at 01:00 h, 01:30 h, 02:00 h, 02:30 h, 03:00 h, 04:00 h, 05:00 h and 06:00 h after the noon dose (referred to as planned times 150:00, 151:00, 151:30, 152:00, 152:30, 153:00, 154:00, 155:00, 156:00) and at 01:00 h, 01:30 h, 02:00 h, 02:30 h and 12:00 h after the evening dose (referred to as planned times 157:00, 157:30, 158:00, 158:30 and 168:00)

#### *Seven-way cross-over phase*

- before, 00:30 h, 01:00 h, 02:00 h, 03:00 h, 04:00 h, 06:00 h, 08:00 h, 10:00 h, 14:00 h, and 24:00 h relative to drug application time on days 4 of visits 3, 4, 5, 7, and 9 (referred to as planned times 72:00, 72:30, 73:00, 74:00, 75:00, 76:00, 78:00, 80:00, 82:00, 86:00 and 96:00. The 96:00 sample was drawn before the first dosing of the next visit, if a dosing follows)
- before dosing on days 1 of visits 7 and 9 (as trough levels of the last treatment of visits 6 and 8 (during which no complete blood PK profile was performed, referred to as planned time 96:00 of the visit)
- at 48:00 h, 72:00 h and 96:00 h after the last dosing of visit 9 (referred to as planned times 120:00, 144:00 and 168:00)

The total amount of blood collected during the trial (including laboratory) was approximately 310 mL (350 mL maximum, ~210 mL for PPX PK, 100 mL for clinical laboratory).

#### *Urine sampling*

Urine was collected quantitatively on day 7 of visit 2, from dosing (00:00 h) to 06:00 h, 06:00 h to 12:00 h, and 12:00 h to 24:00 h (referred to as planned times 144:00 to 150:00, 150:00 to 156:00 and 156:00 to 168:00).

- On day 1 of visit 3 (“training profile”) and on all days 3 and 4 of visits 3 to 9, from 00:00 h to 04:00 h, 04:00 h to 08:00 h, 08:00 h to 14:00 h, 14:00 h to 22:00 h, and 22:00 h to 24:00 h (referred to as planned times 00:00 to 04:00, 04:00 to 08:00, 08:00 to 14:00, 14:00 to 22:00, and 22:00 to 24:00 for visit 3; referred to as planned times 48:00 to 52:00, 52:00 to 56:00, 56:00 to 62:00, 62:00 to 70:00, 70:00 to 72:00, 72:00 to 76:00, 76:00 to 80:00, 80:00 to 86:00, 86:00 to 94:00, and 94:00 to 96:00 for visits 3 to 9).
- After the last dose (on day 4 of visit 9) additionally from 00:00 h to 24:00 h for days 5, 6 and 7 (referred to as planned times 96:00 to 120:00, 120:00 to 144:00, and 144:00 to 168:00)

In cases of low (less than 200 mL for 4 h intervals, less than 300 mL for 6 and 8 h intervals, less than 100 mL for 2 h intervals) urine volumes about the same volume of water was added in order to avoid precipitation of solids with freezing prior to weighing. Two aliquots of (diluted) urine (each of 5 mL) were then stored at -20°C until analysis.

### **ANALYTICAL PROCEDURES**

#### *Pramipexole in Plasma*

Pramipexole Dihydrochloride

Pramipexole was determined by (b) (4) using a validated HPLC-MS/MS assay. Assay performance was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of quality control (QC) samples. The standard correlation coefficient had to be greater than .98 and 4 of the 6 QC samples had to be within  $\pm 15\%$  of their respective nominal values (2, not at the same concentration, could be outside  $\pm 15\%$ ). Samples were analyzed between 17 August 2004 and 30 August 2004.

<b>A multiple-dose 7-way, cross-over formulation finding study comparing the oral BA of 7 prototype slow-release formulation with 0.75 mg pramipexole in healthy male volunteers.</b>			
<b>PLASMA</b>			
<b>Study Drug</b>	Pramipexole		Batch 0005/1008461
<b>Internal Standard</b>	D7-pramipexole		Batch AGS337/10
<b>Test site</b>	(b) (4)		
<b>Matrix</b>	EDTA Plasma		
<b>Calibration Standard</b>	0.05 to 15.00 ng/mL (8 point curve)		
<b>Regression Method</b>	Weighted linear least-squares regression ( $1/x^2$ )		
<b>% CV (Precision)</b>	3.22 LLOQ; 4.11 ULOQ		
<b>Accuracy (%)</b>	0.60% LLOQ; 0.00% ULOQ		
<b>Calibration Curve n=8</b>	<b>r2= 0.997637</b>		
<b>QC samples (n=23)</b>	0.15 ng/mL	2.00 ng/mL	12.00 ng/mL
<b>Inter-run Precision %CV</b>	6.61	2.75	3.22
<b>Inter-run Accuracy</b>	-3.33	0.00	0.83

#### *Pramipexole Concentration in Urine*

Pramipexole in urine samples were extracted (b) (4) followed by reversed phase liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS). Linear calibration curves for pramipexole in urine ranged from 0.1 – 100 ng/mL using 0.2 mL urine. Assay performance was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of QC samples. 4 of the 6 QC samples had to be within  $\pm 15\%$  of their respective nominal values (2, not at the same concentration, could be outside the  $\pm 15\%$ ). All QC samples were within  $\pm 13\%$  of their respective nominal values. Samples were analyzed between 26 August 2004 and 17 September 2004.

<b>A multiple-dose 7-way, cross-over formulation finding study comparing the oral BA of 7 prototype slow-release formulation with 0.75 mg pramipexole in healthy male volunteers. URINE</b>		
<b>Study Drug</b>	Pramipexole Monohydrate	Batch 0005/1008461
<b>Internal Standard</b>	D7-pramipexole	Batch AGS337/10
<b>Test site</b>	(b) (4)	
<b>Matrix</b>	Urine	

## Pramipexole Dihydrochloride

<b>Calibration Standard</b>	0.1 to 100 ng/mL (8 point curve)		
<b>Regression Method</b>	Weighted linear least-squares regression ( $1/x^2$ )		
<b>% CV (Precision)</b>	8.05 LLOQ; 3.88 ULOQ		
<b>Accuracy (%)</b>	1.00% LLOQ; 2.00% ULOQ		
<b>Calibration Curve n=20</b>	<b>r2= 0.995291</b>		
<b>QC samples (n=27/28)</b>	0.20 ng/mL	3.00 ng/mL	80.00 ng/mL
<b>Inter-run Precision %CV</b>	8.22	7.09	5.10
<b>Inter-run Accuracy</b>	4.00	0.67	4.00

**PHARMACOKINETICS**

ER formulations were compared with the IR formulation in the primary endpoints by calculating the respective ratio SR/IR. Pharmacokinetic parameters of pramipexole were determined by non-compartmental procedures.

Seven different extended-release (ER) formulations, 2 based on matrix-tablet technology and 5 based on (b) (4), were tested. None of the formulations revealed any dose dumping. The summary PK parameters are shown in the following table.

	AUC <sub>0-24,ss</sub>		C <sub>max,ss</sub>		C <sub>min,ss</sub>	
	[ng·h/mL]		[ng/mL]		[ng/mL]	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
IR	16.0	26.7	1.09	13.5	0.383	26.5
SR_B	16.3	22.5	0.918	18.2	0.387	33.6
SR_C	17.4	20.7	0.967	14.9	0.455	44.0
SR_D	18.8	24.1	1.08	41.4	0.400	44.4
SR_E	14.4	22.0	0.889	35.2	0.377	46.3
SR_F	12.7	28.2	0.657	27.5	0.329	41.5
SR_G	11.3	25.4	0.598	21.7	0.321	33.3
SR_H	17.9	20.1	1.22	27.2	0.396	39.8

Matrix tablets: formulations B (fast in vitro) and C (slow in vitro)

- gMean (gCV) AUC<sub>0-24,ss</sub>
  - B= 16.3 ng·h/mL (22.5%); (↔)
  - C= 17.4 ng·h/mL (20.7%), (↑)
  - IR formulation= 16.0 ng·h/mL and 26.7%

(b) (4) tablets: formulations D (fast in vitro) and E (slow in vitro)

- gMean (gCV) AUC<sub>0-24,ss</sub>
  - D=18.8 ng·h/mL (24.1%);(↑)
  - E=14.4 ng·h/mL (22.0%);(↓)

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(b) (4): formulations F (fast in vitro) and G (slow in vitro)

- gMean (gCV) AUC<sub>0-24,ss</sub>
  - F=12.7 ng\*h/mL (28.4%)(↓)
  - G=11.3 ng\*h/mL (25.4%)(↓)

(b) (4): formulations H (slow release increased at pH 7.3 in vitro)

- gMean (gCV) AUC<sub>0-24,ss</sub>
  - H=17.9 ng\*h/mL (20.1%)(↑)

C<sub>max,ss</sub> was lower for both formulations, B and C (gMean and gCV 0.918 ng/mL and 18.2% and 0.967 ng/mL and 14.9%, respectively) than for IR (1.09 ng/mL, 13.5%), C<sub>min,ss</sub> was higher with 0.387 ng/mL (33.6%) and 0.455 ng/mL (44.0%) for B and C, respectively. The PTF was lower with 75.8% (27.5% gCV) for formulation B and 66.4% (33.7% gCV) for formulation C than IR (104%, 26.0% gCV). Formulation G had the lowest exposure (gMean AUC<sub>0-24,ss</sub> = 11.3 ng\*h/mL), formulation D had the highest exposure (gMean AUC<sub>0-24,ss</sub> = 18.8 ng8h/mL).

#### ***Drug urine concentration of pramipexole***

The amount of pramipexole excreted in urine over 24 h (Ae<sub>0-24,ss</sub>) was comparable between IR and formulations B, C, D, E, and H, ranging on average between 414 µg and 475 µg . Peak-to-trough-fluctuation [PTF] was highest for formulation H (101%) and lowest PTF in formulations F and G (59.5% and 57.1%, respectively).

#### **SAFETY EVALUATIONS**

Overall 21 AE episodes were reported in 11 of the 18 subjects; 5 of these were assessed as possibly drug related and occurred in four of the 18 subjects. Four of the five occurred for the IR formulation in three subjects (two episodes of mild nausea, one episode of mild headache and one episode of moderate orthostatic hypotension). These three subjects discontinued study participation during or at the end of Visit 2 (IR treatment) and thus did not receive any ER treatment.

#### **CONCLUSIONS**

The matrix tablets (formulations B and C) were most comparable to the conventional IR formulation given t.i.d. However, since PTF was slightly better for formulation C (gMean = 66.4%) than for formulation B (gMean = 75.8%), formulation C was chosen as final formulation for further development. The analysis of AE data and vital signs did not raise any concerns regarding the safety and tolerability of repeated once daily dosing of 0.75 mg pramipexole in all seven SR formulations.

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### **4.5 Analytical Method Pramipexole**

**Title:** Development and validation of an HPLC-MS/MS method for the Assay of Pramipexole in Human Plasma

**Location:** (b) (4)

Pramipexole Dihydrochloride

**Date of Report:** 19 January 2005; Amended 24 January 2007 (report of long-term stability)

After (b) (4) on Oasis MCX 30 mg 96 well plate, the samples were injected onto a reversed phase liquid chromatograph with tandem mass spectrometry detection. Data was analyzed by a Dell Computer running Analyst® software. Peak integration was used. No more than 25% of the calibration standards from each series could be excluded. The calibration curve was fitted by the equation  $y=a + bx$  (weighting function  $1/x^2$ ).

For analytical batches containing intra-batch samples, the intra-batch impression and inaccuracy had to be less than or equal to 15% (20% at the LLOQ) to accept the batch. At least 4 values at each concentration level had to be within  $\pm 15\%$  of their nominal concentration ( $\pm 20\%$  at LLOQ).

For analytical batches containing inter-batch samples of VQC samples, at least 7 of the 10 inter-batch samples of VQC samples had to be within  $\pm 15\%$  of their nominal concentration ( $\pm 20\%$  at the LLOQ) with at least one value at each concentration level to accept the batch data. Mean concentrations for stability testing samples were calculated and a deviation of more than 15% from their nominal concentration was considered relevant.

**Chromatography:** retention time of pramipexole and the IS was approximately 2.9 minutes.

**Specificity:** Different matrix samples from 6 individuals were tested. There was no peak in the blank plasma at the retention time of pramipexole or the IS that interfered by more than 20% of the Mean LLOQ and by more than 5% of the mean IS. The summary validation results are given in the following table.

Dates	07 July 2004 to 03 November 2004			
Volume of Sample	0.4mL			
Matrix	Human EDTA plasma			
(b) (4)	51% for pramipexole	53% for IS		
Calibration Standards	0.050 to 15.0 ng/mL	8 calibration standards		
Internal Standard	D7-pramipexole dihydrochloride	Batch AGS 337/10		
Regression Model	Peak Signal Ratio with $1/x^2$ weighted linear regression			
Back-calculated calibration standards	Imprecision	0.46 – 2.02%		
	Inaccuracy	2.67- 4.17%		
Correlation Coefficient $r^2$	0.998892			
Inter-batch	0.05 ng/mL	1.5 ng/mL	2.0 ng/mL	12 ng/mL
Impression	4.88%	4.76%	1.71%	0.95%
Inaccuracy	7.80%	1.33%	2.50%	2.50%
Quality Control Samples	LLOQ 0.05 ng/mL	0.15 ng/mL	2.0 ng/mL	12 ng/mL
Imprecision	12.93%	7.87%	2.80%	2.07%

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Inaccuracy	13.80%	0.00%	1.50%	0.83%
<b>Stability</b>				
freeze/thaw cycles	3cycles	Imprecision	LLOQ=0.97%	ULOQ=3.88%
		Inaccuracy	LLOQ= 0.83%	ULOQ = 4.00%
Room temperature	24 hours	Imprecision	LLOQ=0.53%	ULOQ=6.27%
		Inaccuracy	LLOQ= -0.83%	ULOQ = 0.00%
Autosampler +10°C	105 hours			
Freezer -24°C	3 months	Imprecision	LLOQ=0.42%	ULOQ=5.14%
		Inaccuracy	LLOQ= -4.00%	ULOQ = 3.33%
Long-term stability -24°C ± 6°C	up to 10 months	Imprecision	LLOQ = <13%	
		Inaccuracy	LLOQ = +2%	

## V. PHARMACOMETRIC REVIEW

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### OFFICE OF CLINICAL PHARMACOLOGY

#### PHARMACOMETRIC REVIEW

#### 1. SUMMARY OF FINDINGS

##### 1.1. Key Review Questions

The purpose of this review is to address the following key questions.

2 Page(s) of Draft Labeling have been withheld in full immediately following this page as B4 (CCI/TS)

**1.1.2. Are dosing recommendations for patients with moderate renal impairment (a creatinine clearance between 30 and 50 mL/min) acceptable?**

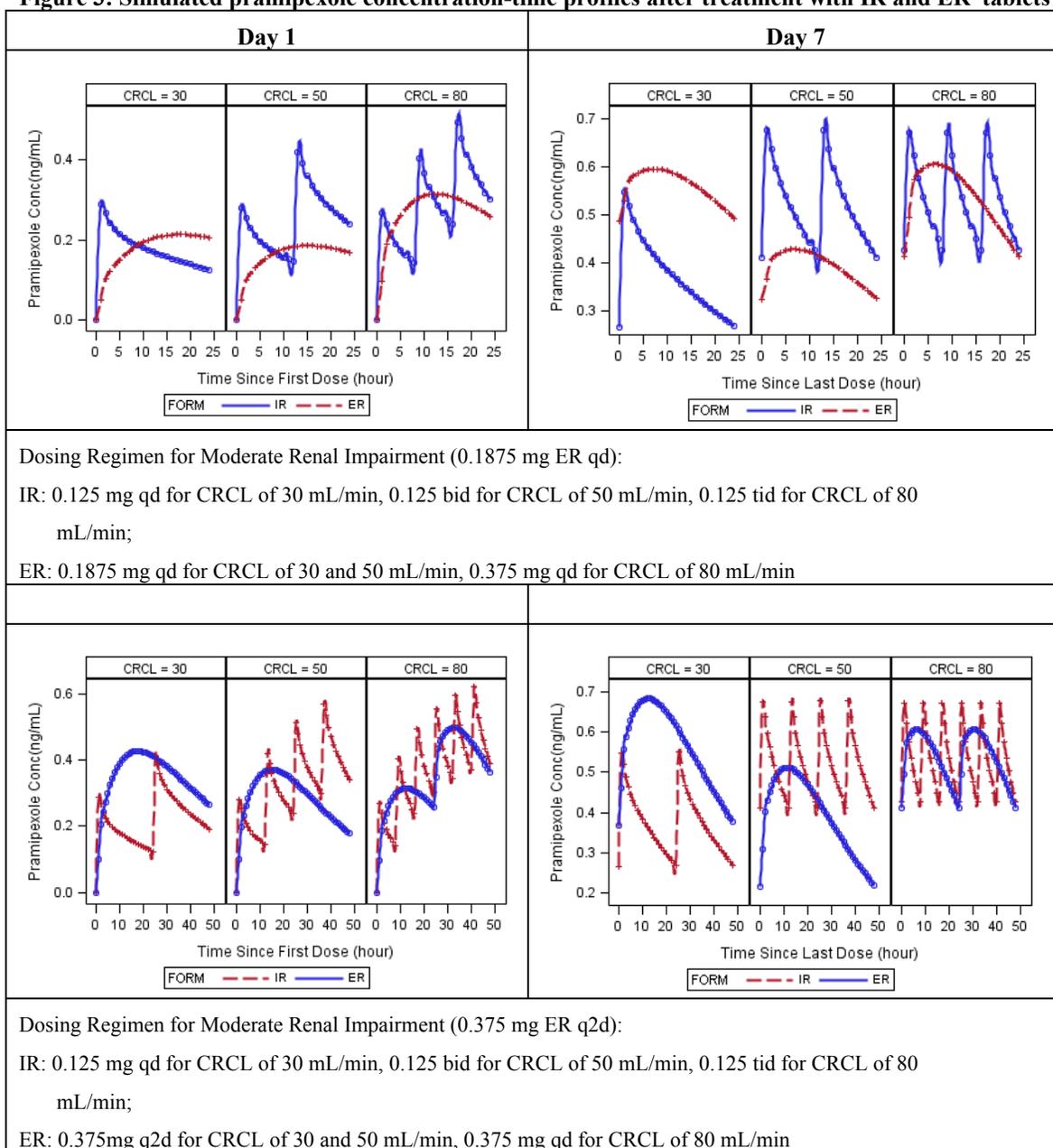
The sponsor used the final model for simulating the impact of creatinine clearance, and body weight on the exposure (AUC) and the maximum plasma concentrations (C<sub>max</sub>) after single and multiple administration of pramipexole ER. Based on the results of simulation, the sponsor suggests that in patients with moderate renal impairment (a creatinine clearance between 30 and 50 mL/min) MIRAPEX ER should initially be taken every other day and then be titrated to daily dosing after one week. Additional titration could then be conducted in 0.375 mg increments up to 2.25 mg per day.

Simulations were conducted by the reviewer based on the proposed dosing regimen with body weight fixed at 75 kg and with initial dose of 0.375 mg q2d for patients with creatinine clearance of 30 and 50 mL/min, 0.375 mg qd for patients with creatinine clearance of 80 mL/min. The simulated pramipexole plasma concentration-time profiles at day 1 and day 7 are shown in Figure 3 (bottom). The steady-state (day 7) AUC<sub>0-48,ss</sub> for creatinine clearance of 30, 50 and 80 mL/min after ER tablets are 27.12, 18.88 and 25.78 ng.h/mL, respectively. In addition, we conducted simulations with a lower dose of 0.1875 mg qd for patients with creatinine clearance of 30 and 50 mL/min and compared with 0.375 mg qd in patients with creatinine clearance of 80 mL/min. The simulated pramipexole plasma concentration-time profiles at day 1 and day 7 are shown in Figure 3 (top). The steady-state AUC<sub>0-24,ss</sub> (Day 7) for creatinine clearance of 30, 50 and 80 mL/min after ER tablets are 13.46, 9.43 and 12.89 ng.h/mL, respectively.

At steady state (Day 7), we observed that patients with creatinine clearance of 50 mL/min following ER tablets have significant lower exposure in either dosing regimens of 0.375 mg ER q2d or 0.1875 mg ER qd than patients with IR tablets. Based on the results of these simulations, it appears that it is not appropriate to treat patients with moderate renal impairment with ER tablets.

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**Figure 3: Simulated pramipexole concentration-time profiles after treatment with IR and ER tablets**



**1.2. Recommendations**

The sponsor’s proposed doses are acceptable from clinical pharmacology perspective except the part in treating patients with moderate renal impairment. The labeling statements based on the population PK analysis as proposed by the sponsor are acceptable.

**1.3. Label Statements**

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

## 2. PERTINENT REGULATORY BACKGROUND

FDA approved pramipexole dihydrochloride immediate release tablets under name MIRAPEX as treatment for Parkinson's Disease and for Restless Legs Syndrome on July 1, 1997. The approved dosage ranges from 1.5 to 4.5 mg per day administered in equally divided doses three times per day, with or without concomitant levodopa. The approved dosage strengths are 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, and 1.5 mg. The current application is to seek approval of pramipexole extended-release tablets under name MIRAPEX ER for once daily administration for the same indication as approved for the immediate tablets. The recommended dose range of MIRAPEX ER tablets for treatment of Parkinson's Disease is 1.5 to 4.5 mg per day, and the proposed dosage strengths for commercial distribution are 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg.

In this application, the sponsor submitted data showing that MIRAPEX ER is bioequivalent to the immediate-release formulation of pramipexole tablets (See Dr Carol Noory's review for more details). Additionally, the sponsor submitted data from two Phase III trials to compare the safety and effectiveness of MIRAPEX ER with placebo and to support an overnight switch from pramipexole tablets to MIRAPEX ER. Population PK analysis was conducted to describe the steady state pharmacokinetics of MIRAPEX ER and to investigate the impact of intrinsic (creatinine clearance, sex, age, race) and extrinsic factors (co-medication, food) on the pharmacokinetics of pramipexole in patients.

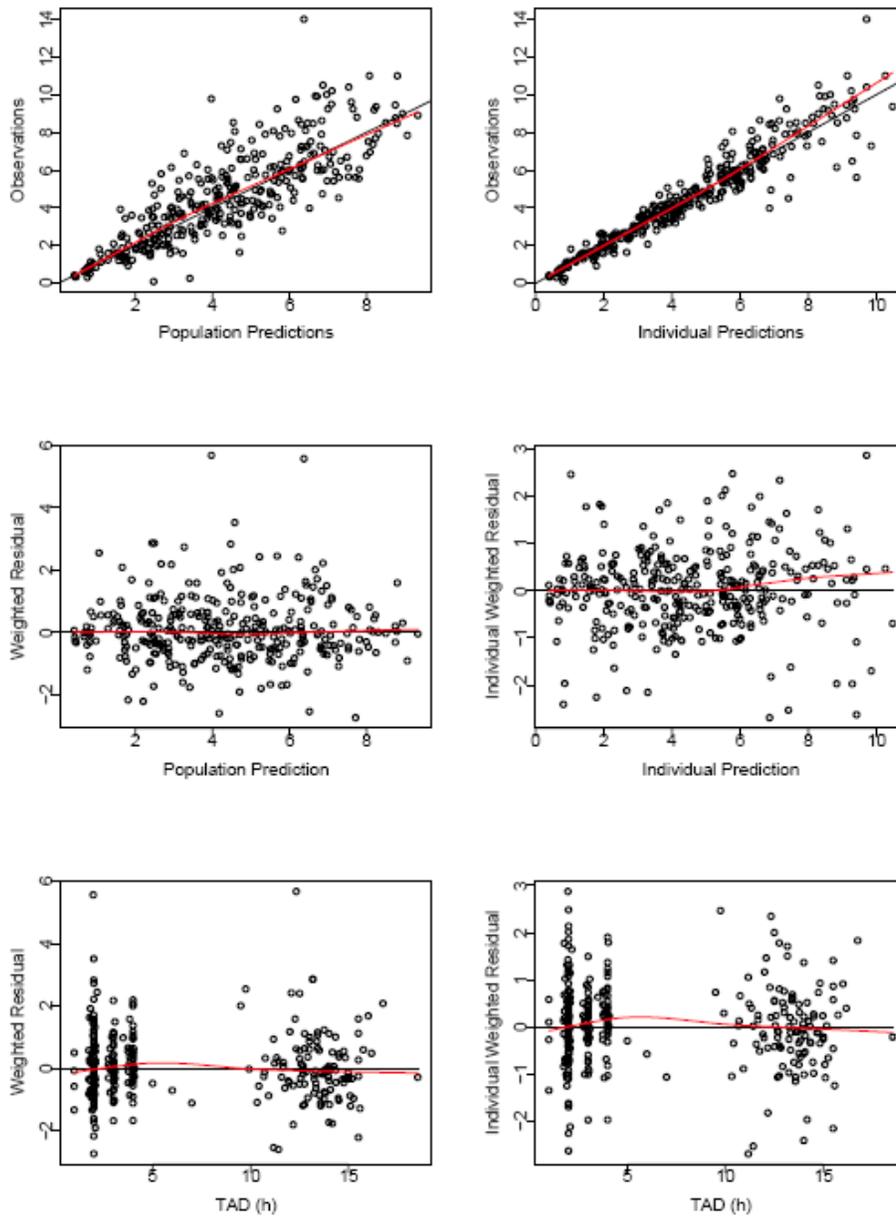
## 3. RESULTS OF SPONSOR'S ANALYSIS

- Population PK analysis was conducted using data from study 248.524. A two-compartment model with first order elimination was an adequate model describing pramipexole concentration-time profiles of early Parkinson's disease patients (study 258.524). The absorption process of pramipexole IR formulation was depicted by the first order process with a lag time in absorption. For ER formulation, the absorption was described by a sequential model of zero and first order. The first order absorption rate of the ER formulation was estimated with 0.0873 h<sup>-1</sup> which would refer to an absorption half-life of about 8 h. The goodness-of-fit plots for the final model stratified by IR and ER formulation are displayed in Figure 4.

**Figure 4: Goodness-of-fit plots for the final population pharmacokinetic model (subset for pramipexole IR (top) and ER (bottom) [line of unity (black line) and trend line (red line)]**

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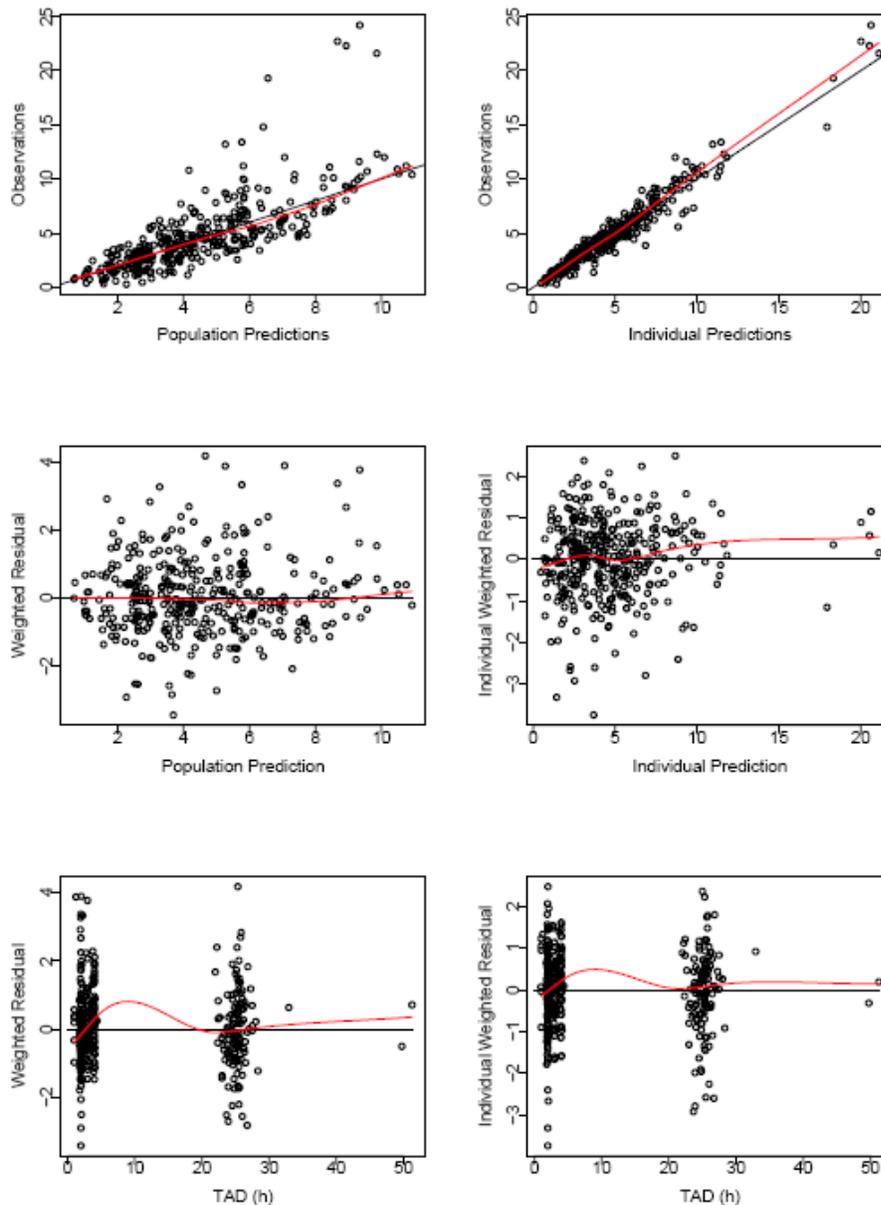
Goodness of Fit, subset for IR , Study 0248\_0524  
For Run 0654



Source: Figure 10.1.4.1:1 Sponsor's Population PK Analysis Report: page 84

## Pramipexole Dihydrochloride

Goodness of Fit; subset for ER, Study 0248\_0524  
For Run 0654



Source: Figure 10.1.4.1:2 Sponsor's Population PK Analysis Report: page 85

- Inter-individual variability was incorporated in the apparent clearance of the ER and the IR formulations and in the apparent peripheral volume of distribution ( $V_3/F$ ) for the ER formulation. Covariate analysis revealed that CRCL had an effect on the clearance of pramipexole. The estimates of the typical  $CL/F$  was 29.2 L/h when CRCL was greater or equal to 121 mL/min. Otherwise, the typical individual  $CL/F$  is reduced linearly by 0.74% by reducing the CRCL by 1 mL/min. In addition, it was found that body weight (BW) had an impact on  $V_3/F$  for pramipexole ER. The relationship between body weight and  $V_3/F$  was described by a proportional linear

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model. The estimate of the typical V3/F for a 75 kg patient was 313 L. A change in 1 kg body weight changes V3/F by 2.26%.

- Besides these two covariates (CRCL and BW), no intrinsic factors, like sex, age or race did significantly affect the pharmacokinetics of pramipexole. Furthermore, no co-medication was found to significantly interact with either pramipexole formulation.
- The population pharmacokinetic model was applied for finding dosage regimens in patients with renal insufficiency. The initial dose of 0.375 mg pramipexole was suggested to all patients with a CRCL of at least 7.5 mL/min. During maintenance therapy, changing the frequency of dosing (i.e. increase of dosing interval from once daily to every second day) or reduction of the dose may yield comparable peak and total exposure between patients with moderate renal insufficiency and patient with mild or no renal impairment.
- The explorative PK/PD analysis did not reveal any significant relationship between PK and PD measures. This may be due to the design of this study of individual dose adjustment (i.e. dose adjustment was based on individual responses (efficacy and safety)). However, the results would support the recommendation of individual dose adjustment of the new pramipexole ER formulation.

*Reviewer's Comments:*

1. *Available PK data for developing population pharmacokinetic model include Phase I studies conducted in healthy male volunteers (study 248.560, study 248.530) and non-PD patients with renal impairment (study M/2730/0060), where intensive PK samples of pramipexole IR and ER formulation were collected. In addition, sparse PK samples were collected in patients with early Parkinson's Disease in Phase III study 248.524 that was conducted to determine the efficacy and safety of pramipexole ER (0.375 mg to 4.5 mg per day q.d.) in comparison with placebo and with pramipexole IR.*
2. *The sponsor first used PK data from healthy volunteers (study 248.560, study 248.530) to develop a structural model. This structural model was then used to develop the structural model on data from study 248.524. Subsequently, the sponsor developed a final population PK model that describes the pramipexole PK profiles in patients with early Parkinson's disease. The covariates of patients in study 248.524 were then used to evaluate their effect on pramipexole PK profiles from IR and ER tablets. Covariates in healthy volunteers were not used for covariate analysis.*
3. *The sponsor conducted a comprehensive population pharmacokinetic analysis. From the visual check of goodness of fits plots and known clearance pathway of pramipexole, the results are generally acceptable. However, PK data from one trial center were found inaccurate by FDA audit. New analysis was then conducted by the reviewer employing data that excluded those error data.*

#### 4. REVIEWER'S ANALYSIS

##### 4.1. Introduction

The population pharmacokinetic analysis was repeated using modified PK dataset from patients with early Parkinson's disease. Sixty (60) PK records from 11 subjects were removed from the sponsor's final

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NONMEM dataset (pkdata1.xpt) because of the identified inaccuracy in PK data. Covariate analysis was conducted to check whether labeling statements related to population PK analysis are acceptable.

#### 4.2. Objectives

Analysis objectives are:

- To determine the effect of race and drug-drug interactions on the PK of pramipexole.

#### 4.3. Methods

The reviewer's NONMEM dataset was built based on sponsor's dataset pkdata1.xpt by removing the 60 PK records.

##### 4.3.1. Data Sets

Data sets used are summarized in Table 2.

**Table 2: Analysis Data Sets**

Study Number	Name	Link to EDR
Study 248.530, study 248.560	pkdata3.xpt	\\Cdsub1\EVSPROD\NDA022421\0000\m5\datasets\248-524-pop-pk\analysis\pkdata3.xpt
Study M/2730/0060	pkdata2.xpt	\\Cdsub1\EVSPROD\NDA022421\0000\m5\datasets\248-524-pop-pk\analysis\pkdata2.xpt
Study 248.524	pkdata1.xpt	\\Cdsub1\EVSPROD\NDA022421\0000\m5\datasets\248-524-pop-pk\analysis\pkdata1.xpt
Modified Study 248.524	Pk524.csv	Modified based on pkdata1.xpt

##### 4.3.2. Software

Data preparation was conducted using SAS 9.2 for Windows. NONMEM version VI was used for population PK analysis. The diagnostic and other plots were generated with SAS/Graph 9.2 or R.

##### 4.3.3. Models

The base model of the sponsor (a two-compartment model with first order elimination, and first order absorption for IR tablets and a sequential zero and first order absorption for ER tablets, combined with a combined additive and proportional residual error model) were utilized. CRCL was included into the structural model using a hockey stick function  $(CL/F = \theta_{CL} \cdot (1 + \theta_{CRCL} \cdot (CRCL - 121))) \cdot e^{n_{CL}}$ . Graphical analysis of the base model output (goodness-of-fit plots and Eta-covariate plots) was used to evaluate the adequacy of the model and selection of covariates for further evaluation.

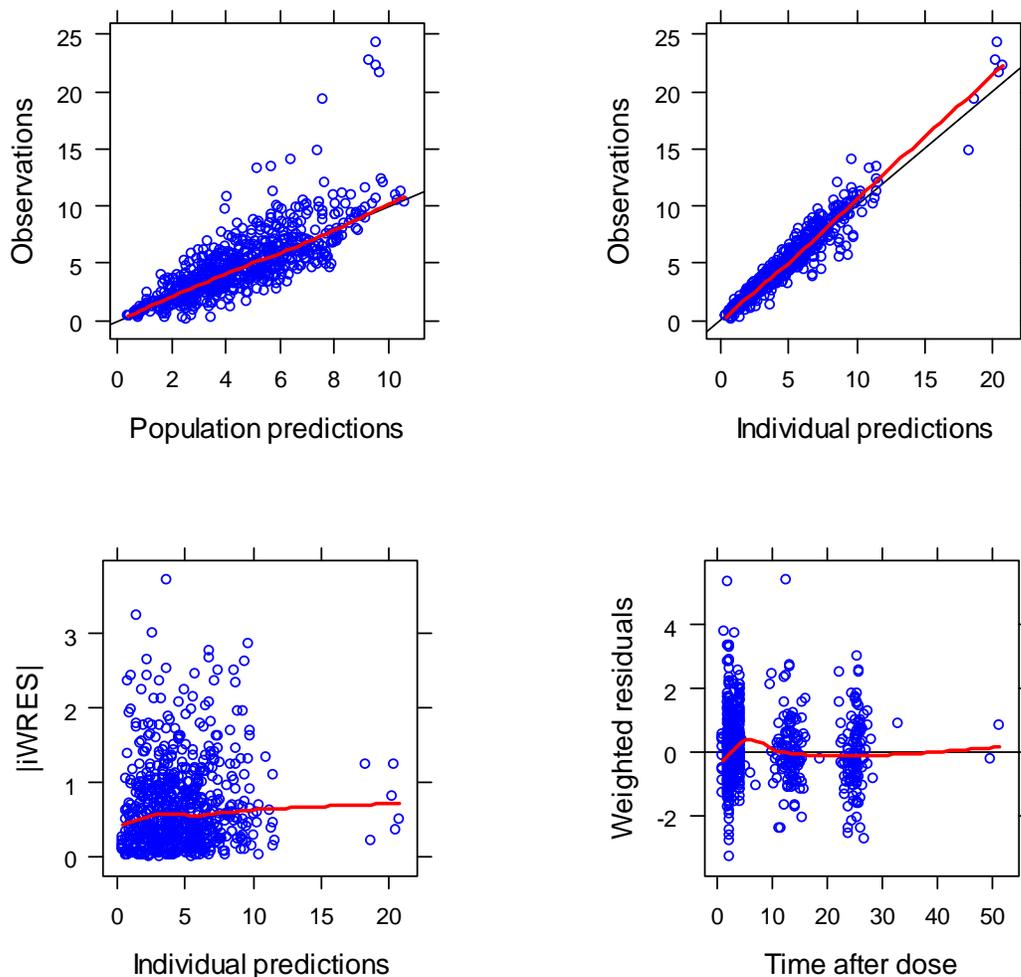
#### 4.4. Results

##### Population pharmacokinetics

##### Structural Model

The structural model reasonably describes the population PK of pramipexole following multiple doses of Mirapex IR or ER tablets (Figure 5).

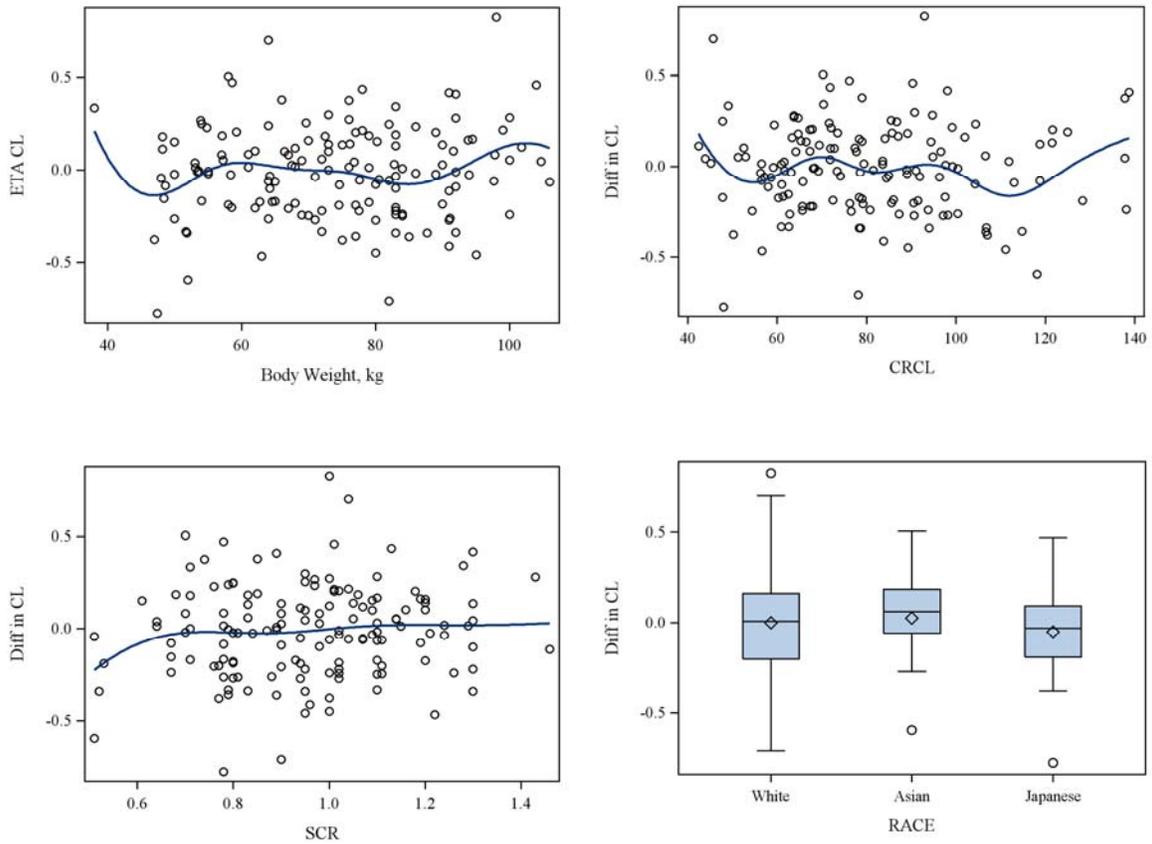
Pramipexole Dihydrochloride

**Figure 5: Goodness-of-fit plots for the base model (run5120.mod) [line of unity (black line) and trend line (red line)]****Basic goodness-of-fit plots (Run 5120)****Covariate Analysis**

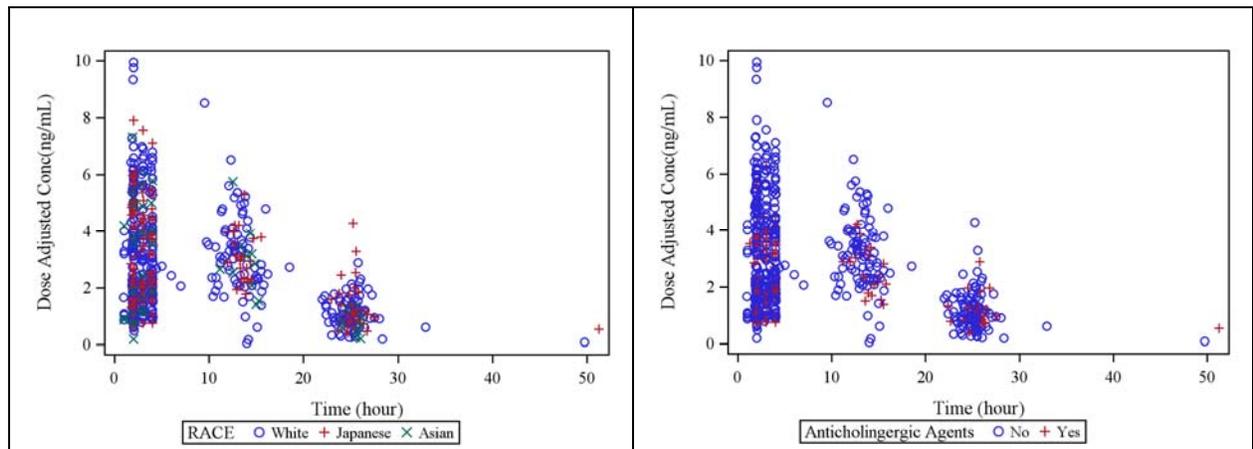
Eta-Covariate plots from the base model revealed that no significant difference in clearance of pramipexole among White, Asian (not Japanese) and Japanese patients (Figure 1). There is no significant change in clearance in the presence of co-administered drugs in class of anticholinergics, propulsives, antacids, H<sub>2</sub>-blockers, and proton pump inhibitors (Figure 2). Relationship between clearance (Eta Clearance) and body weight, CRCL and SCR and race are demonstrated in Figure 6. NO evident trend or pattern was observed in these analyses which are in line with the Sponsor's Analysis. Further plots of dose-adjusted pramipexole concentration-time profile did not reveal significant differences among White, Asian, and Japanese patients and the indicated co-administered drugs (Figure 7).

Pramipexole Dihydrochloride

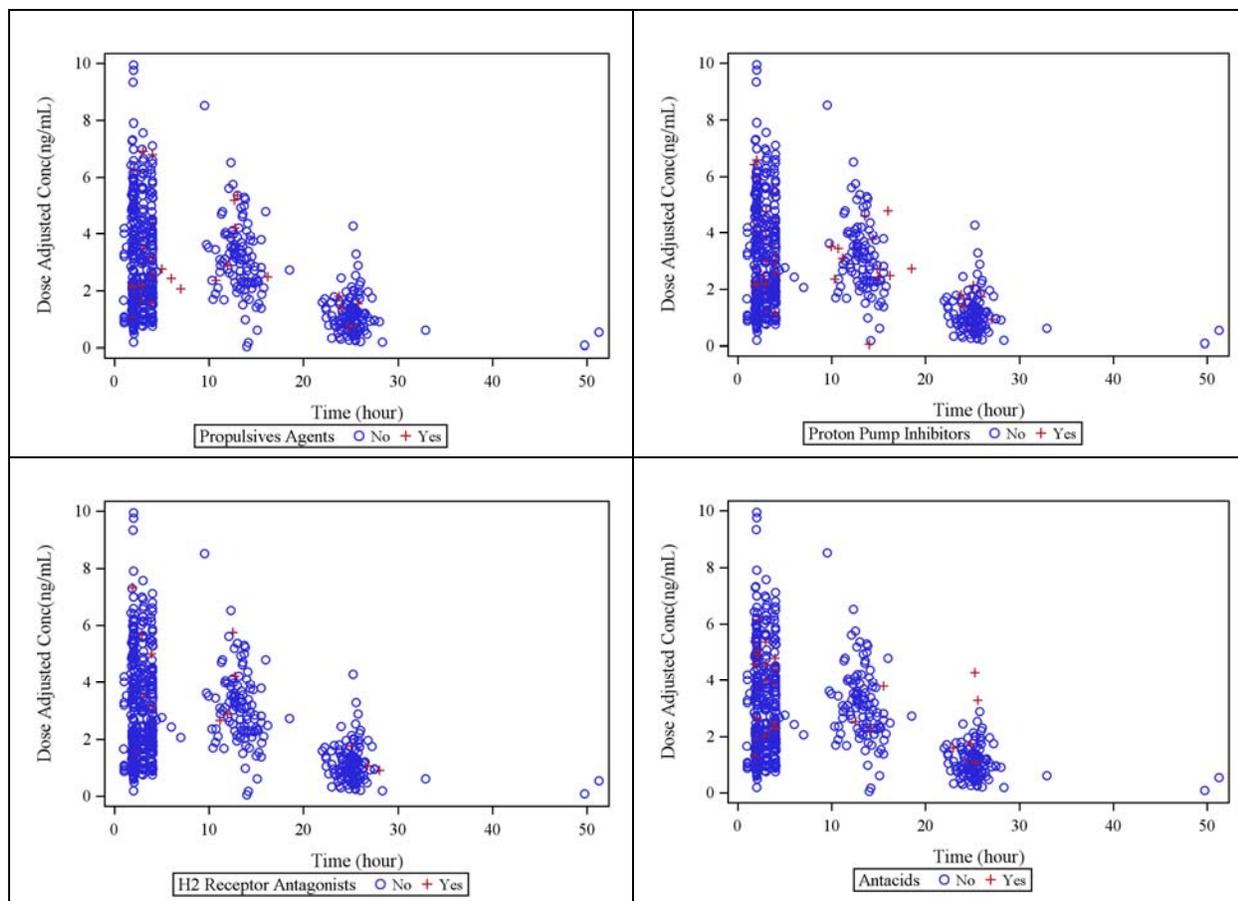
**Figure 6: Covariate analysis of base model(run5120)**



**Figure 7: Comparisons of dose-adjusted pramipexole concentration-time profiles among different races and co-administrated Drugs**



Pramipexole Dihydrochloride



**Final Model**

The parameter estimates and standard errors for the final model from the Sponsor and the FDA Reviewer were compared in Table 3. The values of those parameters were very similar.

**Table 3: Comparison of parameter estimates and standard errors for the final model of the Sponsor and FDA**

Parameter	Population Mean				Magnitude of Interindividual Variability			
	Final Estimate		%SE		Final Estimate (CV%)		%SE	
	Sponsor	FDA	Sponsor	FDA	Sponsor	FDA	Sponsor	FDA
CL (L/h)	29.2	29.1	5.38	5.4	28.1	28.4	15.8	16.2
V2 (L)	35.6	35.6						
Q(L/h)	115	115						
V3-ER	313	313			79.2	55.7	53.6%	65.4
KA-IR(h-1)	0.517	0.525	8.7	8.69				

## Pramipexole Dihydrochloride

KA-ER (h-1)	0.0873	0.0868	6.22	6.49				
ALAG-IR (h)	0.221	0.221						
PRV	0.151	0.151	9.6	9.74				
ARV	0.273	0.277	23.6	23.9				
D1-ER (h)	1.34	1.34						

**5. LISTING OF ANALYSES CODES AND OUTPUT FILES**

File Name	Description	Location in \\cdsnas\pharmacometrics\
Mirapex.sas	Plot of Structure Model	\Mirapex_NDA22421_FL\PPK_Analyses
Mkmm524.sas	Modified pkdata1.xpt for NONMEM analysis	\Mirapex_NDA22421_FL\PPK_Analyses\Structure_Model
Run6542 mod	Simulation program	\Mirapex_NDA22421_FL\PPK_Analyses\Final_Model
str_mirapex rtf	Output of Mirapex.sas, graphs	\Mirapex_NDA22421_FL\PPK_Analyses\Final_Model\Graphs Structure Model

**VI. SPONSOR'S PROPOSED LABELING**

(b) (4)

(b) (4)

42 Page(s) of Draft Labeling have been withheld in full immediately following this page as B4 (CCI/TS)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22421	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRAMIPEXOLE DIHYDROCHLORIDE

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

/s/

CAROL A NOORY  
07/27/2009

FANG LI  
07/27/2009

YANING WANG  
07/27/2009

RAMAN K BAWEJA  
07/27/2009

## ONDQA BIOPHARMACEUTICS REVIEW

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<b>NDA#:</b>	<b>22421</b>
<b>Submission Date:</b>	10/23/08
<b>Brand Name:</b>	Mirapex
<b>Generic Name:</b>	pramipexole
<b>Formulation:</b>	ER Tablets
<b>Strength:</b>	0.375, 0.75, 1.5, 3, and 4.5mg
<b>Sponsor:</b>	Boehringer Ingelheim
<b>Reviewer:</b>	John Duan, Ph.D.
<b>Submission Type:</b>	IVIVC Study and Dissolutions

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### BACKGROUND

Pramipexole (Sifrol) is a non-ergotamine dopaminergic agonist with selectivity for the D3 subtype of the D2 receptor family. Pramipexole is indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease alone or in combination with levodopa. Formulated as immediate release (IR) tablets, it is approved in the USA, and other countries.

Pramipexole IR is administered three times daily. A SR formulation is expected to be beneficial to patients as the sustained-release drug delivery will allow patients to treat their symptoms with a single daily dose thereby increasing patient convenience and compliance. This trial was aimed to establish and validate a level A in vitro/in vivo correlation (IVIVC) for an oral slow release (SR) formulation of pramipexole.

### PHYSICAL-CHEMICAL PROPERTIES

According to the BCS, the drug substance is considered highly soluble due to the fact that the highest dose strength (4.5 mg) is soluble in 250 ml or less of aqueous media over the pH range of 1 - 7.5 as shown in the table below.

Medium	pH-value	Solubility [mg/ml]	Solubility [mg/500 ml]
water	3.3	> 20	> 10000
0.1 N HCL	1	~ 18	~ 9000
0.01 N HCL	2	~ 18	~ 9000
McIlvaine buffer	2.2	> 20	> 10000
McIlvaine buffer	3.0	> 20	> 10000
McIlvaine buffer	4.0	> 20	> 10000
Acetate buffer	4.5	> 20	> 10000
McIlvaine buffer	5.0	> 20	> 10000
Phosphate buffer	6.8	> 20	> 10000
McIlvaine buffer	7.4	~ 16	~ 8200
Phosphate buffer	7.5	> 20	~ 10000

The pKa values were determined by a potentiometric titration using the Sirius GLpKa equipment. The following values were obtained.

pKa1 = 9.7 (protonation of secondary amine moiety)  
pKa2 = 5.2 (protonation of aminothiazole moiety)

The classification of pramipexole dihydrochloride monohydrate permeability was evaluated in a study investigating the pharmacokinetics and metabolism of pramipexole after administration of a single intravenous dose of 0.100 mg and a single oral dose of 0.300 mg [14C]-radiolabeled pramipexole. Nearly the complete dose reaches the systemic circulation resulting in a mean bioavailability greater than 90 % (from normalized AUC's 92.2 % and from renal excretions 95.6%). This classifies pramipexole dihydrochloride monohydrate as a highly permeable drug substance. Therefore, it can be classified as BCS Class I drug.

## DISSOLUTION METHOD AND SPECIFICATIONS

The dissolution method selected includes the following conditions:

Apparatus: USP basket (apparatus 1)  
Agitation: 100 rpm  
Medium: 500 ml phosphate buffer (pH 6.8)  
Temperature: 37°C  
Sampling time: 2, 9 and 24 hours  
Determination: HPLC/UV

Proposed specification:

At 2 hours (b) (4)  
At 9 hours (b) (4)  
At 24 hours (b) (4)

Different test conditions were investigated to establish an appropriate methodology and the associated specification. The impacts of the following variables were investigated during the selection of the appropriate in vitro dissolution test conditions for this extended release solid oral dosage form.

(b) (4)

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Three time points were used to characterize the *in vitro* drug release profile: an early time point to show that potential dose dumping is not probable (b) (4) dissolved), an intermediate time point (around (b) (4) release) to define the *in vitro* release profile of the dosage form, and a final time point to show essentially complete release of the drug (generally = (b) (4)). Shorter test intervals are acceptable in special cases but require justification on the basis of an *in vitro*-*in vivo* correlation.

The proposed dissolution specification of pramipexole dihydrochloride monohydrate ER tablets is established, which aims to substantiate the acceptance limits of the *in vitro* dissolution method along with clinically acceptable batches, including the batches used in pivotal clinical studies, and the primary stability batches.

Three time points are determined at 2, 9 and 24 hours to characterize the *in vitro* drug release profile.

## THE IVIVC STUDY

### 1. Summary

A single center trial was conducted in 15 healthy male volunteers, as an open, randomized, five-way cross-over study applying single dose of oral slow release (SR) tablets, containing 0.375 mg Pramipexole, with three different *in vitro* release profiles: Medium (target formulation, C2), on average (b) (4) release than target (formulation C2A) and (b) (4) release than target (formulation C2B). Additionally a medium release formulation (C) and formulation C2 after a high fat breakfast were administered within the five-way crossover. As the reference, an IR dose of 0.125 mg Pramipexole was applied before the start of the five-way cross-over. This study was aimed to establish and validate a Level A IVIVC for the SR formulation of Pramipexole, which had been selected in the formulation finding study 248.529 [U04-1242], in order to use the *in vitro* dissolution profiles for prediction of the *in vivo* performance of the drug product. The IVIVC was developed by means of individual plasma data. Beside the internal validation

using formulations C2, C2A, and C2B also external validation was performed on a formulation (C) whose in vitro release profile mostly resembled the target formulation C2. A Level A IVIVC could be established resulting in an internal predictability of 4.87% mean absolute percent prediction error (MAPPE) for C<sub>max</sub> and 3.18% for AUC<sub>0-tz</sub> (AUC<sub>0-30</sub>). Further calculation of external predictability based on formulation C amounted to a prediction error of 3.34% and 6.61 % for C<sub>max</sub> and AUC<sub>0-30</sub>, respectively. Using the dissolution lower and upper limits of (b) (4) the predicted parameters C<sub>max</sub> and AUC<sub>0-30</sub> were (b) (4) and (b) (4) lower, respectively, for the lower limit and (b) (4) and (b) (4) higher, respectively, for the upper limit compared with the target.

## 2. Objectives and endpoints

This study was aimed to establish and validate a Level A IVIVC for the slow release (SR) final formulation of Pramipexole in order to use the in-vitro dissolution profiles for prediction of the in vivo performance of the drug product. The primary objective of this study is to estimate the magnitude of the error in the prediction of in-vivo bioavailability (AUC, C<sub>max</sub>) by means of in-vitro dissolution data applying the methods of in-vivo/in-vitro correlation (IVIVC) for SR formulations of Pramipexole.

Primary endpoints are: AUC<sub>0-tz</sub> (= AUC<sub>0-30</sub>) and C<sub>max</sub>.

## 3. Methods

All Pramipexole SR-formulations are based on the matrix-tablet technology. The IVIVC was established by use of three SR-formulations with different in vitro release profiles:

1) Pramipexole SR tablets – 0.375 mg, formulation C2 (b) (4) (b) (4); medium in-vitro release profile = intended target profile with time to (b) (4) release approx. 9 hours). Pharmaceutical code: SND 919 CL2Y TA 99 05B 01A. Batch number: B050612.

2.) Pramipexole SR tablets – 0.375 mg, formulation C2A (b) (4) (b) (4); medium + ca. (b) (4) in-vitro release than target at 9h). Pharmaceutical code: SND 919 CL2Y TA 99 05C 01A. Batch number: B050606.

3.) Pramipexole SR tablets – 0.375 mg, formulation (b) (4) (b) (4); medium - ca. (b) (4) in-vitro release than target at 9h). Pharmaceutical code: SND 919 CL2Y TA 99 05D 01A. Batch number: B050607.

4.) For the external validation. Pramipexole SR tablets - 0.375 mg, formulation C (b) (4) (b) (4); formulation C as in trial 248.529 (U05-2046) using 0.75 mg dose). Pharmaceutical code: SND 919 CL2Y TA 99 05A 01A. Batch number: B050509.

5.) The IR-reference formulation at a dose strength of 0.125 mg.

Pharmaceutical form: IR Tablet

Pharmaceutical code: SND CL2Y 919 TA 1 3A 1A

Batch number: 503806

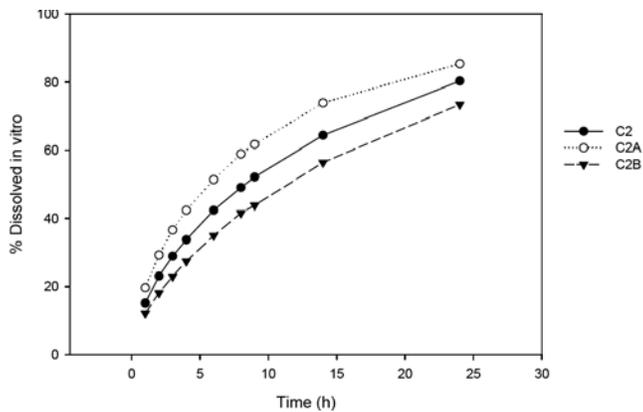
The dissolution method was adapted from the method developed for dissolution testing of the IR-formulation. It comprised dissolution in a phosphate buffer (pH 6.8) at 100 rpm agitation speed, using the USP basket apparatus, and quantitative analysis of the collected samples by means of RP-HPLC and UV/vis detection. The test conditions are summarized below.

Dissolution Apparatus:	Basket (USP)
Rotation Speed:	100 rpm
Medium:	phosphate buffer pH 6.8
Temperature:	37.0 ± 0.5 °C
Volume:	500 mL

#### HPLC-Conditions

Analytical Column:	Agilent Zorbax SB Aq, 50 x 4.6 mm I.D., (b) (4)
Column Temperature:	25 °C
Mobile Phase	10% Methanol + 90% 0.25 M formiate buffer pH 5.0 (V/V)
Flow Rate	1.0 mL/min
Injection Volume	100 µL
Retention time Pramipexole	3.00 minutes
Total Run-time	4.50 min
Wavelength	262 nm
Reference Wavelength	500 nm

Samples were collected after predefined times, mostly resembling the plasma sample collection time points, at: 1, 2, 3, 4, 6, 8, 9, 14, and 24 h. The mean percent dissolution (N = 12) at these time points for each formulation is given in the following figure.



A single center trial was conducted in 15 healthy male volunteers, as an open, randomized, five-way cross-over study applying single doses of three different oral slow

release (SR) tablets (C2, C2A, C2B), containing 0.375 mg pramipexole, each., in fasted conditions. These formulations were used to develop the Level A IVIVC. For confirmation of the established IVIVC another medium/target release formulation, C, was administered within the cross-over phase. This formulation was identical in its composition to the formulation selected from the previous trial (U05-2046). Furthermore, formulation C2 was administered after a high-fat meal. Results from this treatment arm are not presented within the IVIVC report but are solely part of the clinical trial report. As a reference, a single dose of 0.125 mg pramipexole IR was administered before the start of the five-way cross-over period. Plasma concentrations were assessed up to 30h after drug administration in case of the SR-formulations. In case of the IR-formulation plasma concentrations were only measured up to 14 h after drug administration. While the mean plasma concentration – time profile of formulation C2A (faster release) was different to C2B and C2, C2B (slower release) was hardly discernible from the target formulation C2. Comparing AUC<sub>0-30</sub> of all SR-formulations resulted in highly comparable total exposure. Taking C2 as the target formulation, the relative bioavailability (Frel), based on AUC<sub>0-30</sub> geometric Mean (gMean) ratios, ranged from 97.9% for C2B to 109 and 106% for C2A and C, respectively. For C<sub>max</sub> the gMean ratios were 102% for formulation C, 112% for C2A and 94.8% for C2B. The relevant pharmacokinetic parameters are summarized below.

**Table. Mean pramipexole pharmacokinetic parameters (gMean and gCV %) for 4 different SR-formulations and the IR-reference in N = 15 healthy subjects**

Parameter	IR	C2	C2A	C2B	C
Dose (mg)	0.125	0.375	0.375	0.375	0.375
AUC <sub>0-30</sub> [ng·h/mL]	---	5.40 5.29 (22.7)	5.85 5.78 (15.9)	5.24 5.18 (15.1)	5.66 5.6 (14.8)
AUC <sub>0-tz</sub> [ng·h/mL]	1.66 1.65 (13.4)	5.31 5.14 (29.7)	5.85 5.78 (15.9)	5.24 5.18 (15.1)	5.64 5.58 (16.1)
C <sub>max</sub> [ng/mL]	0.221 0.218 (16.3)	0.269 0.268 (10.9)	0.303 0.299 (15.4)	0.259 0.254 (20.1)	0.275 0.273 (13.0)
t <sub>max</sub> <sup>1</sup> [h]	0.983	9.98	6.00	5.02	9.98
apparent t <sub>1/2</sub> [h]	8.14 8.08 (12.9)	10 9.38 (37.6)	9.29 9.04 (24.7)	14.3 11.5 (59)	10.1 9.79 (26.4)
<b>Parameters from mean profiles as used for validation of IVIVC</b>					
AUC <sub>0-30</sub> [ng·h/mL]	---	5.37	5.90	5.27	5.69
C <sub>max</sub> [ng/mL]	---	0.239	0.288	0.241	0.253

<sup>1</sup> t<sub>max</sub> is given as median

Pharmacokinetic parameters (C<sub>max</sub> and AUC<sub>0-30</sub>) were calculated by WinNonlin 4.01 (Pharsight, Mountain View, CA); development of IVIVC as well as assessment of the

internal and external prediction error were performed by (b) (4)

(b) (4) The following steps are included in the development of an IVIVC:

1. Determination of unit impulse response (weighting function), UIR. The unit impulse response (weighting function), UIR, was determined from resulting plasma concentration - time profiles after administration of a single oral dose of the pramipexole reference, IR formulation. A polyexponential function was fitted to the data. The UIR gives the number of exponentials to describe the data. (b) (4)

(b) (4)

## 2. Numeric deconvolution

Numeric deconvolution based on the convolution integral (3) was applied to estimate the in vivo absorption (rabs (t)) from SR-formulations:

$$c(t) = \int_0^t \text{rabs}(\tau) * c\delta(t - \tau) dt \quad (3)$$

## 3. Development of the IVIVC model

Development of the IVIVC model was based on nonlinear regression minimizing differences between predicted and observed in vivo amount absorbed. The IVIVC in PDx is described by a non-linear equation including a linear (time invariant) component -

(b) (4)

(b) (4)

4. Internal and external predictability Plasma concentration - time profiles were predicted from in vitro dissolution data via the convolution integral (3). This was performed for each formulation (C2, C2A, and C2B) used to develop the IVIVC model (internal validation) or for the formulation C, not included in the IVIVC development (external validation). The absolute % prediction error on Cmax and AUC was calculated by [(observed-predicted)/observed]\*100.

The UIR was assessed from each individual's (N = 15) plasma concentration - time profile derived after administration of a single oral does of 0.125 mg pramipexole IR. A

polyexponential function was fitted to the data. The UIR gives the number of exponentials to describe the data. The finally chosen exponentials (finally chosen model) for each individual are given as A, a, and lag time as shown in the following table.

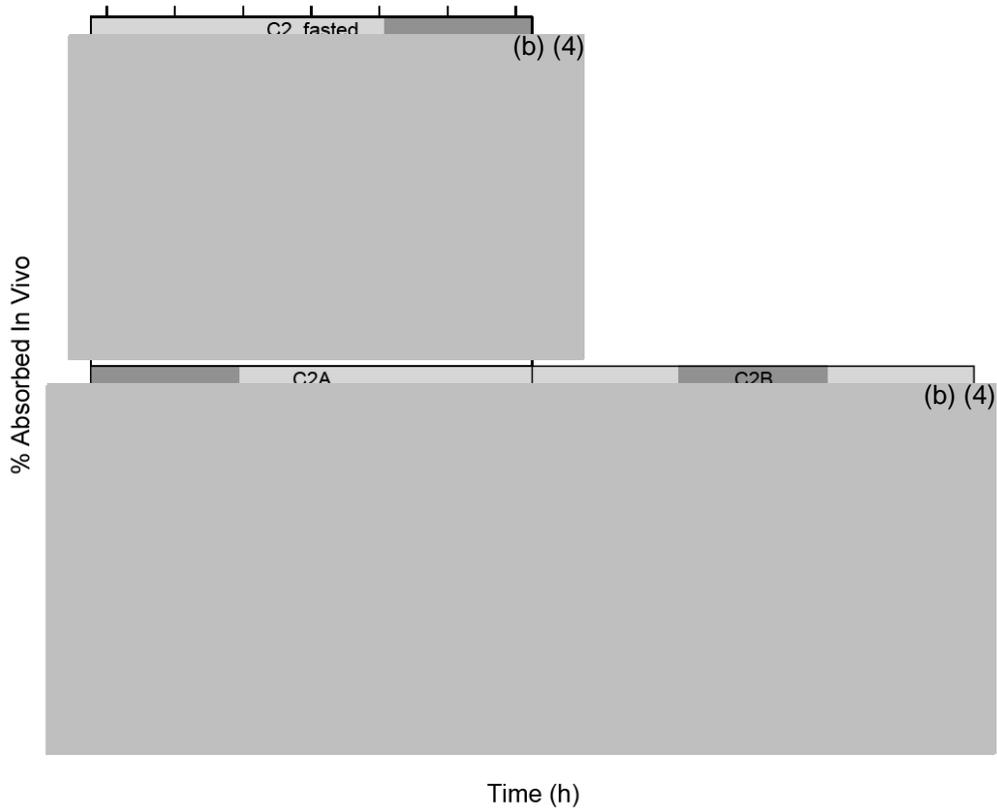
Subject	treatment	a	alpha	lag time
(b) (4)				

The predicted vs. observed concentration - time plots are depicted in the following Figure.

Predicted and Observed Concentration vs. Time

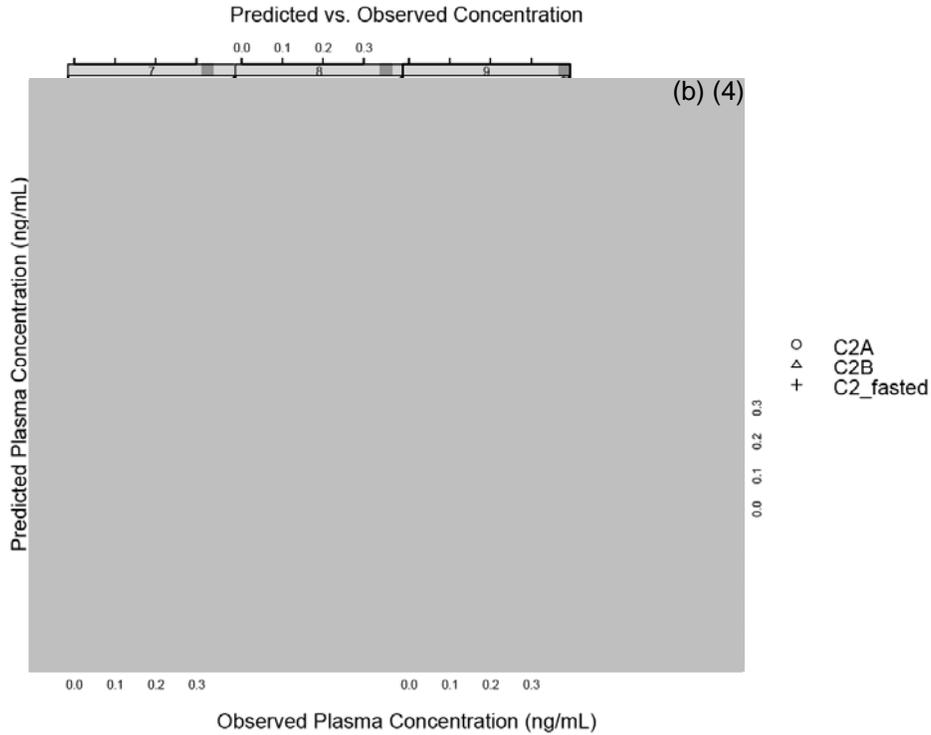


The in vivo absorption was determined by deconvolution from the individual plasma concentration - time profiles of the SR-formulations to be used in the development of the IVIVC, C2, C2A, and C2B. The individual cumulative % absorption - time profiles are shown in the following figure.

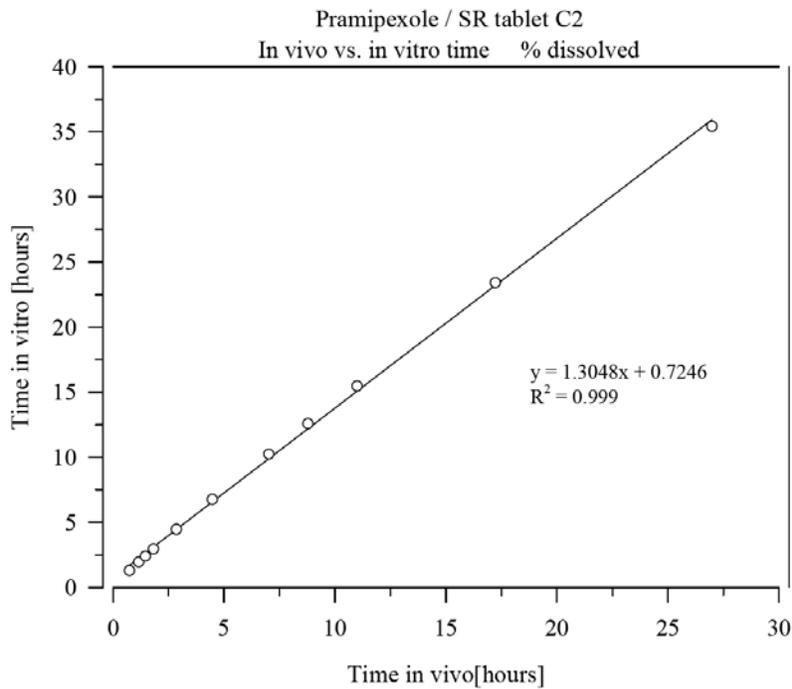


The goodness of fit for the deconvolution was explored by recalculation (prediction) of the plasma concentration - time profiles for each individual and each SR-formulation by

use of the deconvoluted absorption and the convolution integral. A comparison between the predicted and observed plasma concentrations is shown in the figure below.



The Levy plot (only given for the target formulation C2) did not reveal any deviation from linearity over time as depicted in the following figure and the other formulations revealed essentially the same dissolution/absorption behavior as C2.



An IVIVC was developed from the mean dissolution data for the slow release treatments (Percent dissolved vs. time) and the mean absorption data for the slow release treatments (Percent absorbed vs. time). The selected parameters included in the final model are presented in the following table.

Parameters of the final IVIVC-equation for pramipexole SR

Parameter	Final Estimate
a1	3.20
a2	1.08
b1	0.0527
b2	1.15
T	200

The final IVIVC was evaluated regarding internal and external predictability. The IVIVC model was used to predict each formulation's mean plasma concentration profile (and associated C<sub>max</sub> and AUC<sub>0-30</sub>) from the respective mean dissolution data via the convolution integral. The predicted bioavailability parameters (AUC<sub>0-30</sub> and C<sub>max</sub>) were compared to the observed mean bioavailability parameters for each formulation and the prediction error was determined. The internal validation statistics is given as the mean absolute percent prediction error (MAPPE) in the following table.

Treatment	C <sub>max</sub> Obs (ng/mL)	C <sub>max</sub> Pred (ng/mL)	C <sub>max</sub> Ratio	C <sub>max</sub> % Pred Error	AUC <sub>0-30</sub> Obs (ng·h/mL)	AUC <sub>0-30</sub> Pred (ng·h/mL)	AUC Ratio	AUC % Pred Error
C2	0.239	0.245	1.02	<b>2.45</b>	5.37	5.36	0.998	<b>0.151</b>
C2A	0.288	0.287	0.996	<b>0.350</b>	5.90	5.79	0.982	<b>1.77</b>
C2B	0.241	0.213	0.882	<b>11.8</b>	5.27	4.87	0.924	<b>7.63</b>
<b>MAPPE</b>				<b>4.87</b>				<b>3.18</b>

External validation was assessed using formulation C which was not used in the IVIVC development. The results are given in the table below.

Treatment	C <sub>max</sub> Obs (ng/mL)	C <sub>max</sub> Pred (ng/mL)	C <sub>max</sub> Ratio	C <sub>max</sub> % Pred Error	AUC <sub>0-30</sub> Obs (ng·h/mL)	AUC <sub>0-30</sub> Pred (ng·h/mL)	AUC Ratio	AUC % Pred Error
C	0.253	0.245	0.967	<b>3.34</b>	5.69	5.31	0.934	<b>6.61</b>

For the dissolution specification, only mean plasma concentration - time data were applied (mean UIR). The % dissolution at the time points 2, 9, and 24h were used to develop the IVIVC and predict the PK-parameters C<sub>max</sub> and AUC<sub>0-30</sub>. The dissolution of the target formulation C2 and the presumed upper (b) (4) and lower (b) (4) IVIVC in vitro release limit are given in the following table.

Sampling Time (h)	Mean % Released	
	C2	upper limit lower limit
2		(b) (4)
9		
24		

The predicted PK-parameters and their respective prediction error in comparison to the observed parameters are given in the following table.

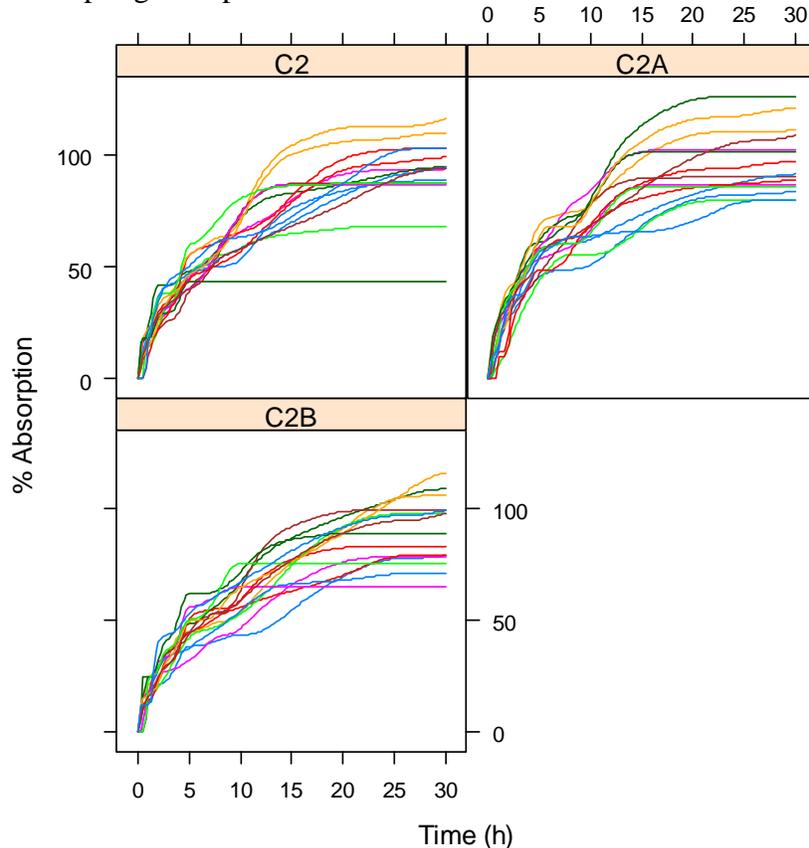
Treatment	C <sub>max</sub> Obs (ng/mL)	C <sub>max</sub> Pred (ng/mL)	C <sub>max</sub> Ratio	C <sub>max</sub> % Pred Error	AUC <sub>0-30</sub> Obs (ng·h/mL)	AUC <sub>0-30</sub> Pred (ng·h/mL)	AUC Ratio	AUC % Pred Error
C2	0.239			(b) (4)	5.37			(b) (4)
C2A	0.288				5.90			
C2B	0.241				5.27			
MAPPE								

The predicted C<sub>max</sub> and AUC<sub>0-30</sub> based on the mean % dissolution of the target formulation and the defined upper and lower limit are given in the following table.

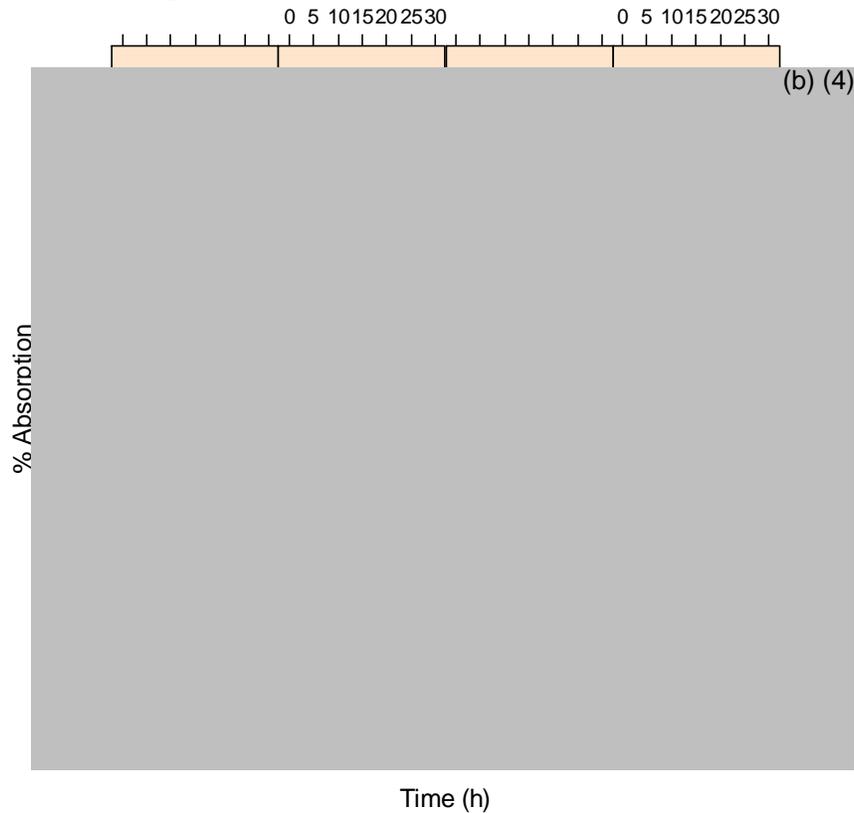
Treatment	C <sub>max</sub> Predicted (ng/mL)	C <sub>max</sub> Ratio	AUC <sub>0-30</sub> Predicted (ng·h/mL)	AUC Ratio
upper target (C2)				(b) (4)
lower				

### The Reviewer's analysis and comments

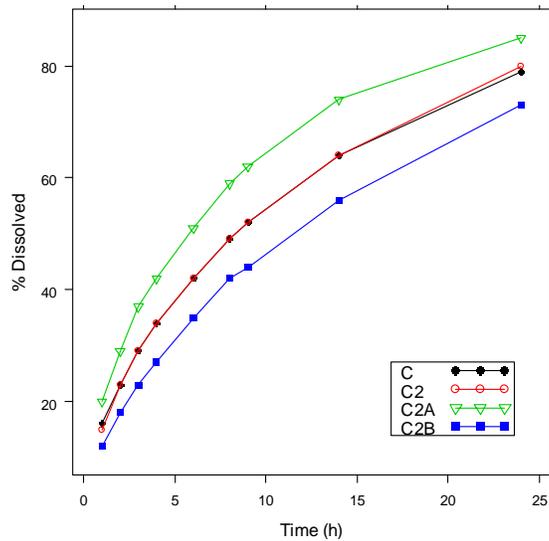
- The final IVIVC model allowed the dissolution data to adequately predict the plasma concentrations of the formulations included in the IVIVC development (internal predictability) as well as of a formulation not included in the IVIVC development (external predictability). As shown in the following figure, the reviewer obtained the similar deconvolution results using different software (WinNonlin) and much more condensed sampling time points.



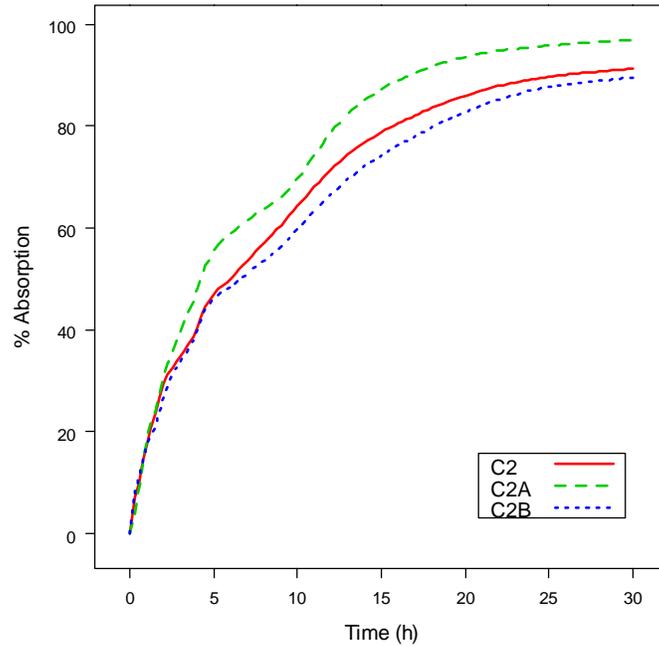
However, the individual plots revealed that for the 15 subjects, the in vivo absorption profiles of the three formulations rarely following the order of their in vitro performance. In the following figure, the red solid lines represent the profile of the target formulation, while the green dashed lines and blue dotted lines are the fast release and slow release formulation, respectively. The subject ID is labeled in the strip.



As seen, except subject #9, the red solid lines for other subjects can be the highest or the lowest, with an extreme case for subject #10. In contrast, the in vitro profiles, as shown in the following figure, present the order with C and C2 in the middle.



Nevertheless, the mean in vivo absorption profiles reserve the order as shown in the following figure.



- Due to the observed discrepancies in the individuals mentioned above, when individual plasma concentration – time profiles were predicted from IVIVC based on mean data, the MAPPE was 12.7% for C<sub>max</sub> and 13.9% for AUC<sub>0-30</sub>. The following table shows the results for C<sub>max</sub>.

Subject	Treatment	C <sub>max</sub> obs	C <sub>max</sub> pred	C <sub>max</sub> ratio	C <sub>max</sub> error
1	C2	0.236	0.239	1.01	1.46
2	C2	0.224	0.218	0.973	2.67
3	C2	0.261	0.241	0.924	7.55
4	C2	0.313	0.261	0.833	16.7
5	C2	0.29	0.215	0.743	25.7
6	C2	0.245	0.238	0.97	3.04
7	C2	0.288	0.22	0.765	23.5
8	C2	0.244	0.257	1.05	5.33
9	C2	0.339	0.273	0.806	19.4
10	C2	0.249	0.261	1.05	4.98
11	C2	0.268	0.274	1.02	2.37
12	C2	0.276	0.211	0.764	23.6
13	C2	0.262	0.21	0.802	19.8
14	C2	0.266	0.291	1.09	9.35
15	C2	0.279	0.273	0.977	2.27
1	C2A	0.228	0.281	1.23	23.1
2	C2A	0.253	0.256	1.01	1
3	C2A	0.354	0.284	0.802	19.8
4	C2A	0.363	0.308	0.848	15.2
5	C2A	0.307	0.254	0.827	17.3

6	C2A	0.256	0.28	1.09	9.24
7	C2A	0.282	0.259	0.918	8.17
8	C2A	0.302	0.301	0.997	0.288
9	C2A	0.38	0.32	0.843	15.7
10	C2A	0.331	0.307	0.928	7.17
11	C2A	0.303	0.321	1.06	5.99
12	C2A	0.304	0.249	0.819	18.1
13	C2A	0.239	0.246	1.03	2.86
14	C2A	0.336	0.341	1.01	1.38
15	C2A	0.301	0.319	1.06	6.14
1	C2B	0.196	0.208	1.06	6.18
2	C2B	0.188	0.195	1.04	3.85
3	C2B	0.264	0.21	0.797	20.3
4	C2B	0.249	0.229	0.921	7.88
5	C2B	0.202	0.189	0.935	6.54
6	C2B	0.235	0.21	0.894	10.6
7	C2B	0.291	0.194	0.666	33.4
8	C2B	0.21	0.223	1.06	6.27
9	C2B	0.356	0.244	0.685	31.5
10	C2B	0.352	0.228	0.647	35.3
11	C2B	0.302	0.238	0.787	21.3
12	C2B	0.227	0.186	0.817	18.3
13	C2B	0.253	0.188	0.744	25.6
14	C2B	0.277	0.253	0.915	8.53
15	C2B	0.281	0.24	0.854	14.6
Mean	C2				11.2
Mean	C2A				10.1
Mean	C2B				16.7
	MAPPE				12.7

The following table shows the AUC results.

Subject	treatment	AUC obs	AUC pred	AUC ratio	AUC error
1	C2	5.14	5.39	1.05	4.96
2	C2	5.41	5.32	0.984	1.6
3	C2	5.57	5.36	0.962	3.77
4	C2	5.78	5.33	0.922	7.79
5	C2	5.66	4.5	0.795	20.5
6	C2	3.88	5.53	1.43	42.7
7	C2	5.07	5.11	1.01	0.831
8	C2	5.57	5.69	1.02	2.16
9	C2	6.62	6.6	0.997	0.293
10	C2	2.43	5.73	2.36	136
11	C2	6.28	6.1	0.97	2.95
12	C2	5.12	4.27	0.833	16.7
13	C2	5.13	4.93	0.96	4.02
14	C2	6.24	6.51	1.04	4.23
15	C2	6.76	6.34	0.937	6.33
1	C2A	4.78	5.83	1.22	21.8
2	C2A	5.32	5.78	1.09	8.74

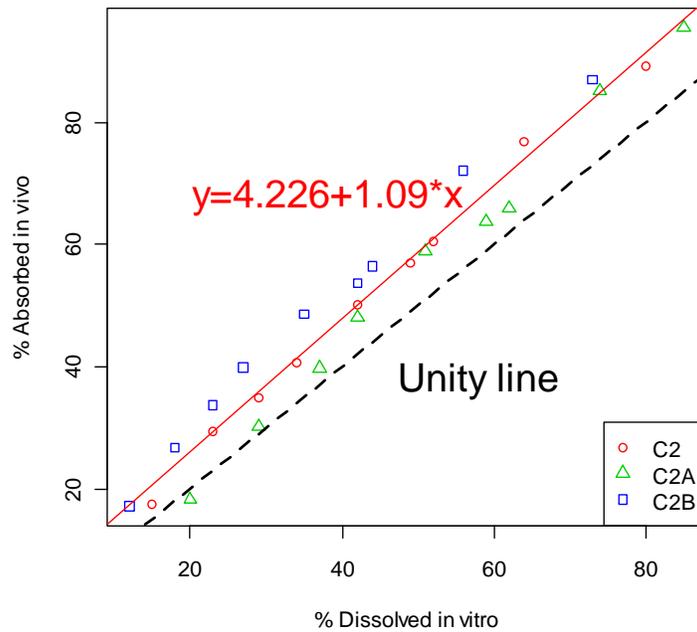
3	C2A	7.42	5.8	0.782	21.8
4	C2A	5.64	5.73	1.02	1.53
5	C2A	5.54	4.85	0.875	12.5
6	C2A	4.86	5.98	1.23	23
7	C2A	5.29	5.53	1.05	4.59
8	C2A	5.54	6.14	1.11	11
9	C2A	7.79	7.17	0.92	8.01
10	C2A	6.72	6.19	0.921	7.94
11	C2A	5.94	6.59	1.11	10.9
12	C2A	5.55	4.58	0.825	17.5
13	C2A	4.96	5.35	1.08	8.03
14	C2A	7.46	7.03	0.942	5.78
15	C2A	5.62	6.86	1.22	22
1	C2B	4.27	4.89	1.14	14.4
2	C2B	4.44	4.81	1.08	8.25
3	C2B	6.08	4.86	0.799	20.1
4	C2B	4.56	4.84	1.06	6.32
5	C2B	4.89	4.08	0.835	16.5
6	C2B	5.63	5.01	0.889	11.1
7	C2B	5.56	4.63	0.834	16.6
8	C2B	4.55	5.16	1.13	13.5
9	C2B	4.91	5.97	1.22	21.5
10	C2B	5.86	5.19	0.886	11.4
11	C2B	5.61	5.53	0.985	1.49
12	C2B	4.83	3.88	0.804	19.6
13	C2B	4.44	4.45	1	0.383
14	C2B	6.61	5.9	0.892	10.8
15	C2B	6.7	5.74	0.856	14.4
Mean	C2	0	0	0	17
Mean	C2A	0	0	0	12.3
Mean	C2B	0	0	0	12.4
	MAPPE				13.9

Although the individually predicted errors (MAPPE) for AUC and Cmax are more than 10%, these are only used for exploratory purposes and not for setting criteria for accepting or rejecting the IVIVC model based on the following considerations.

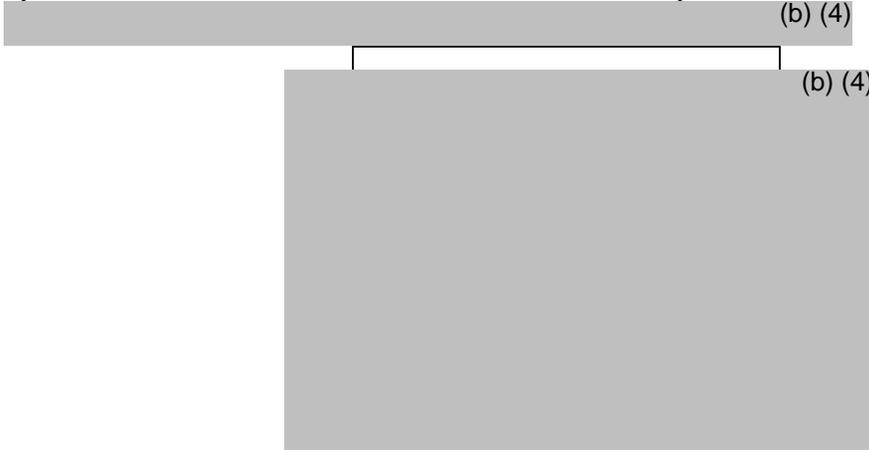
- The purpose of IVIVC model is for building the relationship between in vitro and in vivo performance of the formulation in general, not specifically for defining the in vivo performance of the formulation in a specific individual.
- In this specific case, the IVIVC has been obtained using the average absorption values after deconvolutions, not obtained from individual deconvolution results. It is not reasonable to evaluate the results by applying the average to a specific subject.
- For the presumed IVIVC dissolution limits, an IVIVC based on only three time points in the in vitro dissolution (after 2h at about (b) (4) dissolution, 9h at about (b) (4) dissolution and after 24h at about (b) (4) dissolution) still sufficient precisely

predicted Cmax and AUC0-30 of all three formulations used in the IVIVC development.

- By using the average values of the deconvolution results, the percent prediction error (%PE) values for Cmax and AUC were less than  $\pm 15\%$  for each product and less than 10% for the average of all three formulations (mean absolute percent prediction error MAPPE). The time to reach Cmax (tmax) was also in a similar range comparing observed and predicted data (5h vs. 8h), irrespective of the formulation applied. A Level A IVIVC for pramipexole SR matrix tablets thus is established. The following figure generated by the reviewer shows a levy plot for the IVIVC model established.



- The last time point of proposed dissolution specifications is less meaningful for controlling the quality of the product. For example, the following figure shows any of the four cases represented by the different lines would pass the currently proposed specifications. Therefore, in order to control the shape of the release curve, (b) (4)



Time

**COMMENTS**

1. A level A IVIVC model has been established with the percent prediction error (%PE) values for Cmax and AUC less than ± 15% for each product and less than 10% for the average of all three formulations (mean absolute percent prediction error MAPPE).
2. The dissolution specification is recommended to be modified by adding a time point at (b) (4)

**RECOMMENDATION**

From biopharmaceutics perspective, the IVIVC model and proposed dissolution specifications based on the model are acceptable. However, the dissolution specification should be modified by adding a time point at (b) (4)

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John Duan, Ph.D.  
Reviewer  
ONDQA Biopharmaceutics

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Date

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Patrick Marroum, Ph.D.  
ONDQA Biopharmaceutics

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Date

cc: NDA 22421  
Patrick Marroum, John Duan

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22421	----- ORIG 1	----- BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	----- PRAMIPEXOLE DIHYDROCHLORIDE

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JOHN Z DUAN  
07/27/2009

PATRICK J MARROUM  
07/27/2009

*Office of Clinical Pharmacology and Biopharmaceutics*  
*New Drug Application Filing and Review Form*

**General Information About the Submission**

	Information		Information
NDA Number	22421	Brand Name	Mirapex® ER
OCPB Division (I, II, III)	DCP-1	Generic Name	Pramipexole Dihydrochloride
Medical Division	HFD-120	Drug Class	Dopamine D2 Receptor Agonist
OCPB Reviewer	Jagan Mohan Parepally	Indication(s)	Treatment of Parkinson's Disease
OCPB Team Leader	Veneeta Tandon	Dosage Form	Extended Release Tablet
Date of Submission	10/23/2008	Dosage Range	1.5 to 4.5 mg per Day
Estimated Due Date of OCP Review	7/6/2009	Route of Administration	Oral
PDUFA Due Date	8/24/2009	Sponsor	Boehringer Ingelheim
Division Due Date	7/23/2009	Priority Classification	S

**Clin. Pharm. and Biopharm. Information**

Summary: Pramipexole (INN) is a non-ergot dopamine D<sub>2</sub> receptor agonist. Pramipexole immediate release tablets are marketed worldwide for the treatment of Parkinson's disease and for the treatment of Restless Legs Syndrome. This application is an extended-release formulation of pramipexole dihydrochloride tablets for once daily administration in the treatment of Parkinson's disease. The following dosage strengths are proposed for commercial distribution: 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg.

Dosage of Pramipexole IR in Parkinson's Disease: A dose range 1.5 to 4.5 mg/day administered in equally divided doses three times per day with or without concomitant levodopa was found to be effective in Parkinson's disease. Dosage was gradually increased starting with dose of 0.375 mg/day given in three divided doses.

Renal impairment study conducted in support of NDA for pramipexole IR was submitted. Different strengths of pramipexole formulations are compositionally proportional.

Following studies pertaining to the pharmacokinetics and pharmacokinetics/pharmacodynamics of pramipexole ER are presented to support the NDA:

- Study 248.530[U07-1551]: This was a **multiple dose study** in healthy male Caucasians, assessing the **dose proportionality** of the new pramipexole ER-formulation between 0.375 and 4.5 mg q.d., (lowest and highest strength) the relative bioavailability in comparison to the immediate release (IR) formulation and the **influence of food at 4.5 mg**.
- Study 248.607[U07-3136]: This was a multiple dose study in healthy male Japanese subjects, assessing the **dose proportionality** of the new pramipexole ER-formulation between 0.375 and 1.5 mg q.d. and the **relative bioavailability** in comparison to the IR formulation.
- Study 248.560: This was a single dose in vitro- in vivo correlation (IVIVC) and **food effect study** in healthy male Caucasian subjects. Single dose IR and ER comparisons was done in this study (0.375).

- Study 248.529[U05-2046]: This was a prototype **formulation finding study** in which the new pramipexole ER-formulation was first administered to healthy male Caucasian subjects.
- Study 248.524 [U08-1904-01]: This is a **multiple dose pharmacokinetic study** of pramipexole ER tablets administered once daily to patients suffering from early Parkinson’s disease. The PK and pharmacokinetics/pharmacodynamics results of this study are compiled in the **population PK (PopPK) report**. This includes exploratory PK/PD for efficacy and safety.

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
<b>I. Clinical Pharmacology</b>				
Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:	-	-	-	
multiple dose:	X	-	-	
<i>Patients-</i>				
single dose:	-	-	-	
multiple dose:	-	-	-	
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	X	-	-	Study 248.113
hepatic impairment:	-	-	-	
<b>PD:</b>				
Phase 1:	X	-	-	
Phase 3:	-	-	-	
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:	X	1	-	Study 248.524 (also PopPK report)
Phase 3 clinical trial:	-	-	-	
<b>Population Analyses -</b>				
Data rich:	-	-	-	

Data sparse:	-	-	-	
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:	-	-	-	
Relative bioavailability -	X	3		Study 248.529, Study 248.530, Study 248.607,
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	-		Study 248.530 (also food effect and dose proportionality)
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
Dissolution:	X	-	-	Study 248.560
(IVIVC):				
In vitro Alcohol Dose Dumping Analysis	X	-	-	
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X	-	-	
Total Number of Studies		4 + 1 PopPK		
		+1 Assay		
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		Sponsor should submit relative bioavailability data as xpt file for study 248.530 with pharmacokinetic parameters in the format given below: "Subject, Period, Sequence, Treatment, AUCinf, AUCt, Cmax and Cmin"		
QBR questions (key issues to be considered)		What is the relative BE of pramipexole ER compared to pramipexole IR tablets Is there a dose proportionality between 0.375 and 4.5 mg tablets? Is there a food-effect on pramipexole ER formulation?		
Other comments or information not included above		In vitro alcohol dose dumping analysis provided		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22421 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Veneeta Tandon, Ramana Uppoor, Mehul Mehta)

## **Appendix: Tabular listing of clinical studies**

Type of Study	Study Identifier (Report Number)	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (Total)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	248.529 (U05-2046)	5.3.1.1	Dose formulation (comparison of seven prototypes SR formulation)	Open, randomized, seven-way cross-over  Seven different pramipexole SR tablets/capsules	Tablets/ capsules ; 0.75 mg QD; oral	18 for run-in phase and 14 for the seven-way cross-over phase	Healthy male subjects	4 days	Complete; Full
BE	248.530 (U07-1551)	5.3.1.2	Evaluate BA of PPX ER versus PPX IR; Define PK of PPX ER; Evaluate food effect at highest daily dose of 4.5 mg	Double-blind, double-dummy, randomized, three-way cross-over, active-controlled (PPX IR)	Tablets; 0.375 to 4.5 mg QD (PPX ER), 1.5 mg t.i.d. (PPX IR); oral	39	Healthy male subjects	7 weeks	Complete; Full
BE	248.607 (U07-3136)	5.3.1.2	Evaluate BA of PPX ER versus PPX IR; Define PK of PPX ER in Japanese Subjects	Open, randomized, two-way cross-over, active-controlled (PPX IR)	Tablets; 0.375 to 1.5 mg QD (PPX ER), 0.125 to 0.5 mg t.i.d. (PPX IR); oral	24	Healthy male subjects	4 weeks	Complete; Full
BA	248.560 (U06-1598-01)	5.3.1.3	In vitro/ in vivo correlation; Evaluate food effect	Open, randomized, five-way cross-over	Tablets; 0.375 mg QD (PPX ER), 0.125 mg QD (PPX IR); oral	15	Healthy male subjects	Single dose	Complete; Full

Type of Study	Study Identifier (Report Number)	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (Total)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	248.545 (U08-1652-01)	5.3.3.1	Evaluate influence of PPX on QT interval of the ECG (thorough QT trial)	Double-blind, randomized, placebo-controlled and active-controlled (moxifloxacin), two-way cross-over	Tablets; 0.375 to 4.5 mg QD (PPX ER), 0.75 and 1.5 mg t.i.d. (PPX IR); oral	60 (including 48 with PK profile)	Healthy male and female subjects	7 weeks	Complete; Full
PK	7215-96-006 248.113 (U96-0093)	5.3.3.3	PK and tolerability in renally impaired subjects	open label, single dose	0.25 mg pramipexole IR, single oral dose Lot No 27092	27 (17M/10F) Age 54 (31.0-77.5)	Renally impaired subjects	Single dose	Complete; Full
PK	248.524 (U08-1904-01)	5.3.3.5	Pop PK Analysis from 248.524 study of Efficacy and safety in early PD patients	Double-blind, double-dummy, randomized, placebo-controlled and active-controlled (PPX IR)	Tablets; Flexible dose of 0.375 to 4.5 mg QD (PPX ER), 0.125 to 1.5 mg t.i.d. (PPX IR); oral	Total PPX: 147 PPX ER: 75 PPX IR: 72	PD patients	13 weeks	Ongoing; Full (pop PK Report)
Efficacy	248.524 (U08-1826-01)	5.3.5.1	Efficacy and safety in early PD patients using UPDRS	Double-blind, double-dummy, randomized, placebo-controlled and active-controlled (PPX IR)	Tablets; Flexible dose of 0.375 to 4.5 mg QD (PPX ER), 0.125 to 1.5 mg t.i.d. (PPX IR); oral	PPX ER: 223 PPX IR: 213 PBO: 103 (539)	PD patients	33 weeks, with confirmatory efficacy analysis at week 18	On-going; Interim clinical report

Type of Study	Study Identifier (Report Number)	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (Total)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	248.525 (U08-1962-01)	5.3.5.1	Efficacy and safety in advanced PD patients using UPDRS	Double-blind, double-dummy, randomized, placebo-controlled and active-controlled (PPX IR)	Tablets; Flexible dose of 0.375 to 4.5 mg QD (PPX ER), 0.125 to 1.5 mg t.i.d. (PPX IR); oral	PPX ER : 147 PPX IR: 164 PBO: 165 <b>(476)</b>	PD patients	33 weeks, with descriptive efficacy analysis at week 18	On-going; Interim clinical safety report
Efficacy	248.610	5.3.5.1	Efficacy safety and PK in advanced PD in Japan (DB part followed by OL extension part)	Double-blind, double-dummy, randomized, active-controlled (PPX IR) for 12 weeks, then open-label (PPX ER) for 52 weeks	Tablets; Flexible dose of 0.375 to 4.5 mg QD (PPX ER), 0.25 QD to 1.5 mg t.i.d. (PPX IR); oral	PPX ER / IR: <b>61</b>  (trial still blinded at cut-off date)	PD patients	64 weeks	Ongoing; None
Safety	248.633	5.3.5.2	OL extension in early PD patients from studies 248.524 and 248.636	Double-blind for up to 6 weeks (transfer phase), then open-label with PPX ER	Tablets; Flexible dose of 0.375 to 4.5 mg QD (PPX ER); oral	PPX ER: <b>241</b>	PD patients	Up to 81 weeks	Ongoing; None
Safety	248.634	5.3.5.2	OL extension in advanced PD patients from study 248.525	Double-blind for up to 6 weeks (transfer phase), then open-label with PPX ER	Tablets; Flexible dose of 0.375 to 4.5 mg QD (PPX ER); oral	PPX ER: <b>74</b>	PD patients	Up to 81 weeks	Ongoing; None

Type of Study	Study Identifier (Report Number)	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (Total)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	248.636 (U08-1964-01)	5.3.5.4	Efficacy and safety in early PD patients of an overnight switch from PPX IR to PPX ER; Conversion dose ratio	Double-blind, double-dummy, randomized, active-controlled (PPX IR)	Tablets; 0.375 to 4.5 mg QD (PPX ER), 0.125 to 1.5 mg t.i.d. (PPX IR); oral	PPX ER: 104 PPX IR: 52 (156)	PD patients	Up to 13 weeks	Complete; Full

PPX = pramipexole dihydrochloride

QD = once daily

DB = double-blind

SR = sustained release

BA = bioavailability

UPDRS = Unified Parkinson Disease Rating Scale

PBO = placebo

t.i.d. = three times daily

OL = open-label

ER = extended release

PD = Parkinson's disease

PK = pharmacokinetic

IR = immediate release

**Appendix 2: Composition of Pramipexaole ER formulations**

Table 8: Composition of pramipexole dihydrochloride monohydrate ER tablets, 0.375 mg, 0.75 mg, 1.5 mg, 3 mg and 4.5 mg per tablet

<b>Dosage strength</b>	<b>0.375 mg</b>	<b>0.75 mg</b>	<b>1.5 mg</b>	<b>3 mg</b>	<b>4.5 mg</b>
<b>Ingredient</b>	<b>[mg/tablet]</b>	<b>[mg/tablet]</b>	<b>[mg/tablet]</b>	<b>[mg/tablet]</b>	<b>[mg/tablet]</b>
Pramipexole dihydrochloride monohydrate (b) (4)	0.375	0.750	1.500	3.000	4.500 (b) (4)
Hypromellose (b) (4)					
Maize starch					
Carbomer (b) (4)					
Silica, colloidal anhydrous					
Magnesium stearate					
<b>Total</b>	<b>250.000</b>	<b>330.000</b>	<b>350.000</b>	<b>425.000</b>	<b>500.000</b>

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